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Quantification of Hemodynamic Wall Shear Stress in Patients with Bicuspid Aortic Valve Using Phase-Contrast MRI

Alex J. Barker¹, Craig Lanning^{2,3}, and Robin Shandas^{1,2,3}

¹ Department of Mechanical Engineering, University of Colorado, Boulder, CO 80309, USA

² Division of Pediatric Cardiology, The Children's Hospital, Denver, CO 80045, USA

³ Center for Bioengineering, University of Colorado Denver Medical Campus, 13123 E. 16th Avenue, B100 Aurora, CO 80045, USA

Abstract

Bicuspid aortic valve (BAV) is often concomitant with aortic dilatation, aneurysm, and dissection. This valve lesion and its complications may affect positional and temporal wall shear stress (WSS), a parameter reported to regulate transcriptional events in vascular remodeling. Thus, this pilot study seeks to determine if the WSS in the ascending aorta (AAo) of BAV patients differs from control patients. Phase-contrast magnetic resonance imaging (PC-MRI) was used to perform flow analysis at the level of the AAo in 15 BAV and 15 control patients. Measurement of the aorta dimensions, flow rates, regurgitant fraction (RF), flow reversal ratio (FRR), temporal and spatial WSS, and shear range indices (SRI) were performed. The BAV and control group showed a significant difference between the circumferentially averaged WSS ($p = 0.03$) and positional WSS at systole (minimum $p < 0.001$). Regressions found that SRI ($r = 0.77$, $p < 0.001$), RF ($r = 0.68$, $p < 0.001$), and WSS at systole ($r = 0.66$, $p < 0.001$) were correlated to AAo size. The spatial distribution and magnitude of systolic WSS in BAV patients (-6.7 ± 4.3 dynes/cm²) differed significantly from control patients (-11.5 ± 6.6 dynes/cm², $p = 0.03$). The SRI metric, a measure of shear symmetry along the lumen circumference, was also significantly different ($p = 0.006$) and indicated a heterogenic pattern of dilatation in the BAV patients.

Keywords

BAV; WSS; Aorta; Artery; Valve lesion; Viscous forces; Blood flow; Dissection; Dilation; Aneurysm

INTRODUCTION

Bicuspid aortic valve (BAV) occurs in 0.5–2% of the population and is accompanied by a significant incidence of morbidity and mortality related to aortic valve dysfunction, aortic dilatation, aortic aneurysm, and aortic dissection.^{5,10,24} The pathogenesis of this valve malformation and the resulting heterogeneous complications describe a complex disease with many cofactors, the importance of which continue to be debated. Among these cofactors, the most commonly identified vascular manifestation is aortic dilatation.⁵ Many reports have demonstrated aortic diameter and rates of dilatation in BAV patients to be statistically greater than in patients with normal tricuspid leaflet morphology.^{2,4,9,20,23} There are two hypotheses

Address correspondence to Robin Shandas, Center for Bioengineering, University of Colorado Denver Medical Campus, 13123 E. 16th Avenue, B100 Aurora, CO 80045, USA. barkeraj@colorado.edu, Shandas.Robin@tchden.org.

for this association: the first postulates the coexistence of BAV and genetically based aortic fragility^{8,10,33}; the second proposes that BAV morphology and abnormal valve mechanics induce hemodynamic forces that influence structure and function at the aorta.^{1,31}

Regardless of the initial mechanism driving aortic dilatation in BAV patients, an enlarged aorta will further alter spatial velocity gradients and thus the viscous forces at the artery wall. These forces, measured by wall shear stress (WSS), are a known pathophysiological stimulus leading to gene expression and extracellular matrix remodeling.^{3,7} Thus, the quantification of WSS is important in order to fully understand the progression of this disease at the cellular level. However, due to the difficulty of measuring WSS *in vivo*, very few BAV studies have reported hemodynamic forces at the artery wall.¹ Therefore, the purpose of this pilot study is to formulate and report shear-based metrics using phase contrast MRI (PC-MRI) to understand the hemodynamic forces acting on the lumen wall. We apply this technique to determine if these viscous forces differ in BAV patients as compared to a control population.

METHODS

In Vitro Validation

An unsteady flow phantom which mimicked the smallest eligible ascending aorta (AAo) size (diameter = 1 cm) was used for WSS measurement validation. A nominally sinusoidal flow of ± 4.2 L/min was prescribed to a long straight tube (~ 1 Hz, Fig. 1a) and the resulting temporal velocity fields were measured using PC-MRI (using the sequence described in the 'PC-MRI Acquisition' section). The Womersley solution to the Navier–Stokes equations was used to calculate the theoretical axial velocity profile and WSS drag forces.^{12,32} Root mean square error (RMSE) was calculated to quantify the differences between the experimental and expected parameter pairs:

