Published in final edited form as:

J Magn Reson Imaging. 2020 February ; 51(2): 481–491. doi:10.1002/jmri.26804.

Effect of Aortic Valve Disease on Three-Dimensional Hemodynamics in Patients with Aortic Dilation and Trileaflet Aortic Valve Morphology

Kenichiro Suwa, MD¹, Ozair Abdul Rahman, MD¹, Emilie Bollache, PhD¹, Michael J. Rose, MS², Amir Ali Rahsepar, MD^{1,3}, James Carr, MD¹, Jeremy D. Collins, MD¹, Alex J. Barker, PhD¹, Michael Markl, PhD^{1,4}

¹Department of Radiology, Northwestern University Feinberg School of Medicine, Chicago, IL, United States,

²Department of Medical Imaging, Ann & Robert H. Lurie Children's Hospital of Chicago, Chicago, IL, United States,

³Department of Radiology, Yale New Haven Health System, Bridgeport hospital, Bridgeport, CT, United States

⁴Department of Biomedical Engineering, Northwestern University McCormick School of Engineering, Chicago, IL, United States.

Abstract

Background: The effect of different expressions of aortic valve disease on three dimensional (3D) aortic hemodynamics is unclear.

Purpose: To investigate changes in aortic hemodynamics in patients with dilated ascending aorta (AAo) but different severity of aortic valve stenosis (AS) and/or regurgitation (AR).

Study Type: Retrospective.

Population: A total of 111 subjects (86 patients with AAo diameter ≥ 40 mm and 25 healthy controls, all with trileaflet aortic valve (TAV)). Patients were further stratified by TAV dysfunction: n=9 with combined moderate or severe AS and AR (ASR, 56 ± 13 years), n=14 with moderate or severe AS (AS, 64 ± 14 years), n=33 with moderate or severe AR (AR, 62 ± 14 years), n=30 with neither AS nor AR (no AS/AR, 63 ± 9 years).

Field Strength/Sequence: 4D flow MRI on 1.5/3T systems for the in-vivo analysis of aortic blood flow dynamics.

Assessment: Data analysis included grading of 3D AAo vortex/helix flow and AAo flow eccentricity as well as quantification of systolic peak velocities and wall shear stress (WSS).

Statistical Tests: Continuous variables were compared by one-way analysis of variance or Kruskal-Wallis, followed by pair-wise Tukey or Dunn test if there was significant difference.

Results: All patients demonstrated markedly elevated vortex and helix flow compared to controls ($p<0.05$). Peak velocities were significantly elevated in ASR, AS and AR patients compared to controls ($p<0.05$). Increased flow eccentricity was observed in entire AAo for AR, at the mid and distal AAo for ASR and AS, and at the proximal AAo for no AS/AR. Compared to controls, WSS in the AAo was significantly elevated in ASR and AS patients ($p<0.05$) and reduced in no AS/AR patients ($p<0.05$).

Data Conclusions: The presence of TAV dysfunction is associated with aberrant hemodynamics and altered WSS which may play a role in the development of aortopathy.

Keywords

4D flow MRI; Aortic dilatation; Aortic valve stenosis; Aortic valve regurgitation; Hemodynamics; Wall shear stress

Introduction

Thoracic aortic aneurysm (TAA) is a known risk of aortic dissection or rupture which commonly involving the ascending aorta (AAo) (1). Patients with aortic dilation are at risk for complications including dissection or rupture (2). Although there are known relationships between the aortic size and risk of complications, it is clear what other factors can influence the risk for dissection or rupture (3).

Aortic valve stenosis (AS) in patients with trileaflet aortic valve (TAV), the most common valvular disease in the aging population, is thought to be implicated in the development of progressive AAo dilatation (4). AS can coexist with aortic valve regurgitation (AR) in severely calcified aortic valve (5). In addition, severely dilated AAo is often accompanied by AR by malcoaptation of valve leaflet (5). However, the pathophysiology underlying the development of aortic dilatation and the role of aortic valve dysfunction (AS, AR) are still not fully understood (6,7).

AAo hemodynamics may help to elucidate the relationship between aortic valve disease and AAo dilatation. A number of recent studies provide evidence that aberrant hemodynamics and elevated wall shear stress (WSS) in the AAo can result in aortic wall degeneration and remodeling in patients with bicuspid aortic valve (BAV) (8–10). In TAV, flow patterns and WSS are investigated in healthy volunteers (11,12), and in patients with AAo dilatation (7,13,14). However, the severity of AS and/or AR is highly variable and a systematic investigation of the impact of aortic valve dysfunction on AAo hemodynamics is lacking. It is the purpose of this study to systematically investigate the impact of different phenotypes of aortic valve dysfunction (combined AS and AR, isolated AS or AR, no AS/AR) on aortic hemodynamics assessed by 4D flow magnetic resonance imaging (MRI) in a large cohort of patients matched for aortic dilatation. We hypothesized that the presence and severity of AS and AR might be associated with deranged AAo hemodynamics and WSS.

