Bicuspid Aortic Valve Is Associated With Altered Wall Shear Stress in the Ascending Aorta

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Background—Hemodynamics may play a role contributing to the progression of bicuspid aortic valve (BAV) aortopathy. This study measured the impact of BAV on the distribution of regional aortic wall shear stress (WSS) compared with control cohorts.

Methods and Results—Local WSS distribution was measured in the thoracic aorta of 60 subjects using 4-dimensional (4D) flow-sensitive magnetic resonance imaging. WSS analysis included 15 BAV patients: 12 with fusion of the right-left coronary cusp (6 stenotic) and 3 with fusion of the right and noncoronary cusp. The right-left BAV cohort was compared with healthy subjects (n=15), age-appropriate subjects (n=15), and age-/aorta size–controlled subjects (n=15). Compared with the age-appropriate and age-/aorta size–matched controls, WSS patterns in the right-left BAV ascending aorta were significantly elevated, independent of stenosis severity (peak WSS=0.9±0.3 N/m² compared with 0.4±0.3 N/m² in age-/aorta size–controlled subjects; P<0.001). Time-resolved (cine) 2D images of the bicuspid valves were coregistered with 4D flow data, directly linking cusp fusion pattern to a distinct ascending aortic flow jet pattern. The observation of right-anterior ascending aorta wall/jet impingement in right-left BAV patients corresponded to regions with statistically elevated WSS. Alternative jetting patterns were observed in the right and noncoronary cusp fusion patients.

Conclusions—The results of this study demonstrate that bicuspid valves induced significantly altered ascending aorta hemodynamics compared with age- and size-matched controls with tricuspid valves. Specifically, the expression of increased and asymmetric WSS at the aorta wall was related to ascending aortic flow jet patterns, which were influenced by the BAV fusion pattern. (Circ Cardiovasc Imaging. 2012;5:457-466.)

Key Words: bicuspid aortic valve  ■  aorta  ■  wall shear stress  ■  magnetic resonance imaging

Bicuspid aortic valve (BAV) occurs in 0.5% to 1.5% of the population and is accompanied by a high incidence of morbidity and mortality related to aortic valve dysfunction, aortic aneurysm formation, and dissection.1,2 The cause of these complications, specifically whether aortopathy is genetic or hemodynamic in origin, is an ongoing debate with important implications for interventional planning.3-8 Previous studies have provided evidence for the presence of BAV as an inheritable disorder.9-11 However, this alone does not preclude abnormal hemodynamics as a risk factor for postvalvular aortopathy. Growing evidence shows that BAV and cusp fusion morphology can alter the hemodynamic environment at the level of the ascending aorta (AAo).12-17 These changes can result in abnormal aortic wall shear stress (WSS), a well-known stimulus leading to the expression of transcriptional factors implicated in vascular remodelling.18

Recent advances in cardiovascular magnetic resonance imaging (MRI) permit the assessment of aortic valve morphology and 3-dimensional (3D) blood flow velocity. As a result, BAV fusion patterns and their lesions can be studied in parallel with the resulting 3D flow patterns distal to the valve. Bicuspid cusp morphology has been identified using the steady-state free precession (SSFP) cine imaging.19 Flow-sensitive MRI with full volumetric coverage of the thoracic aorta (4D flow MRI) can measure and visualize aortic 3D blood flow patterns, such as flow jets, vortex, or helical flow patterns.16,20-22 Moreover, analysis tools have been developed to quantify the distribution of WSS in the entire aorta. Recently reported applications indicated altered WSS in the presence of BAV-related flow abnormalities.15,23-26 These studies showed that BAV was associated with altered aortic flow patterns (nested flow, helical flow, or retrograde flow) and elevated or asymmetrically expressed WSS along the circumference of the aorta wall. However, a detailed investigation of the WSS...
distribution in the AAo, its expression as a function of BAV cusp fusion, and a systematic comparison to controls with tricuspid valves matched for age and aortic dimension has not been performed.