$$\begin{aligned} \text{RMSE}_{\text{velocity}} &= \sqrt{\frac{1}{nk} \sum_{t=1}^k \sum_{i=1}^n (u_{\text{MRI } t,i} - u_{\text{Womersley } t,i})^2} \\ \text{RMSE}_{\text{WSS}} &= \sqrt{\frac{1}{nk} \sum_{t=1}^k \sum_{i=1}^n (\text{WSS}_{\text{MRI } t,i} - \text{WSS}_{\text{Womersley } t,i})^2} \end{aligned} \quad (1)$$

where n denotes the number of velocity or WSS ($u_{\text{MRI } t,i}$ or $\text{WSS}_{\text{MRI } t,i}$) samples at k time steps, and $u_{\text{Womersley } t,i}$ or $\text{WSS}_{\text{Womersley } t,i}$ are the corresponding theoretical velocity and WSS values calculated using Womersley's equations. The RMSE quantity allowed for a single numerical value to be assigned to assess the accuracy of the spatially and temporally varying MRI parameters (velocity and WSS).

Patient Population

With Institutional Review Board approval, 15 BAV and 15 control patients referred to the radiology department at The Children's Hospital, Denver for cardiac PC-MRI were retrospectively enrolled in this study. In order to eliminate extraneous hemodynamic or confounding structural factors, patients with a prior history of aortic or left ventricular surgery, Marfan's syndrome, acute aortic valve vegetation, or abscess were excluded. Patients with a poor slice position through the ascending aorta, sternal wire susceptibility artifacts, or poorly defined aorta lumen boundaries were also excluded ($n = 5$). Table 1 lists the demographics of the remaining patients.

PC-MRI Acquisition and Scan Parameters

A fast low-angle shot gradient echo sequence was used to obtain retrospectively gated tissue intensity and phase velocity maps in the through-plane direction (1.5T Siemens Magnetom Avanto, Erlangen). Double oblique imaging slices were positioned approximately 1–3 cm above the most distal feature of the sinotubular junction in order to orthogonally bisect the ascending aorta (AAo) in the longitudinal axis (position was determined by the distance of 1 equivalent diameter from the most distal portion of the sinotubular junction, Figs. 2a and 2b). A typical sequence used repetition times of 39 ms, echo times of 2.7 ms, and a flip angle of 25 degrees with 75% of the k -space sampled. The temporal resolution ranged from 10 to 30 ms with 15–58 phases. Depending on patient size and field of view, the cross-sectional pixel resolution ranged from 0.82×0.82 to 1.56×1.56 mm with slice thicknesses of 5 mm. This resulted in a minimum number of 19–43 pixels spanning the AAo diameter. Velocity encoding (VENC) values were adjusted according to the maximum velocities encountered during scout sequences to optimize the velocity map resolution (typical values ranged from 200 to 250 cm/s).

Post Processing and Ascending Aorta Size

Slice position accuracy was confirmed in the patients by overlaying the 2D AAo velocity slice on patient specific contrast-enhanced 3D MR-angiogram and computationally calculating orthogonality to the AAo (within a 10% error tolerance for slice angle). Each temporal phase of the AAo lumen was segmented using the ARGUS flow analysis software (Siemens, Erlangen). The image and contour files were loaded into a Matlab (Mathworks, Inc., Natick, MA) program developed for this study, which allowed for the automation of: AAo temporal diameter measurements, flow quantification (positive, negative and net), peak velocity calculation ($V_{\max}$), vessel bulk motion correction, calculation of regurgitant fraction (RF), temporal shear field, oscillatory shear index (OSI), and shear range index (SRI) calculation. To determine the degree of error due to the segmentation process, inter and intra-observer variability studies were carried out on six patients.

Height and weight were used to calculate body surface area (BSA) by Haycock's formula.¹⁶ Measurements of the maximum and minimum area of the AAo over the cardiac cycle were used to calculate the effective systolic and diastolic AAo diameter. The diastolic diameter measurements were then indexed by the square root of the BSA to normalize age and size effects.^{17,29}

Flow & WSS Quantification Parameters

The average flow rate (Q_{avg}) and the flow rate at systole (Q_{sys}) were measured and reported in Table 1. In order to initially quantify bulk flow derangement, the degree of retrograde flow at systole was calculated by the following relation for the flow reversal ratio (FRR; expressed as a percentage):

$$\text{FRR} = \frac{|Q_{\text{negative}}(t_{\text{systole}})|}{Q_{\text{positive}}(t_{\text{systole}})} \times 100\% \quad (2)$$

where $Q_{\text{positive}}(t_{\text{systole}})$ and $Q_{\text{negative}}(t_{\text{systole}})$ represent the forward and reverse flow at peak flow systole. As shown in Figs. 2c and 2d, to facilitate the calculation of the shear fields and remove aorta bulk motion, the images were cropped to the AAo size and transformed from Cartesian to polar coordinates using oversampling (sampling at the vessel wall was set to double the original resolution) and bilinear interpolation to retain image integrity at the region of interest (ROI) edges. A linearized axial shear stress approximation was used to obtain the axial AAo shear field over all time-steps (Figs. 2e and 2f)⁶:

