JACC: CARDIOVASCULAR IMAGING VOL. 4, NO. 7, 2011

ISSN 1936-878X/$36.00

PUBLISHED BY ELSEVIER INC.

DOI:10.1016/j.jcmg.2011.05.004

iCONCEPTS

TECHNOLOGY ON THE VERGE OF TRANSLATION

4D Flow CMR in Assessment of Valve-Related Ascending Aortic Disease

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Blood flow imaging with 3-dimensional time-resolved, phase-contrast cardiac magnetic resonance (4-dimensional [4D] Flow) is an innovative and visually appealing method for studying cardiovascular disease that allows quantification of important secondary vascular parameters including wall shear stress. The hypothesis of this pilot study is that 4D Flow will become a powerful tool for characterizing the relationship of aortic valve–related flow dynamics, especially with bicuspid aortic valve (BAV), and progression of ascending aortic (AsAo) dilation. We identified 46 patients previously studied with 4D Flow: tricuspid aortic valve patients without valvular disease (n = 20), and BAV patients with either normal flow (n = 7) or eccentric systolic jets resulting in abnormal right-handed helical AsAo flow (n = 19). The subgroup of patients with BAV and eccentric systolic AsAo blood flow was found to have significantly and asymmetrically elevated wall shear stress. This increased hemodynamic burden may place them at risk for AsAo aneurysm. (J Am Coll Cardiol Img 2011;4:781–7) © 2011 by the American College of Cardiology Foundation

Blood flow imaging with 3-dimensional (3D) time-resolved, phase-contrast cardiac magnetic resonance (CMR) (4-Dimensional [4D] Flow) is an innovative and visually appealing method for studying cardiovascular disease that allows quantification of important secondary vascular parameters including wall shear stress (WSS) (1,2). The clinical feasibility of using 4D Flow has only recently been established, and the full power of this methodology has not yet been exploited in the management of patients with cardiovascular disease. Progression of aneurysmal disease of the ascending thoracic aorta (AsAo) is poorly understood, but is commonly seen with bicuspid aortic valve (BAV). The hypothesis of this pilot study is that 4D Flow will become a powerful tool for characterizing the relationship of aortic valve–related flow dynamics, especially with BAV, and progression of AsAo dilation.

BAV is relatively common (1% to 2% of the population) and frequently results in AsAo dilation. There is convincing evidence that this aortic dilation is related to intrinsic aortic fragility. However, there is also evidence that demonstrates different disease progression with different aortic leaflet fusion patterns and asymmetry to the aneurysms that develop,

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Manuscript received January 24, 2011; revised manuscript received May 9, 2011, accepted May 9, 2011.

which cannot be easily explained by an intrinsic wall abnormality theory alone. For example, fusion of the right and left coronary leaflets is associated with increased dimensions of the aortic root and development of aortic insufficiency later in life, whereas fusion of the right coronary and noncoronary leaflets is associated with earlier valvular disease and increased dimensions of the aortic arch. Aneurysms of the AsAo with BAV typically bulge asymmetrically toward the right, outer curvature.

A potential explanation for these asymmetric and heterogeneous findings is abnormal blood flow. Increased systolic velocities have been demonstrated by echocardiography at the anterolateral AsAo wall in patients with BAV. Computer modeling has demonstrated eccentric flow jets and turbulence along the right convexity of the AsAo. Furthermore, elevated hemodynamic stress at this location has been linked to early smooth muscle cell apoptosis. However, eccentric systolic blood flow in the AsAo is difficult to reliably characterize by echocardiography.