It was thus the objective of this study to quantify time-resolved aortic 3D blood flow and WSS in the most common BAV morphology, a so-called fusion of the right-left (RL) coronary cusp, and to compare the results to control groups matched for age and AAo size. Our aim was to investigate the hypothesis that BAV significantly alters WSS in the AAo compared with controls with tricuspid valves. In addition, we analyzed the relationship between BAV morphology and differences in 3D aortic jet flow patterns to investigate the structure–function relationship between valvular lesions and aortic hemodynamics.

Methods

Study Cohort

The study included 60 participants, divided into 4 groups. Study group 1: n=15 patients with BAV, who were consecutively referred for a clinical cardiac magnetic resonance examination to assess aortic valve morphology and function; control group 1: n=15 healthy young volunteers with a morphologically normal tricuspid valve and no history of aortic, heart, or valve disease; control group 2: n=15 age-appropriate subjects with a morphologically normal tricuspid aortic valve; and control group 3: n=15 age- and aortic size–controlled subjects with a morphologically normal tricuspid aortic valve and an AAo aneurysm, defined as a diameter in the AAo >4.0 cm or >2.2 cm/m². All patients gave informed consent, and the institutional review boards approved the study. Demographic details are provided in Table 1.

Magnetic Resonance Imaging

All subjects underwent MRI in our respective clinics (Berlin: 1.5 T Avanto; Freiburg: 3 T, Trio; Siemens Healthcare, Erlangen, Germany; Avanto; Freiburg; 3 T, Trio; Siemens Healthcare, Erlangen, Germany). ECG-gated, breathhold SSFP cine imaging and echocardiography were performed to assess BAV morphology and lesion severity (Figure 1). Slice positioning and imaging parameters were selected, as previously reported. In subjects, in whom these valvular planes were not acquired, transthoracic echocardiography was used to assess valve morphology and function after international guidelines. Aortic size measurements were obtained from axial SSFP imaging of the thorax, as described earlier. Four-dimensional flow MRI was acquired in a sagittal oblique covering the thoracic aorta using prospective ECG gating and a respiratory navigator placed on the lung–liver interface (1.5 T scan parameters ranged from echo times=2.3–3.4 ms, repetition times=4.6–6.6 ms, flip angle=7–15°, and temporal resolution=38.4–52.5 ms). The field of view was 340–400×200–300 mm, with a voxel size of 1.8–2.1×1.8–2.1×2.0–2.8 mm³ (3 T scans used echo times=2.5 ms, repetition times=5.1 ms, flip angle=7–15°, and temporal resolution=40–60 ms). The field of view was 400×308 mm with a voxel size of 2.1×2.1×2.4 mm³. Velocity encoding was adjusted to minimize velocity aliasing (velocity encoding=1.5 m/s for nonstenotic and 2.0–3.0 m/s for stenotic subjects).

Data Analysis

SSFP cine images were evaluated by a cardiologist regarding aortic valve morphology, and orifice area was quantified by manual segmentation (CMR42, Circle Cardiovascular Imaging, Calgary, Canada). Aortic stenosis severity was graded according to international guidelines on the basis of the orifice area. Aortic size was assessed on the level of the midpoint between sinotubular junction and origin of the innominate artery in accordance with international guidelines. The presence of an ascending aortic aneurysm was defined as a diameter of the AAo >2.2 cm/m² or >4.0 cm. All 4D flow MRI data were corrected for eddy currents, Maxwell terms, and velocity aliasing.

Quantification of WSS Distribution

For all 60 subjects, 8 measurement planes were placed at landmark-based positions in the thoracic aorta covering the proximal AAo, distal AAo, arch region, and descending aorta (S1S8: Figure 2). For these 480 individual aorta planes, the aortic lumen contours were manually segmented for all time frames to calculate peak velocity and time-resolved WSS distribution, as described previously. Systolic WSS (WSSsystole) was calculated at the peak of the flow waveform in S1 and averaged with the preceding and 3 subsequent time steps to mitigate measurement noise. Both WSSsystole and WSS averaged over the cardiac cycle (WSSave) were calculated at local anatomic positions (anterior, left-anterior, left, left-posterior, posterior, right-posterior, right, and