$$\tau_{rz}(r, \theta, t) = -\mu \left[\frac{dv_z(r, \theta, t)}{dr} + \frac{dv_r(r, \theta, t)}{dz} \right] \approx -\mu \frac{\Delta v_z(r, \theta, t)}{\Delta r} \quad (3)$$

where τ_{rz} , v_z , and v_r are the axial shear stress, axial velocity, and radial velocity. These were evaluated at a given radius, r , and angular position, θ , from the ROI centroid at time, t . Thus, shear stress was simply implemented as the kinematic viscosity, μ , times the radial through-plane velocity gradient. As is commonly assumed for large blood vessels, blood was assumed a Newtonian fluid with a constant viscosity, $\mu \approx 0.032$ g/cm/s.²⁸ Using the ROI boundary to determine wall location, the shear field, τ_{rz} , was interrogated along the entire vessel circumference to obtain the spatial and temporal axial wall shear stress, $WSS(\theta, t)$. The axial WSS was then sampled at 45° increments along the AAO lumen to create a localized, position specific, shear waveform with resolution over the whole cardiac cycle (Fig. 2e). These positions are referred to in the text and figures as L, LP, P, RP, R, RA, A, and LA representing the left, left-posterior, posterior, right-posterior, right, right-anterior, anterior, and left-anterior AAO lumen locations. A diagram showing the relative measurement location for each of these local WSS values (with respect to the overall aorta morphology) is shown in Fig. 3.

To further quantify flow derangement at the vessel wall, we calculated a parameter which measured the WSS asymmetry along the circumference of the lumen, referred to as the ‘SRI’ (shear range indice):

$$SRI = \frac{\max[WSS_{\max}(\theta, t)] - \min[WSS_{\min}(\theta, t)]}{WSS_{t-avg}} \quad (4)$$

$$WSS_{t-avg} = \frac{1}{T} \int_0^T WSS \cdot dt \approx \frac{1}{N} \sum_{n=1}^N WSS$$

where $WSS_{\max}(\theta, t)$ and $WSS_{\min}(\theta, t)$ are the maximum and minimum wall shear stress values experienced along the circumference of the AAO at a single time, t , normalized by the temporal and circumferential mean of the wall shear stress, WSS_{t-avg} . T and N are the R–R time interval and total time steps, respectively. In addition to calculating WSS_{t-avg} , $WSS_{systole}$ was also calculated, which was the circumferentially averaged WSS at flow systole. The degree of time varying shear was calculated both circumferentially and locally with OSI.⁶

Statistical Analysis

All data are expressed as mean $\pm$ SD. For comparison of flow and geometry parameters, a two sample F -test was used to determine if variances could be assumed equal for the study populations. A paired two-tailed t -test for equal or unequal variances was then used to determine if the parameter values were statistically significant. Linear regression analysis was performed to evaluate the association between the morphologic and hemodynamic parameters using a custom Matlab program. A probability value of $p \leq 0.05$ was considered statistically significant.

RESULTS

In Vitro Validation

As seen in Fig. 1a, a slight alteration of the nominally sinusoidal flow waveform (measured at the pump) occurred due to compliance in the tubing connecting the pump to the phantom. Thus, as with previous studies,¹² it was necessary to construct a flow waveform at the position of the PC-MRI measurements. This waveform was then Fourier decomposed into the first five harmonics and each individual harmonic was used to calculate a corresponding axial velocity

profile. The overall axial velocity profile was then obtained by summing the five harmonic velocity profiles (after weighting by the Fourier series coefficient). Figure 1b shows the resulting comparison of temporal profiles and Figure 1c shows the correlation of the resulting velocity pairs. An $RMSE_{\text{velocity}} = 0.8 \text{ cm/s}$ and $RMSE_{\text{WSS}} = 1.3 \text{ dyne/cm}^2$ were calculated for the MRI measured values.

Control Patient Flow Field

A flow quantification summary for a typical control patient is shown in Fig. 4. As expected, this population was characterized by morphologically normal aortic leaflets, with little to no regurgitation, and very little retrograde flow in the AAO slice at systole (Table 1 and Figs. 4a–4c). The velocity map (Fig. 4c) shows an axisymmetric flow profile, while the shear map shows that the WSS is uniform in magnitude and direction along the vessel circumference at systole (Figs. 4d–4f). The local WSS waveforms (Fig. 4d) show this to be the case over the entire cardiac cycle, translating to a relatively low $SRI = 8.5 \pm 3.1$ for the control population.