Materials and Methods

Study Population

Based on 410 patients with TAV who were identified via Institutional Review Board (IRB)-approved retrospective chart review, 91 patients met inclusion criteria of AAo dilatation and left ventricular (LV) ejection fraction (EF) $\geq 45\%$. AAo dilatation was defined as a sinus of Valsalva (SOV) or mid ascending aorta (MAA) diameter ≥ 40 mm by contrast-enhanced MR angiography (15). Patients with aortic dissection ($n=1$), known connective tissue disease ($n=1$), and functional BAV ($n=3$) were excluded. Finally, 86 patients (69 male, 62 ± 12 years) were recruited for this study and were divided into four groups according to TAV function as follows, ASR: coexistence of AS and AR (both moderate or severe) ($n=9$, 8 male, 56 ± 13 years), AS: moderate or severe AS without AR ($n=14$, 14 male, 64 ± 14 years), AR: moderate or severe AR without AS ($n=33$, 25 male, 62 ± 14 years), no AS/AR: neither AS nor AR ($n=30$, 22 male, 63 ± 9 years) (Figure 1). Moderate or severe AS was defined as systolic peak velocity (sysPV) at the aortic valve ≥ 3.0 m/s and aortic valve area (AVA) ≤ 1.5 cm². Moderate or severe AR was defined as regurgitant fraction $\geq 30\%$. From an existing IRB-approved cohort of prospectively enrolled healthy volunteers, 25 subjects (19 male, 57 ± 10 years) were selected to form an age and gender matched control group. Written informed consent was obtained from all volunteers. Patients were retrospectively enrolled with IRB-approved waiver of consent.

Magnetic Resonance Imaging Acquisitions

All subjects underwent MRI scans on 1.5T ($n=88$: 79 patients and 9 controls) or 3T ($n=23$: 7 patients and 16 controls) systems (Magnetom Avanto, Aera, Skyra, and Espree, Siemens, Erlangen, Germany). The MRI protocol included ECG-gated 2D cine balanced steady state free precession (bSSFP) images to assess cardiac function and contrast-enhanced MR angiography of the thoracic aorta for the quantification of aortic dimensions. 2D cine phase contrast (PC) MRI was performed at 2 planes at, and below the aortic valve for the quantification of the regurgitant fraction. In addition, free-breathing, ECG- and respiratory navigator-gated 4D flow MRI data were acquired with full volumetric coverage of the entire thoracic aorta including the aortic valve, and three-directional velocity encoding. 4D flow MRI parameters were as follows: field of view = $320\text{--}450 \times 240\text{--}366$ mm², matrix size = $128\text{--}192 \times 96\text{--}160$, spatial resolution = $2.14\text{--}4.15 \times 1.67\text{--}2.81 \times 2.2\text{--}4.0$ mm³, temporal resolution = $36.8\text{--}43.2$ ms, TE/TR/FA = $2.2\text{--}2.8$ ms/ $4.6\text{--}5.4$ ms/ $7\text{--}20^\circ$, velocity sensitivity (VENC) = $150\text{--}400$ cm/s.

Evaluation of Cardiac and Aortic Valve Function, as well as Aortic Size

2D cine bSSFP images in short axis orientation covering the entire ventricle were used to quantify global LV and right ventricular (RV) function and volume parameters which were normalized by the patient's body surface area (BSA) including EF, end-diastolic volume index (EDVi), end-systolic volume index (ESVi), and stroke volume index (SVi) for both LV and RV using a commercially available software (CVI⁴² V5.3, Circle Cardiovascular Imaging, Calgary, Canada). TAV morphology was confirmed using 2D cine bSSFP images through the aortic valve plane. AS severity was assessed based on the sysPV at the aortic valve using 4D flow MRI velocity MIPs as described previously (16) and AVA using bSSFP

image (CVI⁴²). Grading scale for AS was based on guidelines: mild; sysPV<3.0 m/s, AVA>1.5 cm², moderate; sysPV=3.0–3.9 m/s, AVA=1.0–1.5 cm², severe; sysPV ≥ 4.0 m/s, AVA<1.0 cm² (5). AR severity was quantified using 2D cine PC MRI (CVI⁴²): mild; <30%, moderate; 30–49%, severe; ≥ 50% (5). The caliber of the thoracic aorta at the SOV, MAA, arch and descending aorta (DAo) was quantified on a 3D workstation with multiplanar reformatting capabilities (Leonardo, Siemens, Germany). Measurements were performed by recording the maximal orthogonal diameter from outer-edge to outer-edge. SOV diameter was determined as the maximum of the three sinus-to-sinus diameters.

4D flow MRI Data Analysis

All 4D flow MRI data were corrected for eddy currents, Maxwell terms, noise, and velocity aliasing using an in-house tool (MatLab, MathWorks, Natick, MA) (17,18). A time-averaged 3D phase contrast angiogram (PC-MRA) was computed as described previously (19) and used as an anatomical guide for semi-automatic 3D segmentation of the thoracic aorta (Mimics, Materialise, Belgium). 3D blood flow visualization with the segmented 3D aorta volume was performed using dedicated software (Enight, CEI, Apex, NC) to generate time-resolved pathlines resembling spatio-temporal blood flow patterns and systolic streamlines representing tangent lines to the flow vectors at peak systole (Figure 2).

