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MRI-based protocol to characterize the relationship between bicuspid aortic valve morphology and hemodynamics

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Abstract

Bicuspid aortic valve (BAV) is the most common congenital heart defect and can lead to severe complications. Many studies have been conducted to evaluate the potential of geometric and hemodynamic biomarkers to predict BAV-related aortopathy. This work proposes a novel semi-automatic protocol to characterize geometry and hemodynamics of aorta and aortic valve based on 2D cine and 4D Flow MRI data. The protocol was applied to 12 BAV and 12 control subjects. Statistical differences between the groups were identified and linear regression models were investigated to elucidate the potential of this protocol to investigate the risk of disease progression. Statistical differences between the groups were found for orifice eccentricity, aorta diameter, velocity, jet angle and flow displacement. Key findings of the regression analysis include the association in the proximal ascending aorta between aorta diameter and mean velocity (negative), jet angle (positive) and flow displacement (positive), in the combined cohort. Positive association between flow displacement in the proximal aorta and orifice jet angle in TAV subjects was found. This study represents a pilot application of a protocol for standardized assessment of aortic geometry and hemodynamics associated with BAV disease. Its limited need for user input is advantageous for large cohort studies.

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Conflicts of Interest

No benefits in any form have been or will be received from a commercial party related directly or indirectly to the subject of this manuscript.

Keywords

Magnetic Resonance Imaging; Blood flow; 4D Flow; Hemodynamics; Geometrical Characterization

Introduction

Bicuspid aortic valve (BAV) is the most common congenital heart defect, in which 1-2% of the general population¹⁴ exhibits a bi-leaflet aortic valve morphology rather than a tri-leaflet morphology. The disease is commonly classified by the apparent leaflet fusion pattern, such as a fusion between the right and left coronary leaflets (most common) or the less common fusion of the right and non-coronary leaflets or left and non-coronary leaflets^{14,28}. BAV has been associated with progressive secondary pathologies, such as aortic valve calcification, stenosis or regurgitation, aortic root dilatation, and aortic aneurysm or dissection^{7,31,32}. Both genetic and hemodynamic causes of the aortic pathology associated with BAV have been postulated and investigated^{1,13,21}. However not all patients exhibit symptoms or develop aortopathy and the exact link between BAV morphology and disease progression is not fully understood.

Previous studies have investigated the relationship between BAV, aortic dilatation¹⁵, helical and eccentric flow in the ascending aorta^{4,16}, flow jet angle at the valve plane¹¹, wall shear stress^{2-4,17,19,24,26}, and aortic aneurysms²³. Large cohort studies have also been carried out to identify standard and advanced predictors of aortic dilatation and growth^{9,10,25}. However, previous studies have been hampered by the need for lengthy manual data analysis which may limit their reproducibility and/or integration into a clinically feasible workflow.

This study presents a robust semi-automatic pipeline to characterize the aorta and valve morphology, and extracts blood velocity field information along the aorta centerline, using data from two magnetic resonance imaging (MRI) techniques: a 2D time-resolved MRI acquisition across the valve plane and a 4D flow MRI (time-resolved 3D phase contrast MRI with three-directional velocity encoding) dataset covering the thoracic aorta. The same protocol is applied to both BAV patients and tricuspid aortic valve (TAV) controls in order to understand if and where geometric and hemodynamic differences occur between these two cohorts. The protocol was developed such that user dependent steps were minimized, and automatic and objective evaluations were employed whenever possible. The endpoints were chosen to be applicable to any type of aortic valve anatomy and included: orifice and aortic root area, orifice and aortic root circularity, orifice eccentricity, mean and maximum velocity, jet angle and flow displacement.

In order to demonstrate the feasibility and potential of this approach, a pilot study using the proposed protocol was performed on a cohort of 12 BAV and 12 TAV subjects. Linear regression models were investigated to identify associations between easily measurable parameters (such as those between geometry and hemodynamics at the valve plane) and quantities that require more sophisticated computation - but are important in the study of aortopathy (for example, hemodynamic parameters along the longitudinal direction of the aorta).

Materials and Methods

Subject Enrollment

Two groups of subjects were retrospectively constructed from a database of 151 subjects (BAV or TAV healthy control) who underwent cardiac MRI between December 2011 and November 2012. Exclusionary criteria for both groups included aortic stenosis or insufficiency greater than moderate. The BAV and healthy TAV cohorts were age-matched and consisted of: 1) 12 healthy volunteers with normal tricuspid aortic valve function and no history of cardiovascular disease, and 2) 12 patients with BAV, referred for cardiovascular MRI to diagnose, monitor, or assess function of the aortic valve. The retrospective study was approved by the Institutional Review Board of Northwestern University. Demographic data were collected from the clinical reports and include: age, gender, diameter of the aorta at the mid-ascending aorta (MAA) and at the sinuses of Valsalva (SOV) locations (Table 1).