BAV Patient Flow Field

On examination of the BAV patients, two subpopulations were apparent: those with minimal retrograde flow ($FRR \leq 10\%$, $n = 8$) and those with considerable retrograde flow ($FRR > 10\%$, $n = 7$). As seen in Table 1 and flow summaries similar to Fig. 4, those with minimal retrograde flow exhibited bulk flow characteristics (Q_{avg} , Q_{sys} , V_{max} , FRR , and RF) and WSS waveforms comparable to the control population. These patients had an axisymmetric flow profile and shear field throughout the cardiac cycle and a relatively low, although statistically different, $SRI = 11.8 \pm 3.6$ ($p = 0.03$) indicating a slight increase in WSS asymmetry at the vessel wall.

The BAV patients with considerable retrograde flow exhibited a drastic alteration in the flow metrics compared to the other groups (Table 1). These patients exhibited an FRR at least 30 times greater than both the control and BAV patients with minimal retrograde flow and a significant difference in normalized Q_{avg} , V_{max} , RF , WSS_{systole} , and SRI . These metrics were indicative of a drastic change in the flow dynamics at the lumen wall. A representative flow summary for a BAV patient with considerable retrograde flow is shown in Fig. 5. Like all patients in this group, the case shown in Fig. 5 exhibits a highly asymmetric velocity and shear map (Figs. 5c–5f). As a result, the WSS waveforms (Fig. 5d) experienced large ranges in magnitude and direction over the cardiac cycle, translating to an average SRI of 31.2 ± 10.4 . A representative summary of the flow field temporal evolution and the corresponding bulk flow metrics for all patient groups are shown in Fig. 6. In this figure a ‘skewed’, or asymmetric flow pattern is observed in the retrograde flow BAV patients (Figs. 6i–6l)—while a pattern more consistent with the ‘top-hat’ shaped control velocity profile is found in the minimal retrograde flow population (Figs. 6e–6h).

Valve Morphology and Aorta Size

Table 1 shows the AAO diameter, normalized AAO diameter, and valve morphology of the patient groups. As seen in the table, the AAO and normalized AAO of the BAV group are significantly larger than the controls. Of particular interest is the significant AAO size difference between the retrograde flow BAV group ($2.4 \pm 0.4 \text{ cm/m}$) to the control patients ($1.7 \pm 0.2 \text{ cm/m}$, $p < 0.001$). In addition, the minimal retrograde flow group did not show a significant size difference to the controls. Those patients with stenotic aortic valves were solely contained in the BAV retrograde flow group ($n = 4$), having an average normalized AAO size of $2.1 \pm 0.4 \text{ cm/m}$.

In Vivo WSS Quantification

Table 1 shows a significant difference between the control and BAV population regarding the circumferentially averaged $WSS_{systole}$ and SRI. As can be seen in the table, this difference appears to be the contribution of the retrograde flow BAV group. In addition, Fig. 7 shows that the local WSS for the entire BAV population is significantly different ($p < 0.05$) at the LA, L, LP, and P positions (4 of 8 sampling positions). On examination, this difference also appears to be contributed by the WSS values in the retrograde flow group (Fig. 7c).

Regression of Structure/Function Parameters

Linear regression analysis of the hemodynamic metrics shown in Table 1 found that SRI, RF, $WSS_{systole}$, FRR, and WSS_{t_avg} were significantly correlated to the normalized AAO size ($r = 0.77, p < 0.001$; $r = 0.68, p < 0.001$; $r = 0.66, p < 0.001$; $r = 0.55, p < 0.05$; $r = 0.52, p < 0.05$, respectively). The remaining hemodynamic metrics, Q_{avg} , Q_{sys} , and V_{max} , were not significantly associated with the AAO size by linear regression.

Intra and Inter-Observer Variability

Intra and inter-observer variability studies of 6 patients (3 BAV and 3 control) found that the error for WSS_{t_avg} was 6.9%.

DISCUSSION

Numerous echocardiogram-based BAV studies have used ordinal or indirect measures to correlate proximal aortic flow derangement as it relates to aortic dilatation. These studies have used either aortic regurgitation, classified as: ‘none’, ‘mild’, ‘moderate’, or ‘severe’; or stenosis, classified by pressure gradient or max velocity.^{4,9,17,20,30} Given the relative ease of recording these ordinal factors in the clinical setting, it is a reasonable compromise to use indirect measures to investigate etiology in this complex disease. However, these metrics do not measure activity at the artery wall. In this study and elsewhere, PC-MRI has been shown to resolve unsteady, complex velocity fields with remarkable accuracy.^{11,12,22,26} Recently, PC-MRI velocity data was used to quantify the pulse wave velocity in BAV patients, an indicator of wall elasticity.¹⁵ We build on these studies and use PC-MRI to interrogate the viscous wall forces using temporal and spatial WSS. In addition, the temporal velocity fields allow for the numeric calculation of Q , V_{max} , RF, FRR, OSI, and SRI in vivo. With this data, continuous numeric structure/function correlations can be calculated. This is of interest because aorta size may further influence flow derangement (or vice versa). Most importantly, the quantitative measurement of WSS is important in order to understand if the hemodynamic forces in BAV patients are different from morphologically and functionally normal patients.