Table 1. Population Demographics

<table>
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<tr>
<th>Study Group</th>
<th>Control 3</th>
<th>Control 2</th>
<th>Control 1</th>
</tr>
</thead>
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<tr>
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<td>Age</td>
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<td>Nonstenotic</td>
<td>Stenotic</td>
<td>RL BAV All</td>
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<tr>
<td>Severe</td>
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AAo indicates ascending aorta; AI, aortic insufficiency; BAV, bicuspid aortic valve; RL, right-left; RN, right and noncoronary cusp.

Values are displayed as mean±SD.

No significant differences were found for the RL BAV cohorts as tested against the age/size controls (P>0.05).

Aneurysm defined as AAo diameter >4 cm or 2.2 cm/m².
right-anterior, ie, A, LA, L, LP, RP, R, and RA, respectively) and also circumferentially averaged. The eccentricity of WSS along the circumference of the aorta wall was defined by the difference between the RA and LP systolic WSS (ie, RA-LP WSS\text{	extsubscript{systole}}). As previously proposed, and as confirmed from the maximum measured RA-LP WSS values in the control populations (Table 2), a WSS eccentricity threshold (RA-LP) >0.2 N/m\textsuperscript{2} was used to categorize flows as eccentric.\textsuperscript{25}

Three-Dimensional Flow Visualization and Coregistration With Valve Morphology

The 2D SSFP scans were interpolated to match the temporal resolution of the 4D flow data. Coregistration of the valve images with the flow data (Figure 2) allowed the valve cusp morphology to be visualized in parallel with the 3D blood flow pattern in the aorta (EnSight, CEI Inc, Apex, NC). The 3D flow visualization was based on 3D streamlines (lines tangent to the velocity field) at peak flow systole.

Statistical Analysis

A Lilliefors test was used to determine parameter normalcy and whether an analysis of variance or Kruskal-Wallis test was performed. An F or $\chi^2$ statistic <0.05 determined whether a multiple comparison using Bonferroni correction was performed. Significance differences were defined by $P<0.05$. All data are expressed as mean±SD.

Results

Valve Morphology and Aortic Dimensions

SSFP cine images (n=12) and echocardiography (n=3) allowed the assessment of the valve lesion morphology in all BAV subjects. The BAV cohort (n=15) included 12 patients with a RL fusion of the aortic cusps and 3 patients with a right and noncoronary cusp (RN) fusion.\textsuperscript{10,37} Six of the 12 RL BAV patients and 2 of the 3 RN BAV patients had moderate (mean orifice area: 1.32±0.26 cm\textsuperscript{2}) or severe (mean orifice area: 0.87±0.15 cm\textsuperscript{2}) aortic stenosis. SSFP valve images demonstrating a healthy valve, a nonstenotic RL BAV, and stenotic RL BAV are shown in Figure 1B and 1C. In addition, 10 of the 12 RL BAV patients and 2 of the 3 RN BAV patients were classified as having an AAo aneurysm. The average aorta size between the age/size controls and the RL BAV population were well-matched with no significant differences ($P>0.05$). The age-appropriate population was found to be significantly different to the RL BAV population for aorta size ($P<0.001$). Additional details are provided in Table 1.

General Flow Characteristics

Hemodynamic parameters calculated directly distal to the aortic valve (position S1) are summarized in Table 2. The average cardiac output between all groups of the RL BAV population, the age/size-controls, and the age-appropriate group was matched with no significant differences ($P>0.05$). Peak velocity was significantly elevated in the RL BAV-all and RL BAV-stenotic cohorts compared with the age/size control cohorts ($P<0.001$). Compared with the age-appropriate population, all RL BAV groups exhibited significantly elevated velocity ($P<0.05$ or $P<0.001$).
Table 2. Hemodynamic Quantification at Position S1