Magnetic Resonance Imaging

Cardiac MRI included ECG-gated, two dimensional breathheld Balanced Steady-State Free Precession (bSSFP) cine imaging which was used to assess BAV morphology and lesion severity. Imaging parameters and slice position were as described previously³. In addition, time-resolved 3D phase-contrast MRI, with three-directional velocity encoding (4D flow MRI) was acquired in a sagittal oblique volume covering the thoracic aorta and using prospective ECG gating with a respiratory navigator placed on the lung liver interface²². Imaging was performed at 1.5T or 3T, using a previously described protocol (Magnetom Espree, Avanto or Skyra, Siemens Medical Systems, Germany)³. Velocity encoding was adjusted to minimize velocity aliasing (typical settings were VENC=1.5 m/s for healthy controls and 1.5-3 m/s for BAV subjects).

Data processing protocol

Post-processing was composed of the following steps: 2D bSSFP analysis, preprocessing of the 4D flow data, 2D data registration to the 3D data, and extraction of the 3D geometric and hemodynamic metrics.

1. Aortic valve segmentation based on 2D cine MRI data—For each subject, the 2D bSSFP cine slice was processed using OsiriX® (v5.6; Pixmeo SARL, Bernex, Switzerland)²⁷. The aortic root and orifice were manually contoured by selecting control points and automatically interpolated using a spline approximation. The software allowed the alteration of the location of the control points as necessary to accurately segment the aortic root and orifice. This process was repeated for each cardiac time frame during valve opening. This step provided the coordinates of each contour point as well as the area of each contour. The cardiac time frame with the largest orifice area was selected as the peak systolic time and used for all subsequent analyses (Figure 1). On average, 16.4 control points were placed to contour the orifice or the aortic root at peak systole.

2. Anatomy and velocity segmentation of 4D Flow MRI dataset—For each subject, the 4D Flow MRI data was initially processed volumetrically using a custom MATLAB program (The MathWorks, Inc., Natick, MA, USA) which included denoising,

velocity anti-aliasing and eddy current correction for all cardiac time frames of the 3D data⁵. To enhance contrast for aorta lumen segmentation, the weighted sum over the resulting magnitude and phase contrast 3D stack of images, normalized by their maximum value in time, was calculated. The resulting 3D intensity field corresponding to peak systole (determined from 2D bSSFP cine slice at step 1) was processed using VMTK software (www.vmtk.org) and a level-set based 3D segmentation was performed to obtain the aorta lumen from the left ventricle outflow tract to the descending aorta, past the aortic valve plane. The magnitude and phase contrast weights were tuned to facilitate the segmentation of the aortic lumen distal to the SOV location, starting at the sinotubular junction. The geometrical information obtained from 4D data upstream this location (on the orifice) was therefore not included in the analysis. Geometrical information there were instead obtained from the 2D cine MRI acquisition and the corresponding hemodynamic information were linearly interpolated from the 4D MRI data onto the orifice area segmented from 2D cine MRI data. The supra aortic branches were disregarded (Figure 2).

3. Spatial registration of 2D and 4D data to extract velocity and geometrical metrics in the valve region and along the aorta—The DICOM scanner coordinates and rotation matrix were used to co-register the 2D data with the 3D data. Minor manual registration adjustments were performed in cases where the breathheld 2D images were misaligned with the free-breathing 4D flow sequence. Paraview software³⁰ (v3.14, Clifton Park, NY, USA) was used to align the 2D and the 3D MRI data, whereby a rigid translation was applied to correct for any mismatch in the two datasets.

VMTK was used to compute the centerline (Figure 2) from the 3D segmentation of the aortic lumen and subsequently used to project the 2D aorta and orifice outlines onto a plane orthogonal to the centerline at the position of the orifice location, using a custom MATLAB program. This eliminated the variability across subjects due to the arbitrary choice of the 2D cine MRI acquisition plane, and standardized the metrics to all subjects.

The 4D flow velocity field was extracted using planes positioned at the valve orifice and at 10 equally spaced 2D cross sections along the aorta using VMTK tools (Figure 2).

To compute the hemodynamic metrics, a reference system was generated at the valve orifice and on the 10 cross sections as follows (indicated as S_i , $i = 0 \dots 10$)(Figure 3):

1. The direction orthogonal to each plane was defined as the vector tangent to the centerline at its intersection with the plane, $u_t(S_i)$.
2. On the most proximal of the sections, a vector $u_n(S_0)$ was defined as orthogonal to $u_t(S_0)$ and pointing in the direction connecting the ascending and the descending aorta centerline.
3. Using the “parallel transport framework” $u_p(S_i)$ defined on the centerline by VMTK, the direction $u_n(S_0)$ was transported to the other 10 planes, defining $u_n(S_i)$, such that the angle between $u_n(S_i)$ and $u_p(S_i)$ is equal to the one between $u_n(S_0)$ and $u_p(S_0)$, and the $u_n(S_i)$ lays on the plane orthogonal to $u_t(S_i)$.