In Vitro Validation

The in vitro phantom experiment was necessary to validate the in vivo methods used in the clinical portion of this study, more specifically to validate the clinical pulse sequence velocity and WSS accuracy in a ‘worst-case’ geometry (i.e., AAO diameter ~1 cm). As mentioned, previous PC-MRI flow and velocity quantification validations have shown good correlation between MRI-measured velocity-fields and theory. For example, Hagen–Poiseuille flow is commonly reported to have an accuracy of 5% of the mean velocity, which is what we found in our preliminary experiments.^{11,22} For unsteady straight tube and complex geometries, the velocity field accuracy has been reported to be accurate to within 7.5–11.5% of the mean velocity.^{12,26} For the unsteady phantom used in this study, the $RMSE_{velocity}$ as a percentage of the spatio-temporal mean velocity was 2.4% and the $RMSE_{WSS}$ difference as a percentage of the spatio-temporal mean WSS was 8.3%. These excellent velocity and WSS accuracies

matched and (in some cases) exceeded the error reported in previous studies. Thus, these results indicated that proceeding with the clinical study was feasible.

In Vivo Bulk Flow Quantification and Patient Demographics

The bulk flow parameters (Q_{avg} , Q_{sys} , V_{max} , RF, and FRR) that showed a significant difference between the control and the entire BAV population were the FRR and Q_{avg} . Those BAV patients with considerable retrograde flow also exhibited the following significantly different parameters (from the control population): an enlarged aorta, a reduced Q_{avg} , a large V_{max} (possibly due to jetting, abnormal valve opening, or stenosis),^{5,27} a large RF, a small $WSS_{systole}$, and an elevated SRI (Table 1). In addition, a characteristic ‘skewing’ of the flow in retrograde flow BAV patients can be seen in Fig. 6. Note that retrograde flow (high FRR) does not imply that aortic regurgitation is present. However, the reduction in Q_{avg} , as is seen in the BAV population can be partly attributed to regurgitation. As mentioned, all BAV patients with valvular stenosis ($n = 4$, as identified by Doppler echocardiography) had an FRR > 10% (average FRR = $26.8 \pm 4.8\%$, $V_{max} = 1.8 \pm 0.5$ m/s, SRI = 30.7 ± 11.5). Note that one outlier value for RF (RF = 0.37) value was removed from the calculation of the average RF for the BAV population. This value was determined an extreme outlier by boxplot analysis which identified values greater than three times the range of the first and third quartile. Results with the outlier RF value included are shown in the footnote of Table 1. All other values were calculated without any exclusions.

BAV patients with minimal retrograde flow (FRR < 10%) exhibited a slightly larger, but insignificant ($p = 0.08$) difference in the BSA normalized AAO size from the control population. This population was significantly older, with all hemodynamic parameters except the SRI statistically similar to the control population. The characteristic flow pattern of this population can be seen as similar to the axisymmetric flow pattern of the control population (Fig. 6). Absent of stenosis, jetting, and regurgitation, the age difference of this cohort to the control population may be due to the functional nature of the valve, therefore reducing the chance of surgical intervention and maintaining eligibility for this study as the patient aged. Previous studies of BAV patients have reported conflicting findings regarding AAO dilation in the presence of functionally normal bicuspid valves.^{2,4,23}

WSS Quantification and Reason for SRI

The temporal flow field evolution (Fig. 6) and bulk flow parameters calculated in Table 1 provide insight regarding the degree of flow derangement in the patients. The quantification of WSS is important because it directly measures the resulting viscous forces at the AAO wall due to these flow anomalies. However, care must be taken when measuring WSS parameters clinically. For example, we found that averaging WSS over time and space diluted important time dependant (i.e., systolic phase) and spatial activity (such as localized jetting). This can be seen in the progression of the values measured for WSS_{t_avg} , $WSS_{systole}$, local systolic WSS, and SRI in the BAV retrograde flow patients (Table 1 and Fig. 7). Similarly, WSS_{t_avg} did not show any significant differences between populations, possibly due to the effect of averaging over hemodynamically inactive portions of the cardiac cycle. However, $WSS_{systole}$ showed a reduction in value for the BAV retrograde flow patients. On inspection, this difference was attributed to two phenomena: AAO size and flow reversal (note the absence of Q_{sys} in this discussion, which did not significantly vary between populations). Size plays an inverse cubic role in the determination of WSS as highlighted by the simple steady state Hagen–Poiseuille relation: $WSS \sim \text{flow}/\text{radius}^3$.²⁵ Although aortic flow does not meet the steady-state, fully developed assumptions of the Hagen–Poiseuille formula, the general inverse power relationship between WSS and radius is still applicable. This phenomenon, combined with spatially averaging the effect of retrograde flow, reduced the $WSS_{systole}$ magnitude. This flow reversal factor emphasizes the fact that even after removing temporal artifacts, spatial

averaging across the lumen can mask important local WSS information. Thus, we evaluated local OSI and local WSS. While no pattern was found for OSI between cohorts, a significant pattern in positional WSS values between populations emerged (Fig. 7). This local pattern of asymmetric WSS is best illustrated in Fig. 7c, which shows a number of locally abnormal BAV WSS magnitudes.