<table>
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<th>Control Group 1</th>
<th>Cardiac Output, L/min</th>
<th>WSSsystole RA, N/m²</th>
<th>WSSsystole LP, N/m²</th>
<th>WSSsystole Circum Avg, N/m²</th>
<th>WSSavg RA, N/m²</th>
<th>WSSavg LP, N/m²</th>
<th>WSSavg Circum Avg, N/m²</th>
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<td>Volunteer</td>
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<td>0.3±0.1</td>
<td>0.4±0.1</td>
<td>0.2±0.1</td>
<td>0.3±0.1</td>
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<td>Age appropriate</td>
<td>4.1±1.0</td>
<td>0.5±0.2</td>
<td>0.3±0.1</td>
<td>0.4±0.1</td>
<td>0.3±0.1</td>
<td>0.2±0.1</td>
<td>0.3±0.1</td>
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<tr>
<td>Control Group 3</td>
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<tr>
<td>Age/Size control</td>
<td>5.4±2.6</td>
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<td>0.4±0.2</td>
<td>0.2±0.1</td>
<td>0.2±0.1</td>
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</tr>
</tbody>
</table>

Study Group

|                    |                      |                    |                    |                             |                |                |                      |
|--------------------|----------------------|--------------------|--------------------|-----------------------------|----------------|----------------|                      |
| RL BAV all         | 5.3±1.9              | 0.9±0.3**‡‡        | 0.5±0.2            | 0.8±0.2**‡‡‡†††           | 0.4±0.1*‡       | 0.3±0.1        | 0.5±0.1***†††‡‡‡‡   |
| RL BAV nonstenotic | 6.3±1.7              | 0.8±0.3‡           | 0.4±0.2            | 0.7±0.1***†††‡‡‡          | 0.4±0.1         | 0.3±0.1        | 0.4±0.1*†††‡       |
| RL BAV stenotic§   | 4.3±1.6              | 1.0±0.3†           | 0.6±0.2*†         | 0.9±0.2**†††‡‡‡           | 0.5±0.2‡        | 0.3±0.1        | 0.5±0.1*‡‡‡‡       |
| RL BAV-AI          | 6.5±2.4              | 1.0±0.4            | 0.5±0.1            | 0.8±0.1**†††‡‡            | 0.5±0.1†        | 0.3±0.1        | 0.5±0.1*‡‡‡‡       |

Overall F or χ² statistic 0.996 <0.001§§ 0.003 <0.001 <0.001§§ 0.325 <0.001

AI, aortic insufficiency; RL BAV, right–left bicuspid valve fusion pattern; WSS, wall shear stress.

Values are displayed as mean±SD. Footnotes indicate multiple comparisons.

* or ** denotes P<0.05 or P<0.001 compared with volunteers.
† or †† denotes P<0.05 or P<0.001 compared with age appropriate.
‡ or ‡‡ denotes P<0.05 or P<0.001 compared with age/size control.
§ P<0.05 for all values compared with RL BAV nonstenotic.
§§ χ² obtained from Kruskal-Wallis test.

WSS Measurements

Table 2 reports WSS parameters measured at position S1. Notably, significantly elevated WSS occurred for both the nonstenotic and the stenotic RL BAV patient groups compared with the age/size controls. All RL BAV subgroups were significantly elevated compared with the age/size controls for the circumferentially averaged WSS (P<0.001) and WSSavg (P<0.05 or P<0.001).

Significant regional differences were found for the right-anterior WSS and WSSavg (P<0.001 or P<0.05). Figure 3 compares WSSsystole in the RL BAV group to the age-appropriate, age/size control groups throughout the thoracic aorta. WSSsystole was significantly elevated and eccentric in the anterior and right-anterior AAo region of S1–S3 for the RL BAV group compared with the control groups. In addition, compared with the age/size controls, 45 of the 56 (80%) RL BAV WSS measurement locations along S1–S7 were significantly elevated at systole. Compared with the age-appropriate values, the systolic RL BAV WSS values were elevated at 12 of the 24 (50%) locations in the AAo (S1–S3), at S4 the significance values decreased, and all measurement locations were statistically similar at the level of the distal arch and beyond (S5–S8; P>0.05).