Blood Flow Pattern Grading

AAo flow patterns were graded according to the presence and severity of vortex and helix flow in systole using time-resolved pathlines. Vortex flow was defined as revolving particles around an axis orthogonal to the vessel centerline. Helix flow was defined as rotational motion around the longitudinal axis of the vessel centerline. As summarized in Figure 2 and displayed more in detail in Video S1–3, vortex and helix severity was graded in a blinded fashion by two independent observers using a 3-point grading scale: 1, no vortex/helix with flow rotation <180°; 2, 1–2 large vortex/helix with flow rotation 180° to 360°; 3, more than 2 large vortex/helix with flow rotation ≥ 360°. Vortex and helix flow grading were added to derive a combined score for flow pattern derangement.

Flow Velocity Quantification

Systolic peak velocities were quantified in nine analysis planes orthogonal to the aorta at the following positions: aortic root, sinotubular junction (proximal AAo), mid-point between proximal and distal AAo (mid AAo), just proximal to the origin of brachiocephalic trunk (distal AAo), between the origin of brachiocephalic trunk and left common carotid artery (proximal arch), between the origin of left common carotid artery and left subclavian artery (distal arch), after the origin of left subclavian artery (proximal DAo), DAo at the same level as aortic root (mid DAo), and the level of diaphragm (distal DAo) (Figure 3A).

Flow Eccentricity in the Ascending Aorta

Blood flow eccentricity at peak systole was evaluated in 3 analysis planes at the proximal, mid and distal AAo, which were color-coded by velocity. As shown in Figure 3B, the aortic cross sections were divided into quadrants as follows: inner-anterior, outer-anterior, outer-posterior and inner-posterior quadrant. Regions with systolic peak velocities >1 m/s in cross-

sectional quadrants were visually identified and scored as '1'. For the evaluation of eccentricity in a plane, the fraction of subjects with velocities $>1\text{m/s}$ (in %) was calculated as $100 \times (\text{cumulative score}) / (\text{total patients' number})$ in each quadrant.

Regional WSS

Peak systolic WSS along the entire segmented aortic wall was calculated based on previously reported strategies (20–22) using in-house tools programmed in MatLab (MathWorks, Natick, MA). Regional WSS was calculated in 10 manually defined regions of interest as shown in Figure 3C: inner and outer curvatures of the proximal and distal AAo (regions 1–4), arch (regions 5 and 6), and proximal and distal DAo (regions 7–10). Systolic peak WSS was quantified by averaging the 2% highest WSS values in each aortic segment.

Reliability Assessment of 4D flow MRI

To assess the accuracy of 4D flow MRI and the other sequence parameters, forward flow at aortic root by 4D flow MRI, forward flow at aortic valve by 2D cine PC and LV stroke volume by 2D cine bSSFP were compared. We also compared peak velocities and regurgitant fractions quantified using 4D flow MRI and 2D cine PC MRI. Consistency between two parameters were evaluated using the intraclass correlation coefficient (ICC) and Bland-Altman analysis.

Inter-Observer Variability

For the assessment of inter-observer variability, analysis was repeated in 28 subjects (AS; $n=6$, AR; $n=4$, no AS/AR; $n=7$, control; $n=11$) by a second blinded independent observer (O.R). For peak velocity, the analysis planes were placed independently, with automatic quantification of the peak velocity in each plane. For regional WSS, delineation of the 10 anatomical segments was performed independently. Inter-observer variability of flow pattern grading and flow eccentricity assessment was evaluated by calculating Cohen's kappa coefficient, while variability for peak systolic velocity and regional WSS was evaluated using the ICC.

Statistical Analysis

Continuous data were expressed as mean $\pm$ standard deviation (SD). Categorical data were presented as numbers and percentages. A Kolmogorov-Smirnov test was used to assess the assumption of normal distribution. Continuous variables were compared by one-way analysis of variance (normal distribution) or Kruskal-Wallis (non-normal distribution). If these tests determined that a parameter was significantly different between groups ($p < 0.05$), multiple comparisons for all groups were performed by the use of the Tukey test (normal distribution) or Dunn test (non-normal distribution). To compare categorical variables, the Chi-squared test or the Fisher's exact test were used. A Jonckheere-Terpstra test was used for the verification of a trend. Pearson correlation coefficient was used to test the correlation of regional WSS and peak velocity. Values of $p < 0.05$ were considered significant. All statistical analyses were performed using a statistical software package (SPSS 17.0; Chicago, IL).