The local WSS observations may be associated with jetting, which can manifest areas of flow separation, retrograde flow, and vortices at the vessel wall. Given that the trajectory and position of the jet is morphologically dependant, leaflet morphology as defined by Cripe,⁸ was examined for a relation between morphology and local WSS patterns. Specifically, BAV patients were grouped according to the ‘fusion’ model of BAV leaflet morphology, with patients classified as having a fusion of the right and left coronary leaflets (R-L) or a fusion of the right and non-coronary leaflet (‘R-Non’, see diagrams in Fig. 6). Although no significant difference in the position of the peak systolic velocity was found between lesion groups, it is reasonable to assume that leaflet morphology and physiologic differences contributed to the large WSS error bars in Fig. 7. These large error bars make it difficult to compare inter-patient shear magnitudes. However, SRI does allow for shear symmetry comparisons to be made since the relative error associated with SRI is low compared to positional WSS measurements. Therefore, SRI was used to index spikes in local WSS. By doing this, the location and magnitude specific information were normalized, reducing the ‘dilution’ of location and patient specific information caused by averaging WSS across the lumen and patient populations. Thus, SRI is not location, morphology, or magnitude specific; rather it indexes an asymmetric elevation in local WSS out of character for the rest of the lumen shear (such as that caused by a jet impinging on the lumen wall). Figure 8 illustrates the effect of asymmetric shear on lumen WSS ranges, and, ultimately the SRI. In addition, this figure illustrates the visible difference between the control and BAV shear-range waveforms as seen by the ‘trough’ and ‘bulb’ shape, respectively. In summary, SRI provides a metric to quantify circumferentially asymmetric viscous forces due to jet impingement or ‘skewed’ flow at the artery wall, and ultimately allows for inter-patient comparisons of viscous wall force derangement to be made.

AAo Size: Hemodynamics and Shear

Among the bulk flow metrics, the derangement metrics (RF and FRR) demonstrated a significant positive correlation to the normalized AAo size. This supports previous studies, which have measured derangement by RF and shown a strong correlation to AAo size.^{9,15,17,20,30} In addition, recent studies using 4D PC-MRI have reported that aortic size shows a strong correlation to the number of vortices and flow anomalies present in the arch.^{13,14}

Among the shear-based metrics, SRI (a measure of derangement at the wall) demonstrated a significant positive correlation to AAo size, while the magnitude of $WSS_{systole}$, and $WSS_{t_{avg}}$ showed a significant negative correlation to size. As mentioned previously, holding all variables constant, an increase in AAo size will decrease the measured WSS, so a negative correlation is understandable. In addition, the spatial average of $WSS_{systole}$ and $WSS_{t_{avg}}$ would be reduced by retrograde flow, as was observed. Thus, the observation of reduced WSS in the presence of BAV seems reasonable (if not surprising). Again, it is emphasized that all of the significant circumferential and local WSS differences were lower in magnitude for the BAV population when compared to the control population. It is also emphasized that the SRI, a metric measuring the direct hemodynamic derangement at the AAo wall, demonstrated the best correlation to AAo size over all other hemodynamic parameters.

An alternative analysis to linear regression (and perhaps a clearer illustration of the relationship this study found between size and flow derangement) is to choose a threshold parameter considered ‘abnormal’. This can be used to group patients displaying unusual hemodynamic characteristics. For example, since SRI was found to be highly correlated to size, the maximum

SRI measured in the control population ($SRI = 14$) was used to identify BAV patients who exceeded this value. These patients were considered to be hemodynamically ‘abnormal’ BAV patients. On examination, this BAV population (with $SRI \geq 14$, $n = 9$) had an average normalized AAO size of 2.4 ± 0.4 cm/m. This translated to an average z -score of 3.2 ± 1.7 ($p < 0.001$), an indication of significant AAO dilation. Of the nine patients, this included all seven BAV patients previously diagnosed with dilated AAO’s by Doppler echocardiography. The BAV patients with $SRI < 14$ did not show a statistically significant size difference from the control population, with an AAO size of 1.8 ± 0.2 cm/m and a z -score = 0.5 ± 0.8 ($p < 0.33$). This expression of heterogeneous dilation as determined by a parameter associated with direct hemodynamic wall forces is very notable; however, care must be taken when interpreting the results of this analysis (see discussion in next paragraph).