In both stenotic and nonstenotic RL BAV patients, the peak systolic WSS location traveled in a right-handed helix, appearing at the AAo right-anterior or anterior location and progressing along the flow direction until reaching the level of the supra-aortic arteries. A comparison of WSS between the nonstenotic and stenotic RL BAV patients yielded no statistically significant differences for planes S1–S4. Highly eccentric (RA-LP≥0.4 N/m²) peak WSS values were observed to be colocated with the position of an elevated velocity jet as shown in Figure 3B and 3C and Figure 4D and 4E (closed and open black arrows). WSS eccentricity did not occur in the volunteers and control populations. The nonstenotic RN patient demonstrated a peak WSS eccentricity at the right-posterior region for the S1 level (Figure 5). For the 2 stenotic RN patients, peak WSS occurred at the left-anterior position of slice S1–S3. A complete WSS comparison matrix for all slice positions and groups is provided in the online-only Data Supplement Figure.

Three-Dimensional Flow Visualization and Coregistration With Valve Morphology

Figure 2A and 2B shows representative images for a healthy tricuspid valve during the ejection period (see also online-only Data Supplement Movie I) and its relationship to the aortic 3D flow pattern. This example illustrates the presence of normal cohesive systolic aortic flow as represented by 3D streamlines distal to a normal tricuspid aortic valve. For the RL BAV patients, the position of the elevated and eccentric WSS was colocated with observations of a systolic blood flow jet propagating in a direction opposite to the position of the fused RL cusp, impinging at the right-anterior region of the aortic wall (Figures 3 and 4, see also online-only Data Supplement Movie II). For the 2 patients with stenotic RN BAV, one displayed a flow jet directed toward the left-anterior wall of the aortic root, and the other patient did not show a conclusive flow direction. The nonstenotic RN BAV in Figure 5 shows a markedly different jetting pattern than the RL BAV pattern. In this RN case, a flow jet is clearly seen to be directed by the fused cusp toward the right posterior of the aortic root (Figure 5F).

Discussion

This is the first study to investigate hemodynamic forces at various levels of the thoracic aorta in BAV patients regarding a specific valve morphology. The main findings of this investigational series were the following: (1) The RL BAV fusion is
associated with significantly elevated WSS at focal regions in the AAo, (2) this elevation is present in both stenotic and nonstenotic RL BAV patients, (3) the direction of a postvalvular blood jet appears to be influenced by the position of the fused cusp, and (4) the aortic wall/jet impingement positions correspond to regions of elevated WSS.

The timing of prophylactic aortic root replacement associated with BAV disease is a complex decision. The guidelines for the management of patients with ascending aortic disease associated with BAV mainly focus on the absolute size of the aorta, the condition of the BAV, and the rate of expansion of the aortic aneurysm. Information about the hemodynamic forces exerted on the AAo wall as described in this study may help to complement the static information of aortic dimensions and to facilitate more individualized patient management.
Association of Aortic Hemodynamics and Valve Morphology

It has been recognized that the BAV demonstrates abnormal cusp motion, including folding or wrinkling of the valve tissue and increased cusp doming during the cardiac cycle. This may result in altered flow characteristics even when the cusps are not stenotic. The present data support this hypothesis. For example, the nonstenotic RN BAV patient exhibited a flow jet that is clearly directed by the fused cusp toward the right posterior of the aortic root (Figure 5F). The RL cusp seen in Figure 4C and 4D also appears to influence the direction of postvalvular jet. The position of these jets corresponded to the peak WSS measurement locations (Figures 3 and 5E). In addition, the maximum systolic WSS for the 2 stenotic RN BAV patients was located at the left-anterior wall, consistent with a high velocity gradient directed away from the position of a fused RN valve.