Results

Study Cohort

Subjects' demographics and MRI findings are summarized in Table 1. MAA and SOV diameters for four patient groups were similar and significantly elevated compared to control subjects ($p<0.01$). LVEF were similar between all subject groups, while LVEDVi and LVSVi were significantly increased in the patients with ASR ($p<0.05$) and AR ($p<0.01$) compared to controls as well as no AS/AR except for LVSVi between the patients with ASR and those with no AS/AR.

Consistency of Parameters by 4D flow MRI Compared with the Other Sequences

As summarized in Supplementary table 1 and 2 and Supplementary figure 1, forward flow at the aortic root quantified by 4D flow MRI showed moderate consistency ($ICC=0.71$) and forward flow by 2D cine PC MRI demonstrated good consistency ($ICC=0.88$) with LV stroke volume obtained by 2D cine bSSFP images. Forward flow by 4D flow MRI and 2D cine PC MRI revealed moderate agreement ($ICC=0.73$). Peak velocity at aortic root by 4D flow MRI was in excellent agreement with 2D cine PC MRI ($ICC=0.95$). 4D flow MRI derived regurgitant fraction showed only moderate agreement with 2D cine PC MRI ($ICC=0.68$).

Aortic Blood Flow Patterns

3D blood flow visualization was successfully performed in all subjects. As summarized in Figure 4, the sum of vortex and helix flow grading in the AAo were markedly elevated in all patient groups compared to controls ($p<0.05$) and there was a trend ($p<0.001$) towards more flow derangement for increasing valve dysfunction (no AS/AR<AR<AS<ASR) between the four patient groups.

Aortic Systolic Peak Velocity

As summarized in Figure 5, patients with ASR and AS showed significantly elevated peak velocities in all analysis planes from the aortic root to the distal arch compared to the other groups ($p<0.05$). Furthermore, peak velocities were significantly increased in patients with AR compared to those with no AS/AR and controls in the aortic root and the mid AAo ($p<0.05$).

Flow Eccentricity Assessment

As shown in Figure 6, patients with ASR and AS showed concentric flow at the proximal AAo which developed into highly eccentric flow along the outer curvature of the mid and distal AAo ($p<0.05$). In patients with AR, eccentric flow was observed along the outer curvature of the entire AAo ($p<0.05$). In contrast, patients without AS/AR demonstrated eccentric flow only at the proximal AAo ($p<0.05$). Control subjects generally showed uniform flow profiles.

Regional WSS

Figure 7 summarizes the results of regional WSS quantification in 10 regions of interest along the thoracic aorta. Significantly elevated WSS throughout the AAo and arch was observed in the patients with ASR and AS compared to the other groups ($p<0.001$). Patients with AR also demonstrated significantly elevated WSS ($p<0.05$) at the distal AAo compared to those with no AS/AR, but showed no differences compared to controls. Significantly reduced WSS ($p=0.02$) was found in patients with no AS/AR at the inner curvature of the distal AAo compared to controls and similar trends were observed for other aortic segments.

Relationship between Aortic Diameter and Hemodynamic Parameters

In all 111 subjects, increasing SOV and MAA diameter resulted in a trend ($p=0.039$ for SOV, $p<0.001$ for MAA) toward increased vortex and helix grading (Figure 8). Subjects with grading >5 demonstrated significantly increased SOV and MAA diameters compared to those with the grading $=2$ (SOV: 41.9 ± 5.3 mm vs. 35.0 ± 3.3 mm, $p=0.008$, MAA: 43.0 ± 4.7 mm vs. 32.1 ± 4.0 mm; $p<0.001$). As shown in Figure 9, there were moderate or strong positive correlations between elevated regional WSS and increased peak velocity in the AAo ($r=0.76$ – 0.82 , $p<0.001$).

Inter-Observer Variability

Inter-observer variability of flow pattern grading (Kappa $=0.94$), systolic peak velocity (ICC $=0.94$), flow eccentricity (Kappa $=0.79$), and regional WSS (ICC $=0.96$) was excellent.

Discussion

In this study, we systematically investigated the influence of aortic valve disease on hemodynamics in the dilated AAo in patients with TAV. The main findings of our study are (1) greater vortex and helix flow were present in all patient groups compared to controls, with a trend towards increased aberrant flow for more severe valve dysfunction; (2) eccentric flow was detected in the entire AAo with AR, in the mid and distal AAo with ASR and AS, and in the proximal AAo with no AS/AR; (3) Compared to controls, WSS in the AAo was significantly elevated with ASR and AS and reduced with no AS/AR.

The disagreement between 4D flow MRI and 2D cine PC MRI can be attributed to differences in image acquisition between two techniques: 4D flow MRI provides a three-directional velocity vector field while 2D cine PC MRI is based on single-direction velocity encoding along the through-plane direction (23). In addition, 4D flow MRI data was acquired using prospective ECG gating while retrospective ECG gating was used for 2D cine PC MRI (23). We speculate that these methodological differences resulted in the observed moderate agreement in forward flow between 4D flow MRI and 2D cine PC MRI. In addition, the omission of late diastole in prospectively gated 4D flow MRI could explain the underestimation in regurgitant fraction by 4D flow MRI.