ABBREVIATIONS AND ACRONYMS

3D = 3-dimensional

4D Flow = 3-dimensional, time-resolved phase-contrast cardiac magnetic resonance

AsAo = ascending thoracic aorta

BAV = bicuspid aortic valve

BAVh = bicuspid aortic valve with helical flow

BAVn = bicuspid aortic valve with normal flow

CMR = cardiac magnetic resonance

LP = left posterior

RA = right anterior

TAV = tricuspid aortic valve

vWSS = vectorial wall shear stress

WSS = wall shear stress

With its high-resolution 3D acquisition unhindered by acoustic windows, 4D Flow allows substantially better characterization of eccentric blood flow in the AsAo of BAV patients than echocardiography does. Additionally, 4D Flow datasets allow for estimation of WSS from near-wall velocity gradients. Stalder et al. (2) have recently developed a new method for calculating shear stress from 3D phase-contrast CMR data, which they have validated with a flow phantom and favorably compared with the results of prior publications regarding aortic shear stress values. We seek to use these capabilities afforded by 4D Flow datasets to further study a subgroup of BAV patients that we have previously identified with eccentric systolic flow jets resulting in abnormal helical AsAo flow (3). Through the mechanism of elevated WSS (4), these eccentric flow jets may promote AsAo dilation.

More broadly, we aim to expand the way in which CMR is used to evaluate cardiovascular disease. Vessel dimensions are currently the principal imaging criteria used clinically to risk stratify patients with aortic disease. Altered blood flow is rarely considered, although there is considerable evidence demonstrating the link between abnormal flow and disease. With this pilot study, we seek to use 4D Flow imaging to change the paradigm for risk stratifying patients with cardiovascular disease by investigating the role that abnormal flow has in the promotion and/or exacerbation of vascular pathology.

Study Design

4D Flow was used to assess blood flow patterns in the thoracic aorta of 102 subjects who presented for CMR between February 9, 2007, and September 20, 2010. From these cases, three subgroups were identified: 1) tricuspid aortic valve (TAV) patients without AsAo aneurysm or aortic valvular disease (n = 20); 2) BAV patients with normal AsAo flow (n = 7); and 3) BAV patients with abnormal helical AsAo flow (n = 19). Determination of aortic valve morphology was made by echocardiography, and characterization of AsAo flow patterns was made by previously reported criteria (3). Patients were excluded from the study if they: 1) did not have an echocardiogram or had insufficient evaluation of the aortic valve; 2) had congenital heart disease other than successfully repaired aortic coarctation; or 3) had poor quality 4D Flow datasets.

Characteristics of the patient groups are included in Table 1. Successfully repaired aortic coarctation was present in 15 of the TAV patients, 3 of the BAV with normal flow (BAVn), and 10 of the BAV with helical flow (BAVh). AsAo dilation (largest AsAo diameter >4.0 cm or >2.2 cm/m^2) was present in 7 of the BAVh patients, 1 of the BAVn patients, but none of the TAV patients. The BAVh group contained 6 patients with mild stenosis and 3 patients with moderate/severe stenosis. Aortic valve leaflet fusion in BAV groups was predominantly of the right and left coronary leaflets (n = 21), with 1 case of right and noncoronary leaflet fusion, and 4 cases of unknown fusion (i.e., the specific leaflet fusion was not confidently identified). The protocol, which is compliant with the Health Insurance Portability and Accountability Act, received Institutional Review Board approval, and informed consent was obtained in all cases.

CMR Technique and Analysis

The 4D Flow technique employed has been previously validated (1,3). Scan times ranged from 8 to 15 min. Prior to visualization, data were corrected for Maxwell phase effects, encoding errors due to the gradient field distortions, and effects from eddy currents. Corrected velocity data were imported into 3D visualization software (EnSight, CEI Inc., Apex, North Carolina). For each patient, a cross-sectional plane was placed at the AsAo just

distal to the sinotubular junction. The planes, complete with embedded velocity and magnitude data, were exported to proprietary software for WSS quantification.

Patients were further subdivided into three groups based solely on the severity of AsAo eccentric flow: 1) normal flow if high velocity systolic flow was centrally focused, occupying the majority of the vessel lumen (Fig. 1A); 2) mild eccentric flow if high velocity systolic flow occupied between one- and two-thirds of the vessel lumen (Fig. 1B); and 3) marked eccentric flow if high velocity systolic flow occupied one-third or less of the vessel lumen (Fig. 1C).