This is compelling evidence regarding the mechanism by which a fused cusp and impaired cusp mobility may elevate local aortic WSS downstream from the aortic valve. This phenomenon is especially of interest, given the heterogenic expression of aortopathy in patients with specific valve fusion patterns and valve lesions. Our findings are consistent compared with previous reports showing that distinct aortic root phenotypes may be associated with various cusp orientations in BAV. If hemodynamic forces do indeed contribute to the progression of this disease, then these observations illustrate a differentiating characteristic between valve fusion groups beyond genetic predisposition and could be used for risk stratification and clinical decision making. Additional patient numbers and longitudinal follow-up are needed to test this hypothesis. Nevertheless, our findings highlight the utility of this multimodal MRI for investigating the structure-function relationship between the valve and the downstream flow characteristics.

Of particular interest were the hemodynamic differences between the age/size controls and the RL BAV population. This control group represents a condition where all controllable hemodynamic influences except valve geometry were similar (ie, age, cardiac output, and aorta geometry). Conversely, the WSS values at the S1–S6 measurement positions displayed the most significant intergroup differences of all cohorts. This highlights patently different WSS present at the AAo wall for these 2 seemingly similar aortopathies. These results emphasize that BAV causes a significant alteration to the AAO hemodynamic environment. However, it still remains unclear what these results mean regarding the controversy between the genetic or hemodynamic aortopathy hypotheses. Further longitudinal study is warranted to provide further insight.

Other studies have applied 4D flow MRI to investigate vortex flow in the sinuses of Valsalva after valve-sparing aortic root replacement contributing to an ongoing discussion.

Figure 4. A–C, Coregistered steady-state free precession images provide anatomic landmarks to locate (D and E) the direction and propagation of a systolic flow jet. Here, for the right-left (RL) bicuspid aortic valve lesion, the jet is directed toward the right-anterior wall of the ascending aorta. The jet impacts and travels along the right-anterior aorta wall in a right-handed helical direction.
about the impact of different types of aortic reconstruction on hemodynamic outcome in valve-sparing surgical repair of aortic root ectasia. Future studies using postinterventional 4D flow MRI and WSS quantification in BAV patients after surgery may have the potential to directly evaluate hemodynamic outcome and thus help optimize interventional techniques.

Comparison of WSS Results to Previous Studies

The measurement of eccentricity and position of elevated WSS in the RL BAV patients correlated well with 2 known studies of WSS in BAV patients. Barker et al previously reported a local WSS eccentricity in a diverse group of BAV patients examined with 2D PC-MRI using through-plane velocity encoding; however, the sole significant BAV WSS differences were noted to be with depressed compared with a control population (located at the left-posterior position AAo), which appears to contradict the findings (ie, elevated WSS) of our present study. In actuality, the WSS differences between these 2 studies stem from the use of through-plane only encoding versus 3-directional velocity encoding. For example, when the in-plane velocity components from this study are not included in the WSS magnitude calculations, the position and significance of the WSS values agrees with the previous study (Figure 6). These calculations are supported by the streamline visualizations in Figures 3 and 4, where the LP region exhibits highly circumferential velocity components. Their presence will increase calculation of the 3D WSS magnitude compared with a simple through-plane magnitude calculation highlighting the importance of measuring all velocity components to examine abnormal flow and WSS in the aorta.

Similar to a recent study, the systolic local WSS values between stenotic and nonstenotic BAV patients were not significantly different. This emphasizes that the presence of a nonstenotic bicuspid valve alone represents a flow obstacle and leads to a significant alteration of the flow pattern.

The previous study also reports a WSS asymmetry similar to that observed here; however, the magnitude of the WSS values reported at the RA position was higher than ours (1.15 N/m² for a normal flow cohort and 1.56 N/m² for helical flow cohort). This is most likely because of the methodology by which the RA WSS values were calculated. In the Hope et al WSS study, a maximum WSS value was selected along an entire quadrant representing the RA position at a single time point. Our study chose to select a single RA location averaged at peak systolic WSS over a time period of systole.