The findings of our study indicate a complex relationship between changes in aortic 3D blood flow, severity and type of aortic valve disease, and aortic dilatation. A previous study reported an association between elevated WSS and aortic wall histological degeneration in

BAV (10). Though the causation was not clarified, TAV patients with AS and AAo dilatation has association with elevated WSS in our study. Conversely, WSS was normal in patients with AR and even decreased in patients with no AS/AR, similar to findings in previous studies (7, 9). In the absence of aortic valve disease, vessel dilatation will thus reduce the flow velocity gradient adjacent to the vessel wall and WSS (24). The results of our study therefore suggest that the underlying etiology for AAo dilatation is different between patient groups and metrics of aortic flow derangement may be an important addition to the simple measurement of aortic size and growth rate currently employed in the management of patients with dilated AAo.

As previously reported by Bürk et al, vortex and helix flow rotational strength in the AAo was associated with an increase in vessel diameter (7). In our study cohort including patients with different types of aortic valve disease, MAA diameters were significantly greater in the patients with higher helix and vortex grading. In the previous study with AS, pronounced helical flow was developed also in non-dilated AAo (13) and its grading was associated with AS severity (25). In our study, the trend towards more flow derangement for increasing valve dysfunction was observed but not significant. The greater AAo diameters for patients in our study (40 mm) compared to that in von Knobelsdorff-Brenkenhoff's cohort (35 ± 7 mm) may mask the independent effect of AS and AR on helix and vortex formation (25).

Mean flow velocity in dilated AAo was decreased compared to non-dilated AAo in a previous study (7). In our study, the patients with ASR and AS demonstrated elevated systolic peak velocities from AAo to arch, not in the DAo as well as significant dilatation at the AAo, rather than in the arch and DAo. This suggests that the location of peak systolic velocity elevation along the aorta is consistent with the location of vessel dilatation. Hence, our results indicate that systolic peak velocity elevation is one of the contributing factors in AAo dilatation.

Eccentric flow in the AAo was previously reported in BAV (9) and AS (24). We demonstrated significantly pronounced eccentric flow in all patient groups but the spatial location is more distal for ASR and AS, entire AAo for AR, and more proximal for no AS/AR. This result would indicate that more distal location was associated with higher systolic peak velocity.

In BAV, WSS analysis in the dilated AAo revealed significant elevation (9,26,27). Furthermore, in-vivo histological assessment demonstrated pathological changes including decreased elastin fiber or increased medial necrosis in aortic wall samples which were contacted directly with the outflow jet or displayed increased WSS in BAV (10,28,29). For patients with AS and mildly dilated AAo, WSS was significantly elevated at the outer curvature of the AAo (25). In this study, ASR and AS patients demonstrated significantly elevated WSS from the proximal AAo to arch compared to controls, which aligned well with the location of elevated peak velocities. Decreased WSS in patients without AS/AR was similar to the findings in the previous study (7), which would be suspected as a result of AAo dilatation. AR patients showed no differences in WSS compared to controls; this WSS normalization could be due to the counterbalance between mildly elevated velocity and dilated AAo diameter. The correlation between peak velocity and regional WSS would

suggest higher WSS along the outer curvature compared to the corresponding inner curvature in locations with eccentric flow. However, regional WSS was generally similar or slightly lower in the outer curvature, except for ASR and AS even in the presence of eccentric flow. ASR and AS patients showed higher WSS in the outer AAo compared to the inner curvature which was consistent with flow displacement to the outer curvature of the aortic plane in the mid and distal AAo. Given elevation in WSS, which is considered as a driver force for AAo dilatation in previous study (10), patients with aortic valve stenosis might demonstrate accelerated AAo dilatation. Reduced WSS, which has association with initiation and progression of atherosclerosis, can accelerate various types of atherogenic change.

Study limitations include small sample size of patients with ASR. This study also did not include patients with aortic valve disease with non-dilated AAo, which may help better understanding of the relation between hemodynamics and AAo dilatation. Male predominance across the patient subgroups and control subject is also a limitation. The incidence of hypertension was similar between patient groups; however, the smoking history was different, which should be considered as a factor to impact AAo dilatation. The accuracy of the assessment of regurgitant fraction in this study suggested underestimation by 4D flow MRI compared to 2D cine PC MRI. Accordingly, 2D cine PC MRI was used for AR assessment instead of 4D flow MRI acquired with prospective ECG gating, which can underestimate the regurgitant volume. Manual setting in post-processing resulted in long analysis time. Nonetheless, low inter-observer variability indicates the utility of our analysis approach to obtain reproducible results. Finally, the design of our cross-sectional retrospective study can be the cause of selection bias and precluded assessment of the influence of AAo hemodynamics on patient's outcome or histological changes.