The question of whether a dilated AAO causes deranged flow or deranged flow causes a dilated aorta is a difficult topic to address. Thus, the data presented in this pilot study merely quantifies the hemodynamic forces in the presence of BAV and demonstrates a correlation (not causality) between AAO size, flow derangement, and low WSS. Previous reports have suggested lumen remodeling, formation of vascular lesions, and genetic expression of proinflammatory mediators in the presence of low WSS and non-uniform flow^{3,7}; however, our study did not control for these factors. With this stated, the results of this study did find a strong correlation to direct hemodynamic derangement at the wall and AAO size, as well as a notable delineation between a threshold SRI value and AAO dilation. Thus, given that the heterogeneous expression of dilation within BAV patients is still an unexplained clinical event, these results warrant further investigation (with more patients and controls for confounding factors).

Limitations

As is common in PC-MRI measurements, intravoxel phase dispersion caused by large velocity gradients might cause signal loss in the velocity field measurements. This is an important effect when considering derivative parameters (such as WSS); however, it is very difficult to quantify. Since the basis of our study lay in comparing values measured in a control population against those in a pathologic population, it would be ideal if phase dispersion errors were relatively consistent across the study population. However, for BAV patients with jet impingement (and large velocity gradients), it is reasonable to expect the WSS to be greater than the measured values due to phase dispersion. Thus, the actual difference in circumferential and local WSS between the BAV and control population might be greater than reported in this study.

An additional limitation to consider is the method used to calculate WSS. We assumed that in-plane velocity gradients were relatively small and therefore not included in the WSS calculations. These considerations were taken into account and deemed to have an insignificant impact in the control population due to the excellent agreement between the pattern and magnitude of control patient WSS waveforms with numerical simulations of normal, compliant aorta models.¹⁹ However, it is important to note that exaggerated helical flow has been recently reported using 4D PC-MRI on a BAV patient with aortic coarctation and a dilated aorta.¹⁸ Thus, future WSS quantification studies may benefit from the application of this (rather time-intensive) sequence.

It also should be noted that care was taken to confirm that the position of the PC-MRI slices were orthogonal to the longitudinal axes of the aorta. Given the prescribed 10% error tolerance for slice angle from aorta centerline, this may cause a maximum error of 1.3% in the measured aorta area (assuming a circular cross section) and a 2% error in the measured $WSS_{systole}$ —which was deemed acceptable. Also, the through-plane motion of the aorta wall was not taken into account. While specialized PC-MRI pulse sequences have been used to track the motion of the valve plane, and thus compensate for the cyclic motion of the aorta, these pulse sequences are not readily available in clinical analysis packages. Further, compensation for valve plane

motion does not produce significant changes in flow calculations. For example, systolic compensated flow causes results to vary by a maximum average of 8%.²¹ Thus, the effect on the WSS values should be minimal and common across the patient population, retaining the relative relationships between patient groups.

CONCLUSIONS

This PC-MRI study demonstrated the implementation of quantitative flow metrics to show that significantly different systolic WSS values were found in the ascending aorta of BAV patients (when compared to a control population). Using methods developed for this purpose, numerically continuous hemodynamic metrics were used to calculate regressions and show a significant correlation to deranged flow, WSS, and AAo size. In addition, a WSS-based parameter (SRI) was found to have the highest correlation to AAo size (over all other flow-based parameters). BAV patients grouped by a threshold SRI value were also found to express a heterogenic pattern of dilatation. This data provides important preliminary data for future hemodynamic studies regarding the causality of BAV-related pathology, whether genetic, hemodynamic, or a combination of both.

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FIGURE 1.

(a) PC-MRI volume flow rate measurements and Fourier series fit of the unsteady flow phantom. (b) Comparison between velocity profiles measured using PC-MRI and velocity profiles calculated using Womersley's equations. (c) PC-MRI measured and Womersley velocity pairs.

FIGURE 2.

(a) Maximum intensity projection showing PC-MRI slice location. (b) Segmented intensity and (c) phase contrast images (AAo outlined in *white*). (d) Post-processed velocity map. (e) Schematic of the velocity map in polar space before the WSS algorithm is applied. The distance, r , from the vessel centroid is plotted on the ordinate and the angular position, θ , is plotted on the abscissa. (f) The resulting axial shear stress map in Cartesian space.

FIGURE 3.

(a) 3D reconstruction from a magnetic resonance angiogram showing the morphology of the aortic root and arch of the control patient shown in Fig. 2. (b) Position of the PC-MRI slice location and (c) an enlarged view of the local WSS measurement points.

FIGURE 4.

(a) Control patient anatomy and (b) flow waveform, (c) systolic velocity map (cm/s), and (d) WSS waveform, sampled at the locations shown in (c). (e) Shear map (dynes/cm²) at systole and (f) the resulting 'unwrapped' WSS map over the cardiac cycle. Marker shade in (c and e) corresponds to waveform shades in (d and f). Closed triangles (▲) represent locations for solid WSS waveforms and open triangles (△) represent dashed WSS waveforms. The vertical dashed line indicates maximum flow.

FIGURE 5.

(a) BAV patient anatomy and (b) flow waveform, (c) systolic velocity map (cm/s), and (d) WSS waveform, sampled at the locations shown in (c). (e) Shear map (dynes/cm²) at systole and (f) the resulting 'unwrapped' WSS map over the cardiac cycle. See Fig. 4 caption for explanation of symbols.