Figure 5. A–D. A right and noncoronary cusp (RN) valve fusion shows a jetting pattern toward the posterior wall of the aorta, opposite from the fused right and noncoronary cusp. E. The peak wall shear stress (WSS) measured for this patient occurs at the RP position (black closed arrow) instead of at the RA position for right-left (RL) bicuspid aortic valve (BAV) patients. F. As with the RL valve fusion patient shown in Figure 4, the incomplete opening of the fused cusp appears to influence the direction of the velocity jet (black open arrow) and thus the position of the peak WSS eccentricity. A indicates anterior; LA, left-anterior; L, left; LP, left-posterior; P, posterior; RP, right-posterior; R, right; RA, right-anterior.
consisting of 5 systolic time steps (to mitigate measurement noise). Neither technique represents a more correct methodology, but this and study demographics may possibly account for slightly different WSS values reported in these studies. Nonetheless, we used a similar eccentricity threshold as the Hope et al study based on the observation that the control groups never exceeded an eccentricity of 0.2 N/m². It should also be noted that both the previous Hope et al and Barker et al. BAV WSS studies did not group or report WSS according to valve lesion (rather they chose helicity or retrograde flow as grouping categories). Qualitative agreement of WSS asymmetry between the 2 morphologically heterogeneous BAV studies may be because of the 70% prevalence of the RL cusp fusion phenotype.

It should also be noted that the Hope et al and Barker et al studies examined WSS at a single analysis position distal to the sinotubular junction. In the current study, WSS was examined at 8 positions throughout the thoracic aorta and carefully selected for reproducibility using anatomic landmarks (such as the bottom third of the RPA for S1). Given the aggregate results from these studies, future analysis should further investigate WSS focally at the AAo with additional analysis planes placed at and just distal to the sinotubular junction.

**Study Limitations**

The scope of the study did not include longitudinal analysis. This is necessary to address the question of whether hemodynamic parameters act as potential prognostic metrics for BAV-related aortopathic events. In addition, although the overall number of subjects examined was satisfactory for an initial pilot study (n=60), the BAV cohort consisted of 15 subjects. Although the power of these numbers was sufficient to establish strong (P<0.001), significant statistical hemodynamic trends for the RL valve fusion cohort (n=12), it was not sufficient for attempting statistical analysis of alternative valve fusion morphologies (n=3).

Six of 15 BAV patients had aortic insufficiency (4 mild and 2 moderate). In the presence of aortic insufficiency, cardiac output will be slightly overestimated because of prospective ECG gating and a portion of the diastolic backflow being truncated. The cases with regurgitation in the nonstenotic RL BAV group and aortic insufficiency RL BAV group may explain the slightly elevated, although statistically insignificant differences regarding cardiac output (Table 2).

The discrete spatial and temporal resolution (≈2 mm³ and ≈40 ms) of the aortic blood flow velocities measured by 4D flow MRI will result in a systematic underestimation of peak velocity and WSS.23-27 This is the primary reason that stenosis degree was measured via magnetic resonance planimetry.29 Nevertheless, the relative differences between the measured velocity-derived parameters can still be reliably inferred, especially if the measurement procedure is consistent between study populations, as in our cohorts. The procedural stability of this technique has been shown in many studies reporting acceptable inter- and intraobserver WSS variability.15,23-25

In addition, we previously performed a detailed investigation of interobserver, intraobserver, and scan–rescan variability WSS error, which used the same 4D flow MRI technique used in this study.42 The estimation of WSS, which included additional errors because of plane placement and segmentation, was found to have a maximum error of <10%. Thus, we applied a 10% worst case error to each measure RA WSSsys value on a subject-by-subject basis and retested for significance (ie, each control RA WSSsys value was increased 10% and each BAV value was decreased 10%). Given this stress test, the RA WSSsys for all RL BAV groups maintained their significance from Table 2 compared with the age/size (RL BAV-all, RL BAV-nonstenotic, RL BAV-stenotic: P<0.05) and age-appropriate groups (RL BAV-all: P<0.05). The variability of local WSS was also addressed in the previous study with a linear regression analysis demonstrating significant correlation (P<0.001) of scan–rescan (r=0.87), inter- and intraobserver comparisons (r=0.88 and r=0.97, respectively).