4. The bi-normal vector $u_b(S_i)$ was defined as the cross product between $u_t(S_i)$ and $u_n(S_i)$.

A custom MATLAB program was implemented to compute the following geometrical and hemodynamic metrics at peak systole:

- Areas of the orifice and of the aorta's cross-section at the same location, on the computed orthogonal projection, A_o and A_a (the latter expressed in terms of diameter D_a).
- Circularity of the orifice and of the aorta, defined as $C_o, C_a = \frac{\int_{\Omega} dx}{\int_{\Phi} dx}$ where Ω is the region enclosed in the considered outline and Φ is the smallest circle enclosing Ω .
- Eccentricity of the orifice, E , defined as the distance between the barycenter of the orifice outline and the barycenter of the aorta outline on the same plane. Its normalized version with respect to the aorta radius is named E_n (Figure 4).
- Equivalent aorta diameter of each cross section, computed from the area as $D_a = 2 \sqrt{Area/\pi}$
- Magnitude of the mean velocity vector on S_i , V_{mean}
- Magnitude of the maximum velocity vector on S_i , V_{max}
- Jet angle, θ_{jet} defined as the angle between the mean velocity vector $\bar{v}(S_i)$ and $u_t(S_i)$ (Figure 5)
- Forward flow displacement (FD), defined as the distance between the forward-velocity-weighted barycenter: $\frac{\sum_{x_i \text{ s.t. } (v \cdot u_t) > 0} \|v(x_i)\| x_i}{\sum_{x_i \text{ s.t. } (v \cdot u_t) > 0} \|v(x_i)\|}$ and the barycenter of S_i (Figure 2), similar to Sigovan et al²⁹.
- Quadrant of the jet, defined as the quadrant onto which the projection of the mean velocity vector on S_i (named v_{proj}) lays:
 - Quadrant 1 (inner curvature, right): if $v_{proj}(S_i) \cdot u_n(S_i) > 0$ and $v_{proj}(S_i) \cdot u_b(S_i) > 0$
 - Quadrant 2 (outer curvature, right): if $v_{proj}(S_i) \cdot u_n(S_i) < 0$ and $v_{proj}(S_i) \cdot u_b(S_i) > 0$
 - Quadrant 3 (outer curvature, left): if $v_{proj}(S_i) \cdot u_n(S_i) < 0$ and $v_{proj}(S_i) \cdot u_b(S_i) < 0$
 - Quadrant 4 (inner curvature, left): if $v_{proj}(S_i) \cdot u_n(S_i) > 0$ and $v_{proj}(S_i) \cdot u_b(S_i) < 0$.

Paraview was used for data visualization and format conversion. All steps described above were performed by a single, interactive script programmed in MATLAB, which performed the necessary computations and guided the user when external software needed to be used.

Statistical analysis

For continuous variables, statistical differences between means in TAV and BAV groups were tested using student's t-test. For jet angle quadrant, the Mann-Whitney U test was employed since it was a discrete variable. The differences for each of the computed variables in the two groups were considered significant for $p < 0.05$.

Linear regression models were investigated to correlate the geometric variables with hemodynamic parameters and to correlate the hemodynamic parameters at the orifice with those in downstream sections. Since BAV related aortopathy primarily manifests in the ascending aorta region, models were investigated to relate hemodynamic metrics only at sections $S_1 \dots S_6$ to geometrical or hemodynamic covariates at the orifice. The group of six sections $S_1 \dots S_6$ was subdivided into two regions – proximal region ($S_1 \dots S_3$) and distal region ($S_4 \dots S_6$). If at least 2 of the 3 sections in a region had a determination coefficient $R^2 > 0.3$, the models were reported in the Tables 3-6. This was applied if the condition was true for the entire cohort or for one of the two groups (BAV or TAV).

To avoid redundancy, the geometrical variables considered were orifice area, orifice circularity, aorta circularity, normalized orifice eccentricity and aorta diameter. The jet quadrant was not considered in the linear regression models, it being a discrete variable. The correlations were tested for each group both separately and as a single whole cohort.

The statistical tests were carried out in Microsoft Office Excel (v. 14.3.9, Microsoft Corporation, Redmond, WA, USA) and the regression analysis was performed with a custom script based on MATLAB.

Results

The proposed protocol was successfully applied to the 24 samples selected without requiring additional processing with respect to the steps described above. For a typical case (either BAV or TAV subject), the time required to perform the user-dependent part of the protocol (2D segmentation, 3D segmentation, 2D-3D MRI registration and call to external software) totaled approximately to 2-3 hours, while the automatic part of the protocol to less than 10 minutes.