WSS Calculations

Proprietary software (*flow tool* 2.0, University of Freiburg, Freiburg im Breisgau, Germany) allowed manual vessel wall segmentation (2). Once segmented, vectorial wall shear stress (vWSS), which takes into account both the axial and circumferential components of WSS that are seen with helical flow, was computed at 12 equally spaced data points along the circumference of the aortic cross section. Maximum vWSS along the right anterior (RA) quadrant was identified by selecting the highest vWSS value along the RA quadrant of the aortic cross section at peak systole. The corresponding peak left posterior (LP) quadrant vWSS was noted as the measurement at the data point opposite from the RA point. Wall segmentation and identification of peak systolic RA and LP quadrant vWSS was carried out twice by 3 observers, resulting in 6 vWSS measurements for both RA and LP data for each patient.

Statistics

Peak RA vWSS for each patient was calculated as the mean of the 6 measurements made by the 3 independent observers, and for each group it was calculated as the mean of the peak RA vWSS measurements for each patient. A measurement of the difference in RA and LP vWSS is provided to show the asymmetry of vWSS. Student *t* tests were used to compare the mean vWSS distributions of the different groups. Both intraobserver and interobserver variability were calculated using the intraclass correlation coefficient.

Table 1. Patient Characteristics

	Tricuspid Control	Bicuspid Normal Flow	Bicuspid Helical Flow
n	20	7	19
Age, yrs	26.9 ± 10.4	20.4 ± 7.9	30.5 ± 12.6
Male	75% (n = 15)	43% (n = 3)	58% (n = 11)
Repaired coarctation	15	3	10
AsAo dilation*	0	1	8†
Aortic valvular disease			
Insufficiency			
Mild	1	1	4
Moderate	0	0	1
Stenosis			
Mild	0	0	6
Moderate	0	0	3
Aortic leaflet fusion			
Right-left	—	5	16
Right-noncoronary	—	1	0
Unknown fusion	—	1	3

Values are n, mean ± SD, or %. *Normal is <4 cm or <2.2 cm/m^2; dilated is ≥4 cm or ≥2.2 cm/m^2. †Only 1 patient had a maximum aortic diameter >5 cm.

TAV Patients

All TAV patients demonstrated a central flow jet with no helical flow at peak systole (Fig. 1A). This group had the lowest RA vWSS with a value of 0.85 N/m^2 and the smallest difference between RA and LP vWSS with a value of 0.24 N/m^2, which is consistent with relatively symmetrical vWSS (Table 2, Fig. 2).

BAV Normal Flow

The BAVn patients demonstrated a central flow jet with no helical flow at peak systole (Fig. 1A). The group had values that were somewhat higher than those of the TAV group with mean RA vWSS of 1.15 N/m^2 ($p = 0.031$) and a difference between RA and LP vWSS of 0.40 N/m^2 ($p = 0.373$).

BAV Helical Flow

The BAVh patients demonstrated right-handed helical flow and asymmetric, RA flow jets at peak systole (Figs. 1B and 1C). Mean RA vWSS was 1.56 N/m^2 and the difference between RA and LP vWSS was 1.65 N/m^2, the highest and most asymmetric vWSS of the 3 groups. The comparison of means between BAVh and both the TAV and BAVn groups were statistically significant: when compared with TAV patients, $p < 0.001$ for both RA and RA-LP quadrants, and when compared