In a separate WSS study, typical values for WSSsys and WSSavg in healthy young control patients were also shown to have a similar intraobserver variability of 1.6±2.0% and 6.4±7.9%, and an interobserver variability of 7.5±6.5% and 14.7±12.6.24 These results also agree with additional inter- and intraobserver variability studies specifically performed on BAV patients, one study which used the exact software tool as this study.15,25 Furthermore, given that our results incorporate values measured at both field strengths; intersystem variability is also an important consideration. Thus, we note that the field dependence of velocity and WSS measurements were recently reported at 1.5 T and 3.0 T with a correlation between peak velocities and WSS of r=0.85 and r=0.65, respectively (P<0.001).43

**Conclusion**

BAV patients with a RL cusp fusion pattern express significantly different eccentric and focally elevated WSS values compared with both age- and age/size-controlled populations. In addition, a distinct flow jet was observed to be associated with the position of the fused cusp and valvular function. The flow jet impingement position at the aorta wall corresponded...
with elevated WSS values and could place this group at-risk for future aorticpathic events. Additional longitudinal data including the analysis of alternative lesion patterns are necessary to evaluate the utility of WSS as a prognostic marker for disease progression.

Sources of Funding
Dr Barker is funded by the Whitaker Postdoctoral and Fulbright Grants. Dr Knobelsdorff-Brenkenhoff is supported by the Else Kröner-Fresenius Stiftung. Dr Markl is supported by the Northwestern Memorial Hospital Excellence in Academic Medicine Program Advanced Cardiovascular MRI Research Center and the Northwestern Memorial Foundation Dixon Translational Research Grant.

Disclosures
None.

References


CLINICAL PERSPECTIVE

This study investigates wall shear stress (WSS) in the thoracic aorta of bicuspid aortic valve (BAV) patients stratified by a specific valve fusion morphology. The main findings of this investigation are that (1) a right-left BAV fusion pattern was associated with significantly and focally elevated WSS in the ascending aorta, (2) this elevation was present both in stenotic and nonstenotic right-left BAV patients, (3) the postvalvular blood flow jet direction was influenced by the position of the fused cusp, and (4) aortic wall/jet impingement positions corresponded to regions of elevated WSS. Evidence is presented showing a mechanism by which impaired cusp mobility may elevate local aortic WSS downstream from the aortic valve. This phenomenon is of interest, given the heterogeneous expression of aortopathy in BAV patients with specific valve fusion patterns and valve lesions. On the basis of previous findings indicating that increased WSS is associated with altered endothelial cell function and vascular remodeling, the results in this study illustrate WSS patterns as a differentiating characteristic between valve fusion groups beyond genetic predisposition and could be used for risk stratification and clinical decision making. The guidelines for the management of BAV patients with concomitant aortopathy mainly focus on the absolute size of the aorta, the condition of the valve, and the rate of aorta expansion. Information about the hemodynamic forces exerted on the ascending aorta wall as described in this study may help to complement these dimensional measurements and to facilitate more individualized patient management.
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_Circ Cardiovasc Imaging_. 2012;5:457-466; originally published online June 22, 2012; doi: 10.1161/CIRCIMAGING.112.973370

_Circulation: Cardiovascular Imaging_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231

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Print ISSN: 1941-9651. Online ISSN: 1942-0080

The online version of this article, along with updated information and services, is located on the World Wide Web at:

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SUPPLEMENTAL MATERIAL

Figure Legend

Supplementary Figure. Comprehensive WSS comparison matrix for all slice positions and groups. The outer curvature (O), inner curvature (I), right (R) and left (L) sides of the aorta are used in combination with the slice positions (S1-S8) to provide the anatomic locations for the WSS measurements.
Movie Legends

**Movie 1.** Time-resolved pathlines illustrating a normal tricuspid valve and cohesive flow throughout the thoracic aorta.

**Movie 2.** Time resolved pathlines illustrating a stenotic RL BAV valve and abnormal post-valve aortic flow.