For each subject included in the study, the analysis protocol resulted in 5 primary geometrical variables for the valve plane, one geometrical variable for each cross sectional plane and 55 hemodynamic parameters distributed along the 11 cross sectional planes. A summary of the geometrical results for the valve plane is reported in Table 2, while parameters computed along the aorta (aorta diameter and hemodynamic variables) are displayed in Figure 6 (means or median along centerline distance).

Aortic Geometry: BAV vs. TAV healthy controls

The following geometric metrics were found to be significantly larger in BAV subjects than in TAV group: eccentricity of the orifice, its normalized version with respect to the aorta radius in the valve plane, E_n , as well as SOV and MAA diameters (Table 2). In addition, the aortic diameter was found larger in BAV group on sections 2 (difference=38.5%, $p < 0.01$), 3

(difference=30.4%, $p<0.01$), 4 (difference=24.0%, $p<0.01$) and 5 (difference=15.2%, $p=0.04$). The aortic diameter in these locations was also larger when the geometric variables were normalized over the body surface area (for area measures) or the square root of the body surface area (for length measures).

Aortic Hemodynamics: BAV vs. TAV healthy controls

Among the hemodynamic variables, mean velocity was found to be statistically lower in the BAV subjects compared to the TAV cohort at sections 2 (difference=49.2%, $p=0.01$), 3 (difference=43.4%, $p=0.01$) and 4 (difference=37.5%, $p=0.02$). The same observations hold for the sections 3 and 4 when the velocities are normalized over the cardiac output. The jet angle was statistically higher in the BAV subjects at sections 1 (difference=93.8%, $p=0.01$), 2 (difference=97.1%, $p<0.01$), and 3 (difference=102.2%, $p=0.03$) and the forward flow eccentricity was significantly increased at sections 1 (difference=140.9%, $p=0.02$) and 2 (difference=136.8%, $p=0.01$) in the BAV subjects.

Associations between Aortic Geometry and Hemodynamics

The results of the linear regression models between hemodynamic metric along the aorta and geometrical features are reported in Tables 3-6. Most significant findings in the proximal ascending aorta for the combined cohort of BAV and TAV subjects showed a negative association between V_{mean} and D_a ($R^2=0.42, 0.62, 0.53$, for S_1, S_2, S_3 , respectively), a positive association between θ_{jet} and D_a ($R^2=0.35, 0.18, 0.39$) and a positive association between FD and D_a ($R^2=0.42, 0.38, 0.24$).

The results of the linear regression models between hemodynamic metrics in the proximal and distal ascending aorta, and hemodynamic features at the valve plane are reported in Tables 5 and 6. The combined cohort showed a positive relationship between V_{max} in the proximal ascending aorta and at the valve plane ($R^2=0.88, 0.63, 0.31$ for S_1, S_2, S_3 , respectively) as well as a positive correlation between θ_{jet} at both locations ($R^2=0.77, 0.51, 0.54$). In TAV patients a positive association was found between V_{mean} and $V_{mean}(S_0)$ ($R^2=0.77, 0.76, 0.57$) and between V_{max} and $V_{mean}(S_0)$ ($R^2=0.83, 0.75, 0.69$). In the same cohort, FD was found positively associated with $\theta_{jet}(S_0)$ ($R^2=0.00, 0.36, 0.61$).

Correlation analysis revealed a negative association between θ_{jet} and $V_{max}(S_0)$ in the combined cohort ($R^2=0.19, 0.34, 0.38$, for S_4, S_5, S_6) in the distal region of the ascending aorta. A negative association was found between V_{mean} and $\theta_{jet}(S_0)$ ($R^2=0.30, 0.32, 0.46$) for the same cohort.

Discussion

Protocol Development

The main focus of this work was the development of a novel and semi-automatic protocol to analyze valve geometry and hemodynamic features in the ascending aorta and the aortic arch. Particular attention has been devoted to limit the tasks potentially affected by user variability. In fact, only the segmentation of the valve plane 2D contours is fully manual, while the 3D segmentation of the aortic lumen is semi-automatic, the user being responsible

for selecting proper initialization and method parameters for the level-set algorithm. The user variability of the manual segmentation of 2D valve contours was assessed in a blind test by 2 readers. The orifice area as a representative end point and is provided in a Bland-Altman plot (Figure 7). To facilitate the 3D segmentation, which is the only time consuming step of the protocol (on the order of one hour) the 4D flow MRI images were pre-processed by creating a PC-MRA dataset at peak systole. This is achieved with a different approach with respect to the current literature^{22,29}. In short, the flow and magnitude data were weighted ad-hoc by the user to improve the segmentation of the vessel geometry (similar to the method reported by Bock et al.⁵). Given the low flip angles used to minimize the specific absorption rate (SAR) during MRI, the signal of the magnitude images is often not feasible alone to obtain an accurate representation of vessel geometry. Thus, since the time-averaged phase images contain high signal in the vessel, these images were used to weight the magnitude images. These weights could in principle be adjusted by the user to account for inter subject flow variation, if needed. In the present study, both the magnitude and the velocity data were normalized over their maximum value in the domain (at the considered time point) and then equal weights were assigned to the normalized data. The resulting data was then used in the 3D segmentation process.