In conclusion, our results indicate that presence and severity of TAV disease may be associated with deranged AAo hemodynamics and WSS. These findings further the understanding of aortopathy in TAV associated with AS and/or AR. Longitudinal cohort studies integrating 4D flow MRI into surveillance strategies for patients with AAo dilatation are warranted to assess the impact of altered hemodynamics associated with AS and/or AR in TAV with outcomes.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgment:

Grant Support: NIH R01 HL115828, K25 HL119608, AHA 16POST27250158 and KAMIKAWA foundation.

References

1. Kim JB, Spotnitz M, Lindsay ME, et al. Risk of Aortic Dissection in the Moderately Dilated Ascending Aorta. *J Am Coll Cardiol*. 2016;68:1209–19. [PubMed: 27609684]
2. Goldfinger JZ, Halperin JL, Marin ML, Stewart AS, Eagle KA, Fuster V. Thoracic aortic aneurysm and dissection. *J Am Coll Cardiol*. 2014;64:1725–39. [PubMed: 25323262]

3. Pape LA, Tsai TT, Isselbacher EM, et al. Aortic diameter $\geq$ 5.5 cm is not a good predictor of type A aortic dissection: observations from the International Registry of Acute Aortic Dissection (IRAD). *Circulation*. 2007;116:1120–7. [PubMed: 17709637]
4. Wilton E, Jahangiri M. Post-stenotic aortic dilatation. *J Cardiothorac Surg*. 2006;1:7. [PubMed: 16722611]
5. American College of Cardiology/American Heart Association Task Force on Practice G, Society of Cardiovascular A, Society for Cardiovascular A, et al. ACC/AHA 2006 guidelines for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (writing committee to revise the 1998 Guidelines for the Management of Patients With Valvular Heart Disease): developed in collaboration with the Society of Cardiovascular Anesthesiologists: endorsed by the Society for Cardiovascular Angiography and Interventions and the Society of Thoracic Surgeons. *Circulation*. 2006;114:e84–231. [PubMed: 16880336]
6. La Canna G, Ficarra E, Tsagalau E, et al. Progression rate of ascending aortic dilation in patients with normally functioning bicuspid and tricuspid aortic valves. *Am J Cardiol*. 2006;98:249–53. [PubMed: 16828602]
7. Bürk J, Blanke P, Stankovic Z, et al. Evaluation of 3D blood flow patterns and wall shear stress in the normal and dilated thoracic aorta using flow-sensitive 4D CMR. *J Cardiovasc Magn Reson*. 2012;14:84. [PubMed: 23237187]
8. Bissell MM, Hess AT, Biasiolli L, et al. Aortic dilation in bicuspid aortic valve disease: flow pattern is a major contributor and differs with valve fusion type. *Circ Cardiovasc Imaging*. 2013;6:499–507. [PubMed: 23771987]
9. Mahadevia R, Barker AJ, Schnell S, et al. Bicuspid aortic cusp fusion morphology alters aortic three-dimensional outflow patterns, wall shear stress, and expression of aortopathy. *Circulation*. 2014;129:673–82. [PubMed: 24345403]
10. Guzzardi DG, Barker AJ, van Ooij P, et al. Valve-Related Hemodynamics Mediate Human Bicuspid Aortopathy: Insights From Wall Shear Stress Mapping. *J Am Coll Cardiol*. 2015;66:892–900. [PubMed: 26293758]
11. Frydrychowicz A, Stalder AF, Russe MF, et al. Three-dimensional analysis of segmental wall shear stress in the aorta by flow-sensitive four-dimensional-MRI. *J Magn Reson Imaging*. 2009;30:77–84. [PubMed: 19557849]
12. Frydrychowicz A, Berger A, Munoz Del Rio A, et al. Interdependencies of aortic arch secondary flow patterns, geometry, and age analysed by 4-dimensional phase contrast magnetic resonance imaging at 3 Tesla. *Eur Radiol*. 2012;22:1122–30. [PubMed: 22207269]
13. Hope MD, Dyverfeldt P, Acevedo-Bolton G, et al. Post-stenotic dilation: evaluation of ascending aortic dilation with 4D flow MR imaging. *Int J Cardiol*. 2012;156:e40–2. [PubMed: 21907425]
14. Biegging ET, Frydrychowicz A, Wentland A, et al. In vivo three-dimensional MR wall shear stress estimation in ascending aortic dilatation. *J Magn Reson Imaging*. 2011;33:589–97. [PubMed: 21563242]
15. Hiratzka LF, Bakris GL, Beckman JA, et al. 2010 ACCF/AHA/AATS/ACR/ASA/SCA/SCAI/SIR/STS/SVM guidelines for the diagnosis and management of patients with Thoracic Aortic Disease: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines, American Association for Thoracic Surgery, American College of Radiology, American Stroke Association, Society of Cardiovascular Anesthesiologists, Society for Cardiovascular Angiography and Interventions, Society of Interventional Radiology, Society of Thoracic Surgeons, and Society for Vascular Medicine. *Circulation*. 2010;121:e266–369. [PubMed: 20233780]
16. Rose MJ, Jarvis K, Chowdhary V, et al. Efficient method for volumetric assessment of peak blood flow velocity using 4D flow MRI. *J Magn Reson Imaging*. 2016;44:1673–1682. [PubMed: 27192153]
17. Bernstein MA, Zhou XJ, Polzin JA, et al. Concomitant gradient terms in phase contrast MR: analysis and correction. *Magn Reson Med*. 1998;39:300–8. [PubMed: 9469714]
18. Walker PG, Cranney GB, Scheidegger MB, Waseleski G, Pohost GM, Yoganathan AP. Semiautomated method for noise reduction and background phase error correction in MR phase velocity data. *J Magn Reson Imaging*. 1993;3:521–30. [PubMed: 8324312]