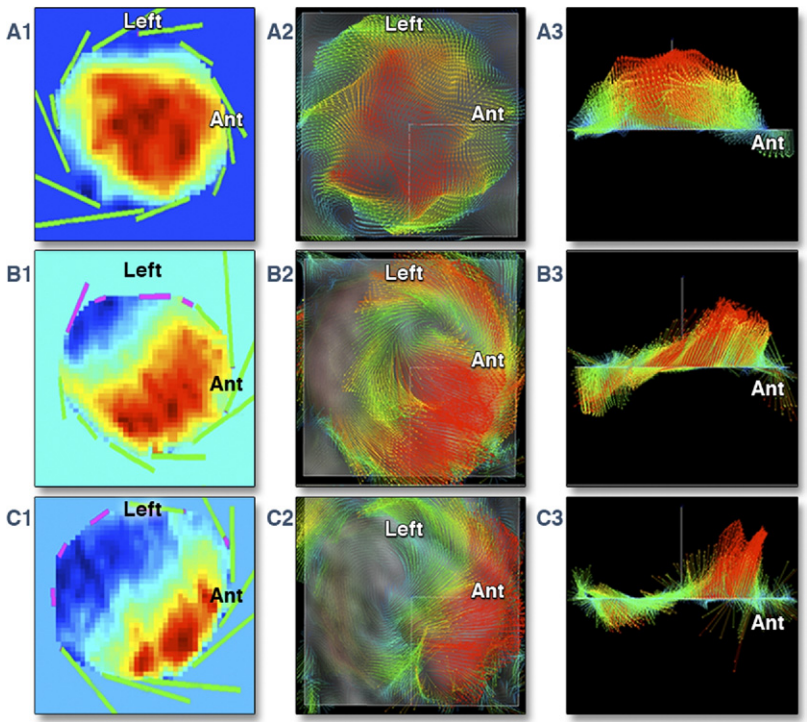

Figure 1. Normal, Mild, and Markedly Eccentric Systolic Flow

Ascending thoracic aorta (AsAo) cross sections just distal to the sinotubular junction demonstrate normal, mild, and markedly eccentric systolic flow. Images from **left** to **right** show software output used for vectorial wall shear stress (vWSS) calculations with relative vWSS values represented by the **green bars (A1, B1, C1),** a corresponding view with velocity-coded vectors using 3-dimensional, time-resolved phase-contrast cardiac magnetic resonance (4D Flow) visualization **(A2, B2, C2),** and a lateral view of the same vector field **(A3, B3, C3).** The orientation of all cross-sectional planes is labeled. **(A)** Image shows normal flow with high velocity vectors centrally located, occupying the majority of the vessel lumen, and decreasing velocity approaching vessel wall. **(B)** Image shows mild eccentric flow, with high velocity vectors occupying between one- and two-thirds of the lumen. The lateral view shows that vectors are oriented anteriorly. **(C)** Image shows marked eccentric helical flow, with high velocity vectors occupying one-third or less of vessel lumen and marked anterior skewing of vectors on the lateral view.

with BAVn, $p = 0.014$ and $p < 0.002$ for the same measurements, respectively.

Flow Eccentricity Analysis

When subdivided by flow eccentricity, significant elevation of RA vWSS values is seen in the eccentric flow groups compared with the normal flow group, but the difference between the mild and marked eccentric flow groups is less striking (Table 3, Fig. 3). Mean RA vWSS for the normal flow group was 0.93 N/m^2; for the mild eccentric flow group it was 1.44 N/m^2; and for the marked eccentric flow group it was 1.67 N/m^2. The differences in vWSS between the RA and LP quadrants for each group are more pronounced, with values for normal, mild, and marked eccentric groups of 0.28 N/m^2, 0.92 N/m^2, and 2.31 N/m^2, respectively (Table 3, Fig. 4). The high value for RA and LP quadrant vWSS difference for the marked eccentric flow group is related to retrograde flow in the LP quadrant in many patients with marked eccentric

Table 2. WSS by Patient Subgroup

	n	RA vWSS	p Value*	RA-LP (LP Value)	p Value
TAV patients	20	0.85	—	0.24 (0.61)	—
BAV normal flow	7	1.15	0.031	0.40 (0.75)	0.373
BAV helical flow	19	1.56	<0.001, 0.014	1.65 (–0.09)	<0.001, 0.002

Units of vectorial wall shear stress (vWSS) are in n/m^2. *Single or first p value is versus TAV patients, and the second versus BAV normal flow.
BAV = bicuspid aortic valve; LP = left posterior; RA = right anterior; TAV = tricuspid aortic valve; vWSS = vectorial wall shear stress; WSS = wall shear stress.

flow. The only comparison within these subgroups where statistical significance was not demonstrated was between the RA vWSS of the mild and marked eccentric flow groups (p = 0.18). All other comparisons between groups had a p value <0.01.