Another key point of the protocol is the possibility to automatically obtain flow features along the whole geometry, at cross sections selected according to an arbitrary user-defined spacing. Previously published studies on the hemodynamics (including jet angle, jet orientation and forward flow displacement) in patients affected by BAV focused their analysis on the ascending aorta at a few landmark-based locations^{11,21,29}. With the approach presented here, an arbitrarily fine distribution of probing locations can be achieved and data can be retrieved automatically from the whole segmented region, allowing for a better understanding of both global and local flow phenomena. It is difficult to isolate or identify aortopathy in BAVs to one specific location along the aorta; hence such a tool may be invaluable in assessing a wider range of BAV patients.

This is the first study that proposes to correlate hemodynamic metrics in the aorta with quantitative metrics describing the geometry of the aortic valve (with or without BAV malformation). The generality of this approach allows adaptation for the study of other pathologies, not necessarily involving the aortic valve, where a thorough investigation of the fluid dynamics inside the lumen is needed. Moreover, provided that a robust and relatively fast segmentation approach is used, the presented protocol can be used in a large cohort study, given its limited user-interaction and standardized approach.

The combination of information regarding aortic valve geometry (via bSSFP cine imaging) and time resolved 3D flow (4D flow imaging) has been combined to obtain precise information regarding the impact of the valve geometry and velocity information on the whole aortic arch. While compressed sensing and parallel imaging have greatly improved scan times²⁰, acquiring 4D flow images in clinical practice is currently limited due to time considerations. Hence, this pilot study is an important step to understand the connection between valve geometry and its impact on ascending aortic flow, especially in those subjects at risk for aortopathy. Ultimately, it may be used to predict flow distal to the aortic valve based on the valve anatomy (acquired either with a single plane SSFP cine MRI or with

other non-invasive modalities as echocardiography). The aim is to rapidly assess disease severity, particularly hemodynamic and aortopathy severity in BAV patients, using standard of care imaging acquisitions. However, more extensive testing of the statistical models investigated here, with a larger sample size, is necessary. Pending additional subjects, higher statistical power could be used to potentially identify predictors for flow features known to be associated with aortopathy development. Predictors from more commonly used imaging modalities (such as transthoracic and trans-esophageal echocardiography or 2D cine MRI only) can also be included in the prognostic model. Additionally, the inclusion of advanced flow metrics such as wall shear stress may also be included, which is relevant given that altered distribution of this parameter has been shown to be associated with the presence and type of BAV^{3,18,21,24}. Finally, it is worth pointing out that the generalized approach of this protocol is also applicable for other forms of valvular and vascular disease, beyond just those related to BAV (e.g. aortic stenosis, aortic regurgitation, coarctation of the aorta etc).

Pilot Study in BAV and TAV Subjects

Despite the small sample size and BAV morphological variations of this pilot study, significant differences between groups and correlations in the dataset have been obtained. As expected, BAV patients presented a higher orifice eccentricity than TAV subjects. Although not significant in this small sample (primarily consisting of non-stenotic subjects), the orifice circularity tended to be smaller in BAV patients than in controls, as would be expected given the elongated shape of the BAV orifice compared to the triangular-like shape of TAV subjects. The geometric orifice area did not exhibit a significant difference between the two cohorts, therefore the degree of obstruction does not represent a confounder in this study. Both SOV and MAA diameters as well as D_a on sections $S_2 - S_5$ were significantly different in BAV and TAV, with TAV subjects being smaller. This may be due to referral selection bias, since patients with ascending aorta dilatation were referred for MRI scans and therefore may represent a large percentage of the BAV database.

The analysis of hemodynamic metrics along the aorta revealed an expected trend in velocity. As reported in Hope et al.¹⁸, the velocity magnitude profile tends to decrease in the transverse aorta and then it increases in the descending aorta. The higher velocity in TAV than BAV group corresponds with the SOV and MAA measurements, as well as D_a , which is larger at these positions in the BAV population. Thus, holding cardiac outputs equal in two different sized aortas results in the larger aorta having a lower mean velocity. A further confirmation of this aspect is given by the regression models, which correlate negatively to the mean velocity and the aorta diameter in the ascending aorta, for all subjects. In addition, by running the same statistical analysis after having normalized the velocities over the cardiac output, we have verified that such relationship disappears.

Previous studies in pediatric and adult populations have reported similar values for BAV flow angle as those found in this protocol (Figure 6). In a relatively young population (16 ± 2 years), Den Reijer et al. found the flow angle to be $18 \pm 0.9^\circ$ degrees in BAV subjects¹¹. In slightly older BAV populations, Sigovan et al. (averaging 23-33 years depending on BAV group)²⁹ and Mahadevia et al (averaging 45-48 years, depending on valve morphology)²¹ reported flow angles ranging between 14 and 31.7° . The flow angle numbers found in our

group are on the high end of the ranges found in the previous papers, most likely due to the older age of the BAV subjects in this study, as sclerotic valve disease and aorta dilation are more likely in older subjects. In addition, good agreement was found for CO(peak) and $V_{\max}$ at S_1 when compared to Barker et al.².