19. Markl M, Harloff A, Bley TA, et al. Time-resolved 3D MR velocity mapping at 3T: improved navigator-gated assessment of vascular anatomy and blood flow. *J Magn Reson Imaging*. 2007;25:824–31. [PubMed: 17345635]
20. Potters WV, van Ooij P, Marquering H, vanBavel E, Nederveen AJ. Volumetric arterial wall shear stress calculation based on cine phase contrast MRI. *J Magn Reson Imaging*. 2015;41:505–16. [PubMed: 24436246]
21. van Ooij P, Potters WV, Collins J, et al. Characterization of abnormal wall shear stress using 4D flow MRI in human bicuspid aortopathy. *Ann Biomed Eng*. 2015;43:1385–97. [PubMed: 25118671]
22. van Ooij P, Potters WV, Nederveen AJ, et al. A methodology to detect abnormal relative wall shear stress on the full surface of the thoracic aorta using four-dimensional flow MRI. *Magn Reson Med*. 2015;73:1216–27. [PubMed: 24753241]
23. Bollache E, van Ooij P, Powell A, et al. Comparison of 4D flow and 2D velocity-encoded phase contrast MRI sequences for the evaluation of aortic hemodynamics. *Int J Cardiovasc Imaging*. 2016;32:1529–1541. [PubMed: 27435230]
24. Papaioannou TG, Stefanadis C. Vascular wall shear stress: basic principles and methods. *Hellenic J Cardiol*. 2005;46:9–15. [PubMed: 15807389]
25. von Knobelsdorff-Brenkenhoff F, Karunaharamoorthy A, Trauzeddel RF, et al. Evaluation of Aortic Blood Flow and Wall Shear Stress in Aortic Stenosis and Its Association With Left Ventricular Remodeling. *Circ Cardiovasc Imaging*. 2016;9:e004038. [PubMed: 26917824]
26. Barker AJ, Markl M, Burk J, et al. Bicuspid aortic valve is associated with altered wall shear stress in the ascending aorta. *Circ Cardiovasc Imaging*. 2012;5:457–66. [PubMed: 22730420]
27. Meierhofer C, Schneider EP, Lyko C, et al. Wall shear stress and flow patterns in the ascending aorta in patients with bicuspid aortic valves differ significantly from tricuspid aortic valves: a prospective study. *Eur Heart J Cardiovasc Imaging*. 2013;14:797–804. [PubMed: 23230276]
28. Girdauskas E, Rouman M, Disha K, et al. Correlation between systolic transvalvular flow and proximal aortic wall changes in bicuspid aortic valve stenosis. *Eur J Cardiothorac Surg*. 2014;46:234–9; discussion 239. [PubMed: 24431167]
29. Girdauskas E, Rouman M, Disha K, et al. Functional Aortic Root Parameters and Expression of Aortopathy in Bicuspid Versus Tricuspid Aortic Valve Stenosis. *J Am Coll Cardiol*. 2016;67:1786–96. [PubMed: 27081018]

Figure 1. Patient recruitment

After the recruitment of 91 patients with dilated ascending aorta and with left ventricular ejection fraction $\geq 45\%$, 5 patients were excluded. Finally, remaining 86 patients were selected for this study and divided into four patient groups according to aortic valve disease.

Figure 2. Three-dimensional visualization of systolic blood flow using streamlines

Representative images of non-vortex/helix flow in a control subject (A) and vortex/helix flow in patients with A Ao dilatation (B-G). Vortex (solid arrow) and helix (dashed arrow) grading was as follows: (B) vortex-grade=1 without vortex, (C) vortex-grade=2 with 1 vortex, (D) vortex-grade=3 with 2 or more vortices, (E) helix-grade=1 with flow rotation less than 180° , (F) helix-grade=2 with rotation between 180° and 360° , (G) helix-grade=3 with rotation above 360° .

Figure 3. Analyses of flow velocity, flow eccentricity, and WSS in aorta using 4D flow MRI
 (A) Three-dimensional segmentation of aorta and nine analysis planes for velocity quantification. (B) Schematic of the flow eccentricity analysis. Each analysis plane was divided into quadrants (left) and the velocity was subsequently scored to calculate the overall eccentricity ratio for each patient group (right). (C) Visualization of systolic peak WSS and ten segments used for regional analysis.