No significant difference in vWSS was seen between BAV patients with and without AsAo dilation (RA vWSS 1.43 N/m^2 and 1.46 N/m^2, respectively). Although there was a trend toward higher vWSS with aortic stenosis, it was not statistically significant (1.71 N/m^2 vs. 1.42 N/m^2, p = 0.12).

Reproducibility Analysis

Intraobserver intraclass correlation coefficients were 0.92 for RA and 0.91 for LP, which is consistent with good correlation. The interobserver intraclass correlation coefficients were 0.97 for the RA, and the LP also demonstrate convincing reproducibility (Table 4).

Discussion

4D Flow allows unique characterization of vessel hemodynamics that may change the current practice of risk stratifying patients with cardiovascular disease. Until the advent of 4D Flow, altered AsAo blood flow was not well visualized and, consequently, not a topic of clinical interest. Vessel dimensions have been the main imaging criteria for evaluating aortic disease. But now with 4D Flow, dynamic high-resolution 3D velocity data for a large vascular territory can be captured in a reasonable scan time. Altered flow patterns and their effects on endothelial cells can be characterized in detail and may help to identify patients at risk for developing aneurysm or dissection who have normal aortic dimensions. Closer imaging surveillance would be indicated for these patients, medical therapy could be initiated earlier, and surgery or intervention may be considered at lower thresholds.

In this pilot study, we have demonstrated significantly and asymmetrically elevated WSS in the AsAo of a selected subgroup of patients with BAV referred for CMR. Deviation of systolic blood flow toward the AsAo convexity is expected based on the normal offset of axes between the left ventricle and aortic root and explains the modest increase in RA versus LP quadrant shear stress values in our TAV patients (0.85 vs. 0.61 N/m^2, or a difference of 0.24 N/m^2). This asymmetry is magnified in patients with BAV; unequal-sized aortic leaflets displace flow, to varying degrees, away from the vessel center. BAV with normal systolic flow has slightly elevated RA quadrant shear stress (1.15 N/m^2) and an increased difference between RA and LP quadrant values (0.4 N/m^2), although these differences do not meet statistical significance. The asymmetries, however, become pronounced and statistically significant in BAV patients with eccentric systolic flow jets resulting from abnormal right-handed AsAo helical flow, with the highest RA quadrant shear values (1.67 N/m^2) and RA versus LP quadrant difference (2.31 N/m^2) in the subgroup with marked eccentric flow (Figs. 3 and 4).

Eccentric systolic blood flow in the AsAo is difficult to characterize with echocardiography, but can be quantified with 4D Flow. A correlation between increasing flow eccentricity and AsAo dimensions in BAV patients has recently been reported, but it is unclear whether the eccentric flow is a cause or a consequence of aortic dilation (5). By demonstrating that eccentric flow in BAV patients is associated with significantly elevated wall

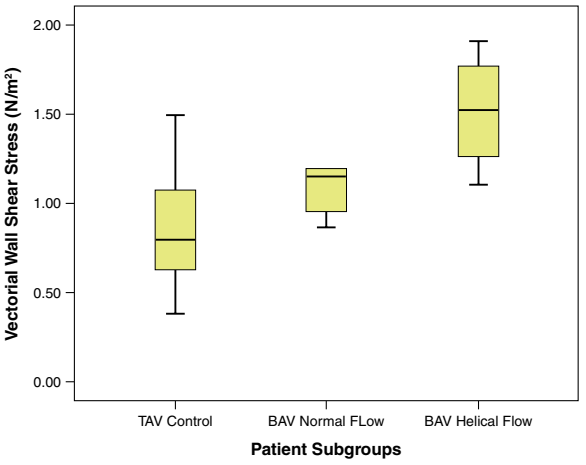

Figure 2. RA Quadrant WSS by Patient Subgroup

Graph of right anterior (RA) quadrant vertical wall shear stress (vWSS) by patient subgroup (tricuspid aortic valve [TAV] patients, bicuspid aortic valve [BAV] normal flow, and BAV helical flow). The **box** contains the middle 50% of values with the mean represented by a **line; whiskers** include all other points. The BAV helical flow group shows much higher vWSS values than the other 2 groups do (p < 0.02).