The jet angle significantly differed between BAV and TAV subjects in the proximal tract of the ascending aorta and was larger in the BAV group, agreeing with the results from Mahadevia et al.²¹. Forward flow displacement measures the eccentricity of the flow. Notably, both jet angle and forward flow displacement exhibit differences between BAV and TAV, but only in the proximal region of the ascending aorta. This suggests that the anatomy of the aorta, with 3D curvature and torsion, tend to smooth differences in flow eccentricity between the two groups as the flow progresses downstream. This is consistent with the predominant presence of BAV-related pathology in the proximal tract of the aorta³². The reported difference in jet angle and forward flow displacement between BAV and TAV groups may be due to the reduced valve motility, reported for BAV patients^{8,29}.

The jet quadrant did not exhibit significant differences between the two groups, except for S_5 . One confounding factor in this case might be the fact that in the considered cohort most of the patients (75%) present the same type of fusion, RL, potentially reducing the quadrant variability in the BAV cohort.

Relationships between hemodynamic metrics along the aorta distance and either geometric or hemodynamic variables on the orifice were investigated. The rationale behind this analysis is to potentially identify easily measurable parameters that could provide knowledge on the hemodynamic status of the patient and potentially identify risk factors for complications. Multi-linear models were not considered to avoid over-fitting of the data, given the small sample size.

The linear regression models between hemodynamic and geometrical metrics are an initial effort which indicates that size of the proximal ascending aorta (in terms of cross section equivalent diameter) is the most recurring predictor explaining the hemodynamic metrics in the whole cohort. This is in spite of the statistically different diameter values in the two groups. It is also interesting to note that both jet angle and forward flow displacement are positively correlated with aorta diameter in the whole sample. While this does not prove any cause-effect relationship between geometry and hemodynamics, this relationship seems meaningful both under the assumption that the hemodynamics influences the aorta shape, where both these phenomena can be interpreted as the tendency of an eccentric and skewed flow jet to enlarge the aorta, or vice versa, with the aortic dilatation to promote unfavorable hemodynamics.

The analysis of correlations between hemodynamics along the aorta distance and on the valve plane shows a number of trends in the proximal ascending aorta. The positive dependencies between each hemodynamic metric in the proximal tract and the respective variable immediately upstream of this tract (parameters on the orifice) are expected from a fluid mechanics perspective. An important finding in the proximal ascending aorta of the TAV subjects is the positive association between forward flow displacement and jet angle at

the orifice location. This shows that in absence of other confounding factors (that might be present in BAV cases) the jet orientation at the orifice is critical for the development of flow asymmetries downstream. This is relevant given recent reports correlating flow displacement and aortic growth in a small cohort BAV study⁶.

As expected, in the distal portion of the descending aorta, the relationships between hemodynamics along the aorta and anatomy and hemodynamics on the valve plane are less significant. However, two relationships that were not significant in the proximal tract, appear to be important in the distal one. Specifically, a negative dependence of the jet angle on the maximum velocity on orifice in the whole cohort and a negative dependence of the mean velocity on the jet angle on orifice in TAV group were observed. The first relationship can be interpreted as the tendency of high momentum jet to be aligned with the geometry, hence with its centerline, originating a low jet angle. It is in fact expected to have a high momentum jet along the aorta if the flow jet has a high momentum at the origin of the aorta. The second one links negatively mean velocity and jet angle on orifice, suggesting that flow well aligned with the geometry enables to reach higher mean velocities. However it must be noted that the jet angle for TAV subjects is very small.

While some of these trends are intuitive and consistent, the primary objective of this study was to report the methodology and the effects of a small cohort must be considered. Therefore this preliminary statistical analysis should be regarded only as pilot application of the developed protocol.

While creating further subgroups based on type of valve fusion is not feasible in the current cohort (due to the limited sample size), the same protocol applied to a larger population would allow for subdivision of the most common valve morphology phenotypes involved with BAV (right-left, right-non coronary and left-non coronary leaflets). This would be an important contribution to the ongoing debate regarding the origin of BAV driven aortopathy^{13,21}. Moreover, the present study can be extended in the future to include more complex flow metrics, which may indicate the presence of flow disturbances (e.g. vorticity, helicity, wall shear stress, oscillatory shear index), or other categorical clinical variables into account in the models. In fact, the work presented here can be regarded as a first step to find geometrical and hemodynamic predictors to assess the severity of the disease or its progression. The combination of using geometrical and hemodynamic predictors for BAV disease can have tremendous clinical impact, by extending knowledge obtained from state of the art hemodynamic imaging modalities and correlating to more commonly available metrics from standard of care assessment.