Figure 4. Aberrant blood flow patterns in the ascending aorta

Vortex and helix flow were graded using 3-point scale and summed in each patient group.

The bar graph shows mean and SD.

* indicate significant differences ($p < 0.001$).

Figure 5. Systolic peak velocities in the 9 analysis planes distributed along the aorta

The individual numbers represent mean±SD for each plane and patient subgroup (from top to bottom; ASR, AS, AR, no AS/AR, and controls). LCCA: left common carotid artery, LSA: left subclavian artery, TB: brachiocephalic trunk. *, † and ‡ indicate significant elevation compared to AR, no AS/AR and controls ($p < 0.05$, respectively).

Figure 6. Aortic flow eccentricity in the ascending aorta

Each color-coded quadrant represents the percentage of patients with peak velocities greater than 1.0 m/s. For each patient group and anatomical location, eccentricity was investigated by comparing the percentages over the 4 quadrants.

* indicates significant difference in the plane ($p < 0.05$).

Figure 7. Systolic peak WSS in the 10 aortic segments distributed along the aorta
 The individual numbers represent mean±SD for each segment and patient subgroup (from top to bottom; ASR, AS, AR, no AS/AR, and controls). *, † and ‡ indicate significant difference compared to AR, no AS/AR and controls ($p<0.05$, respectively).

Figure 8. SOV (A) and MAA (B) diameter according to vortex and helix grading

*, † and ‡ indicate significant differences ($p < 0.001$, $p < 0.01$ and $p < 0.05$, respectively). SOV: sinus of Valsalva, MAA: mid ascending aorta.

Figure 9. Correlations between systolic peak velocities and WSS in AAo

Correlations are between peak velocity at proximal AAo and WSS in the inner- (A) or outer-proximal AAo (B), as well as between peak velocity at mid AAo and WSS in the inner- (C) or outer-distal AAo (D).

Table 1.

Subjects' demographics and MRI findings

	ASR	AS	AR	no AS/AR	control
Number	9	14	33	30	25
Age (years)	55.7±12.9	63.9±13.7	62.2±14.3	63.4±8.7	57.4±10.4
Gender (M/F)	8/1	14/0	25/8	22/8	19/6
Height (cm)	173.6±12.0	178.7±6.5	174.3±13.6	171.8±12.7	173.2±7.3
Weight (kg)	81.8±11.1	96.1±19.8	83.1±17.9	84.9±20.1	87.5±16.5
Hypertension	8 (89%)	11 (79%)	30 (91%)	25 (83%)	NA
Smoking	3 (33%)	9 (64%)	15 (45%)	10 (33%)	NA
AS severity (severe/moderate)	6/3	8/6	-	-	-
AR severity (severe/moderate)	3/6	-	7/26	-	-
<i>Aortic diameter</i>					
SOV (mm)	39.9±4.3 [†]	41.3±3.1 [†]	44.5±4.3 [†]	42.6±5.4 [†]	34.1±3.3
MAA (mm)	46.8±11.3 [†]	42.5±3.6 [†]	44.0±5.0 [†]	42.4±4.0 [†]	32.8±3.4
Arch (mm)	28.1±1.5	27.4±3.3	28.1±3.1	28.7±3.2*	26.3±2.5
DAo (mm)	25.3±2.1	26.0±2.9*	26.1±5.1*	25.2±2.4	22.7±1.7
<i>Global function</i>					
LVEF (%)	60.8±7.9	63.4±6.5	57.8±6.0	58.7±5.2	58.8±7.4
LVEDVi (ml/m ²)	102.7±43.4* [‡]	78.2±16.4	97.9±33.1 ^{†§}	69.6±22.7	67.1±14.3
LVESVi (ml/m ²)	46.6±39.6	28.0±8.1	42.1±17.7* [‡]	28.7±10.7	27.9±9.4
LVSVi (ml/m ²)	56.1±9.1*	50.2±10.9	55.9±17.5 ^{†§}	40.9±13.0	39.2±7.1
RVEF (%)	59.5±12.6	64.6±7.0	59.3±10.4	57.5±5.6	60.1±8.4
RVEDVi (ml/m ²)	80.8±19.9	69.1±13.2	68.6±16.5	70.4±16.6	63.0±11.6
RVESVi (ml/m ²)	34.0±18.1	25.0±8.2	28.2±11.1	30.0±8.9	25.6±9.8
RVSVi (ml/m ²)	46.9±11.7	44.2±7.1	40.4±10.4	40.3±9.7	37.3±5.8

AR: aortic valve regurgitation, AS: aortic valve stenosis, ASR: aortic valve stenosis and regurgitation, DAo: descending aorta, EDVi: end-diastolic volume index, ESVi: end-systolic volume index, EF: ejection fraction, SVi: stroke volume index, LV: left ventricular, MAA: mid ascending aorta, RV: right ventricular, SOV: sinus of Valsalva. * and [†] indicate significant difference compared to control (p<0.05 and p<0.01). [‡] and [§] indicates significant difference compared to no AS/AR (p<0.05 and p<0.01).