FIGURE 6.

Temporal flow field evolution of 12 sample patients. (a–d) The axisymmetric pattern of the systolic phase flow field is apparent in the control population and (e–h) BAV patients with minimal retrograde flow. (i–l) A skewed flow profile is apparent in the retrograde flow BAV patients. The flow waveform, valve morphology, and valve orientation are shown above each evolution plot.

FIGURE 7.

(a) Comparison of local WSS in the AAo of control and entire BAV population; (b) local WSS in the AAo of control and BAV minimal retrograde flow group; (c) local WSS in the AAo of control and retrograde flow group. Significance of WSS differences are denoted by * $p < 0.05$, and ** $p < 0.001$.

FIGURE 8.

The circumferential WSS ranges are plotted at each time step in the cardiac cycle for control and BAV retrograde flow patients. The maximum range of WSS experienced during the cycle is identified by the marker (▼) and shown in red. This range determines SRI (shown at the bottom right of each graph), which is a useful metric to quantify the degree of WSS asymmetry.

TABLE 1

Demographics and flow quantification of study patients.

	Control (n = 15)	BAV (n = 15)	p	BAV FRR ≤ 10%	p (to controls)	BAV FRR > 10%	p (to controls)
Age, y	21 ± 14	29 ± 15	0.14	34 ± 12	0.03	23 ± 17	0.76
Sex, M:F	9:6	9:6		3:5		6:1	
BSA	1.7 ± 0.6	1.6 ± 0.5	0.85	1.6 ± 0.3	0.62	1.7 ± 0.7	0.94
Lesion, RL:R-Non	–	5:6*		3:3*		2:3*	
AAo	2.2 ± 0.6	2.8 ± 0.8	0.03	2.6 ± 0.7	0.19	3.0 ± 0.9	0.02
AAo/BSA ^{0.5}	1.7 ± 0.2	2.2 ± 0.4	0.001	2.0 ± 0.5	0.08	2.4 ± 0.4	<0.001
Q _{avg}	4.3 ± 1.5	3.5 ± 1.3	0.10	3.8 ± 0.8	0.42	3.0 ± 1.6	0.08
Q _{avg} /BSA ^{0.5}	3.3 ± 0.7	2.7 ± 0.9	0.03	3.1 ± 0.6	0.32	2.3 ± 1.0	0.01
Q _{sys}	19.7 ± 6.8	17.7 ± 6.1	0.40	17.3 ± 4.0	0.37	18.2 ± 8.2	0.66
Q _{sys} /BSA ^{0.5}	15.1 ± 3.6	13.7 ± 3.1	0.25	13.7 ± 2.5	0.33	13.7 ± 3.9	0.42
V _{max}	1.2 ± 0.2	1.5 ± 0.6	0.12	1.1 ± 0.4	0.45	1.9 ± 0.5	0.01
FRR	0.3 ± 0.6	13.9 ± 16.2	0.006	0.9 ± 2.4	0.54	28.7 ± 10.9	<0.001
RF	1.7 ± 1.9	3.2 ± 2.7†	0.11†	1.9 ± 1.9	0.86	4.9 ± 3.7†	0.007†
WSS _{L_avg}	–3.1 ± 2.1	–1.9 ± 1.6	0.10	–2.0 ± 1.5	0.24	–1.7 ± 1.9	0.17
WSS _{sysstole}	–11.5 ± 6.6	–6.7 ± 4.3	0.03	–7.6 ± 4.7	0.16	–5.8 ± 4.1	0.05
SRI	8.5 ± 3.1	20.8 ± 12.3	0.006	11.8 ± 3.6	0.03	31.2 ± 10.4	<0.001

Values are mean ± SD.

* Leaflet lesion morphology, as defined by Cripe,⁸ was not available for four patients.

† With outlier removed for RF. When included, BAV population: 5.4 ± 9.0, p = 0.14; BAV FRR > 0.10: 9.4 ± 12.2, p = 0.15; AAo = ascending aorta diameter (cm); AAo/BSA^{0.5} = normalized AAo size (cm/m); BAV = bicuspid aortic valve; BSA = body surface area (m²); FRR = flow reversal ratio (%); Q_{avg} = average flow rate (L/min); Q_{avg}/BSA^{0.5} = normalized Q_{avg} (L/min m); Q_{sys} = peak systolic flow rate (L/min); Q_{sys}/BSA^{0.5} = normalized Q_{sys} (L/min m); RF = regurgitant fraction (%); RL = right-left coronary leaflets; R-Non = right-noncoronary leaflets; SRI = shear range index; V_{max} = max velocity (m/s); WSS_{L_avg} = circumferentially averaged WSS over cardiac cycle (dynes/cm²); WSS_{sysstole} = circumferentially averaged WSS at systole (dynes/cm²).