Limitations

The main limitation of the proposed approach is the need for 2D and 3D segmentation, which are partially manual steps, and therefore time consuming and subject to user variability. However it is important to note that all the hemodynamic variables computed with the proposed protocol, (excluding maximum velocity), namely V_{mean} , θ_{jet} , FD , Q , are based on the mean velocity vector, which is inherently a robust metric, and not highly sensitive to point-wise measurement errors. The accuracy of the results might be further

improved by using more advanced interpolation techniques to compute the blood velocity field on the desired grid points¹².

Conclusions

A semi-automatic protocol for the combined analysis of aortic valve geometry and hemodynamics in the aorta was developed to analyze MRI data obtained with 2D cine acquisition and 4D flow MRI. A pilot study in a cohort of 12 BAV and 12 TAV revealed elevated mean velocity, jet angle and forward flow displacement in BAV subjects in the proximal ascending aorta, and linear regression models demonstrated associations between jet angle, forward flow displacement, velocity and aorta diameter, among the others. This study provides a comprehensive roadmap for larger cohort assessment of correlations between geometry and hemodynamics associated with BAV disease.

Finally, the in-house software that implements the described protocol, as well as the dataset containing values for the variables utilized in the manuscript, can be made available to the interested readers upon contacting the corresponding author.

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Figure 1. Example of orifice and aorta outline using the 2D cine MRI
a: TAV case; b: BAV case. In blue: orifice outline; in red: aorta outline.

Figure 2. Location of measurements on representative patient

Sections 0-10, orthogonal to the centerline, are color coded by the velocity magnitude. The centerline is color coded by the aorta diameter. SOV and MAA location are indicated. 2D bSSFP plane is displayed in greyscale and the orifice and aortic root contour are displayed in blue and red respectively. Section S_0 is not aligned with the 2D bSSFP plane due to the projection applied onto the plane orthogonal to the centerline. Geometrical information on S_0 is obtained from 2D cine data for improved accuracy. Forward flow displacement is displayed on section S_1 .

Figure 3. Reference system to calculate the jet quadrant
Cross sections are color coded by the velocity magnitude.

Figure 4. Orifice and aorta outlines with orifice smallest enclosing circle

In blue: orifice outline; in red: aorta outline; in black: orifice smallest enclosing circle; in green: segment whose length represents the orifice eccentricity.

Figure 5. Graphical representation of jet angle, θ_{jet}

In blue, normal vector to the cross section, $u_t(S_i)$; in yellow, mean velocity vector, $\bar{u}(S_i)$. Cross sections are color coded by the velocity magnitude.

Figure 6. Mean values of the aorta and hemodynamic metrics along the aorta

Jet quadrant is expressed in terms of its median. Red continuous line and "plus" marker: BAV subjects; black continuous line and "square" marker: TAV subjects; blue continuous line and "circular" marker: all subjects. The marker "*" indicates the section with a statistically significant difference between BAV and TAV groups ($p < 0.05$). 7a: mean velocity; 7b: maximum velocity; 7c: jet angle; 7d: forward flow eccentricity; 7e: jet quadrant; 7f: area of aorta cross sections.

Figure 7. Bland-Altman for orifice area

Bland-Altman plot showing the interobserver variability on the area of the aortic valve orifice. Red crosses: BAV subjects. Blue circles: TAV subjects.

Table 1

Demographic information of the subjects cohort

Characteristic	BAV	TAV	p-value (where appropriate)
N	12	12	-
Age (years)	48±13	45±12	0.55
Female	3	5	-
Fusion	RL: 9; LN: 1; RN: 2	-	-
SOV (cm) ($SOV/\sqrt{BSA}(cm/m)$)	3.58±0.50 (2.55±0.33)	3.07±0.39 (2.16±0.26)	0.01 (0.01)
MAA (cm) ($MAA/\sqrt{BSA}(cm/m)$)	3.91±0.62 (2.78±0.39)	3.13±0.45 (2.21±0.30)	0.00 (0.00)
Aortic Stenosis	None: 11; Mild: 1	-	-
Aortic Insufficiency	None: 9; Trace: 2; Mild: 1	-	-
Aortic Insufficiency	None: 9; Trace: 2; Mild: 1	-	-
BSA (m ²)	1.97±0.21	2.02±0.27	0.65
CO(peak) (L/min)	18.71±8.77	16.42±3.89	0.42

RL: right-left fusion; RN: right-non coronary fusion; LN: left-non coronary fusion; SOV: diameter at the sinuses of Valsalva; MAA: diameter at the mid ascending aorta; BSA: body surface area; CO(peak): cardiac output at peak systole, computed on plane S₁.