Table 3. WSS by Flow Subgroup

	n	RA vWSS	p Value*	RA-LP (LP value)	p Value
Normal flow	27	0.93	—	0.28 (0.65)	—
Mild eccentric flow	9	1.44	<0.001	0.92 (0.52)	<0.01
Marked eccentric flow	10	1.67	<0.001, 0.18	2.31 (–0.64)	<0.01, <0.01

Units of vWSS are in n/m^2. *Single or first p value is versus normal flow, and the second is versus mild eccentric flow.
Abbreviations as in Table 2.

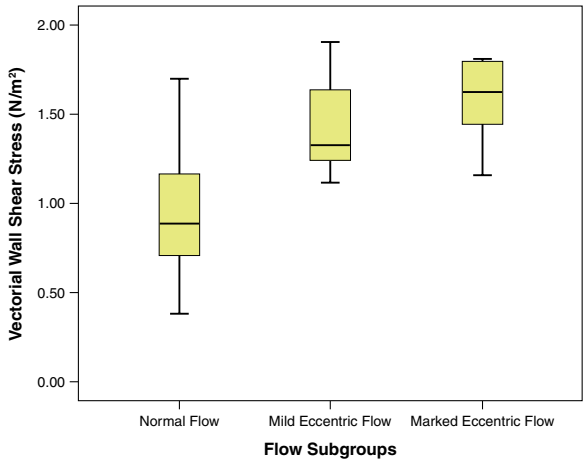

Figure 3. RA Quadrant WSS by Flow Subgroup

Graph of RA quadrant vWSS by flow subgroup (normal, mild, and marked eccentric flow). The **box** contains the middle 50% of values with the mean represented by a **line; whiskers** include all other points. Note the trend toward higher vWSS values with increased eccentricity. Abbreviations as in Figure 2.

shear, our data support a flow-mediated mechanism for aneurysm development. Our results corroborate recent observations of skewed wall shear stress in a heterogeneous group of patients with BAV and confirm computational fluid dynamic simulations that demonstrate focally elevated WSS at the AsAo convexity in a subset of BAV patients with right-left aortic leaflet fusion. Supraphysiologic shear

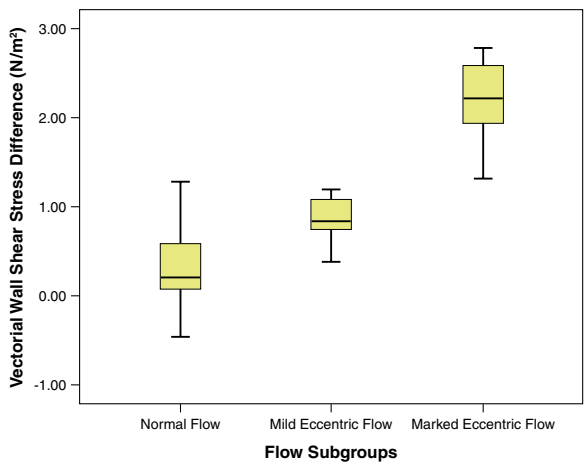

Figure 4. Asymmetry of WSS by Flow Subgroup

Graph of the difference between RA and left posterior (LP) quadrant vWSS, which reflects the asymmetry of vWSS, by flow subgroup. The box contains the middle 50% of all values with the mean represented by a **line; whiskers** include all other points. The group with marked eccentric flow shows highly asymmetric vWSS values when compared with the other groups ($p < 0.01$). Abbreviations as in Figure 2.

Table 4. Reproducibility Analysis

	n	Intraobserver ICC	Interobserver ICC
RA	48	0.92	0.97
LP	48	0.91	0.97

ICC = intraclass correlation coefficient; other abbreviations as in Table 2.

stress has been linked to vessel wall injury and aneurysm formation through mechanisms including smooth muscle cell apoptosis and matrix breakdown (4). Wall strain, though not directly measured in our study, is another force that is likely an important contributor to vessel wall injury with BAV.