Table 2Summary of geometrical metrics at the valve plane (S_0)

	$A_o(\text{cm}^2)$ ($A_o/BSA_o(\text{cm}^2/\text{m}^2)$)	$D_a(\text{cm})$ ($D_a/\sqrt{BSA_o}(\text{cm}/\text{m})$)	C_o	C_a	$E(\text{mm})$	$E_a(\%)$
BAV (avg $\pm$ std)	4.17 $\pm$ 0.69 (2.12 $\pm$ 0.36)	3.58 $\pm$ 0.62 (2.56 $\pm$ 0.38)	0.65 $\pm$ 0.17	0.82 $\pm$ 0.04	3.05 $\pm$ 1.17	15.25 $\pm$ 4.83
TAV (avg $\pm$ std)	4.06 $\pm$ 0.63 (2.03 $\pm$ 0.34)	3.26 $\pm$ 0.29 (2.30 $\pm$ 0.22)	0.73 $\pm$ 0.06	0.80 $\pm$ 0.05	1.83 $\pm$ 0.92	10.03 $\pm$ 4.90
p-value	0.52 (0.69)	0.06 (0.08)	0.17	0.17	0.01	0.02

A_o : orifice area; D_a : diameter of the aorta; C_o : orifice circularity; C_a : aorta circularity; E : eccentricity normalized over aorta radius; E_a : body surface area.

Table 3
Summary of regression models between hemodynamics and geometry in the proximal portion of the ascending aorta

Proximal	Cohort	A_o	C_o	C_a	E_n	D_a
V_{mean}	All					(-) (0.42, 0.62, 0.53)
	BAV		(-) (0.43, 0.43, 0.23)			(-) (0.53, 0.56, 0.46)
	TAV			(-) (0.45, 0.43, 0.17)		(-) (0.21, 0.42, 0.32)
V_{max}	All					
	BAV		(-) (0.37, 0.39, 0.25)			
	TAV			(-) (0.45, 0.42, 0.42)		
θ_{jet}	All					(+) (0.36, 0.18, 0.39)
	BAV					(+) (0.42, 0.01, 0.32)
	TAV					
FD	All					(+) (0.42, 0.38, 0.24)
	BAV					
	TAV					

Sign of significant correlations is reported in the first brackets and R^2 for sections S_1 , S_2 , S_3 are reported in the second brackets.

Table 4
Summary of regression models between hemodynamics and geometry in the distal portion of the ascending aorta

Distal	Cohort	A_o	C_o	C_a	E_n	D_a
V_{mean}	All					(-)(0.47, 0.32, 0.16)
	BAV					(-)(0.35, 0.38, 0.30)
	TAV					
V_{max}	All					(-)(0.40, 0.41, 0.23)
	BAV					(-)(0.32, 0.49, 0.36)
	TAV					
θ_{jet}	All					
	BAV					(+)(0.32, 0.46, 0.47)
	TAV					
FD	All					
	BAV					
	TAV					

Sign of significant correlations is reported in the first brackets and R^2 for sections S4, S5, S6 are reported in the second brackets.

Table 5
Summary of regression models between hemodynamics along the proximal ascending aorta hemodynamics on the valve plane

Distal	Cohort	V_{mean0}	V_{max0}	θ_{jet0}	FD_0
V_{mean}	All				
	BAV		(+) (0.79, 0.46, 0.34)		
	TAV	(+) (0.77, 0.76, 0.57)	(+) (0.77, 0.81, 0.46)		
V_{max}	All		(+) (0.88, 0.63, 0.31)		
	BAV		(+) (0.91, 0.57, 0.27)		
	TAV	(+) (0.83, 0.75, 0.69)	(+) (0.84, 0.86, 0.64)		
θ_{jet}	All			(+) (0.77, 0.51, 0.54)	
	BAV			(+) (0.76, 0.48, 0.61)	
	TAV			(+) (0.80, 0.42, 0.05)	
FD	All				
	BAV				
	TAV			(+) (0.00, 0.36, 0.61)	

Sign of significant correlations is reported in the first brackets and R^2 for sections S_1 , S_2 , S_3 are reported in the second brackets.

Table 6
Summary of regression models between hemodynamics along the distal ascending aorta hemodynamics on the valve plane

Distal	Cohort	V_{mean0}	V_{max0}	θ_{jet0}	FD_0
V_{mean}	All				
	BAV				
	TAV	(+) (0.40, 0.50, 0.43)		(-) (0.30, 0.32, 0.46)	
V_{max}	All				
	BAV				
	TAV	(+) (0.49, 0.40, 0.37)			
θ_{jet}	All		(-) (0.19, 0.34, 0.38)	(+) (0.57, 0.44, 0.43)	
	BAV		(-) (0.31, 0.52, 0.68)	(+) (0.56, 0.45, 0.48)	
	TAV				
FD	All				
	BAV				
	TAV				

Sign of significant correlations is reported in the first brackets and R^2 for sections S4, S5, S6 are reported in the second brackets.