Yet there is convincing evidence supporting an intrinsic wall abnormality that predisposes to aneurysm with BAV. First-degree relatives of patients with BAV, who do not have BAV themselves, have dilated and stiffer aortic roots than controls, which is consistent with a heritable aortopathy. A flow-mediated mechanism and this heritable, intrinsic vessel wall abnormality, however, are not mutually exclusive. Even with Marfan syndrome, the quintessential connective tissue disorder, blood flow plays an important role in disease progression; beta-adrenergic blockade, by blunting the systolic impulse of blood flow in the aortic root, slows the rate of aortic dilation and reduces complications in patients with Marfan syndrome. Unlike Marfan syndrome, however, BAV is associated with asymmetric AsAo aneurysms that bulge toward the right-anterior quadrant, where we have demonstrated asymmetrically elevated systolic WSS, suggesting that blood flow may have a pronounced role in their pathogenesis. Further understanding of the systolic hemodynamics may elucidate why only a subgroup of BAV patients have dilated aortas, and why right-left aortic leaflet fusion, which was the predominant fusion pattern in our BAV patients, is associated with rapid aortic dilation.

Eccentric blood flow in the proximal aorta is not limited to BAV. Stenotic TAV gives rise to similar flow patterns that may be responsible for the long-observed phenomenon of post-stenotic dilation. A unique feature of BAV is that abnormal flow patterns and elevated WSS are seen with normal functioning valves (n = 8), which may explain why prior studies have reported that aortic dilation with BAV is out of proportion to valvular disease. Furthermore, the subgroup of BAV patients with right-handed helical flow that we have studied has uniformly abnormal systolic flow, with RA quadrant flow jets seen in all cases. This permits a focused evaluation of associated changes in

WSS, with results undiluted by heterogeneous flow patterns.

Study limitations. The principal limitation of our study is the lack of follow-up to determine if the abnormal AsAo shear stress we have identified is associated with differences in AsAo growth. This is beyond the scope of the current project, which was aimed at characterizing altered shear stress in subgroups of patients with BAV. To further evaluate the proposed hypothesis that elevated WSS is implicated in AsAo dilation, data documenting increased rates of growth are needed. Additionally, quantification of the degree of jet eccentricity is preferable to the qualitative assessment that we have employed. The high percentage of patients included with successful coarctation repair (61%) did not appear to affect our results; these patients were relatively evenly distributed among the patient groups and showed no correlation with AsAo shear stress values.

WSS is systematically underestimated by phase-contrast CMR due to limited spatial resolution, partial volume effects, and numerical derivation of the velocity field. Although this discounts the absolute value of CMR-derived shear stress measurements, comparison of relative values allows identification and characterization of altered shear stress profiles. As expected, our normal WSS values are somewhat higher than those reported by other groups for the thoracic aorta based on CMR data (0.6 to 0.9 N/m^2 vs. 0.3 to 0.6 N/m^2) because we have measured the peak systolic value, whereas other studies have reported mean values, averaging temporal and spatial data. We have addressed the potential problem of differences in wall segmentation affecting shear stress calculation by demonstrating good intraobserver and interobserver variability (Table 4).

Conclusions

Using 4D Flow, we have provided clear evidence that abnormal, eccentric flow in the ascending aorta of a subgroup of BAV patients is associated with elevated and asymmetric WSS, which may place them at risk for aneurysm. The clinical relevance of this mechanism for aneurysm formation in BAV patients is considerable, as it would allow a noninvasive means of risk stratifying the sizable population of patients with BAV, and it would significantly inform the decision regarding the concomitant replacement of the ascending aorta in patients undergoing operations for bicuspid valve disease. More broadly, our results suggest an expanded role for CMR in the evaluation of patients with cardiovascular disease. Abnormal blood flow patterns and the increased hemodynamic burden they cause can be quantified, and consequently, the risk of vascular pathology including aneurysm or dissection may be anticipated and possibly treated before clinical manifestation.

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Key Words: 4D Flow ■ aorta ■ bicuspid aortic valve ■ cardiac magnetic resonance ■ eccentric jets ■ valves.