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Four-Dimensional Flow MRI Quantification of Blood Flow in Bicuspid Aortic Valve

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Abstract

Background: Four-Dimensional (4D) flow MRI is limited by time-consuming and non-standardized data analysis. We aimed to test the efficiency and inter-observer reproducibility of a dedicated 4D flow MRI analysis workflow.

Methods: Thirty retrospectively identified patients with bicuspid aortic valve (BAV, age=47.8±11.8years, 9 male) and 30 healthy controls (age=48.8±12.5years, 21 male) underwent Aortic 4D flow MRI using 1.5&3T MRI systems (Siemens, Germany). Two independent readers performed 4D flow analysis on a dedicated workstation (Circle; Calgary, Canada) including pre-processing, aorta segmentation, and placement of four 2D planes throughout the aorta for quantification of net flow, peak velocity, and regurgitant fraction. 3D flow visualization using streamlines was used to grade aortic valve outflow jets and extent of helical flow.

Results: 4D flow analysis workflow time for both observers: 5.0±1.4 minutes per case (range 3–10 minutes). Valve outflow jets and flow derangement was visible in all 30 BAV patients (both observers). Net flow, peak velocity, and regurgitant fraction was significantly elevated in BAV patients compared to controls except for regurgitant fraction in plane 4 (91.1±29.7ml/s versus 62.6±19.6ml/s, 37.1% difference; 121.7±49.7cm/s versus 90.9±26.4cm/s, 28.9% difference; 9.3±10.1% versus 2.0±3.4%, 128.0% difference, respectively; p<0.001). Excellent ICC agreement for net flow: 0.979, peak velocity: 0.931 and regurgitant fraction: 0.928.

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Conclusion: Our study demonstrates the potential of an efficient data analysis workflow to perform standardized 4D flow MRI processing in under 10 minutes and with good-to-excellent reproducibility for flow and velocity quantification in the thoracic aorta.

Keywords

Four-Dimensional; Flow; MRI; Bicuspid Aortic Valve; Reproducibility

Introduction

Four-Dimensional (4D) flow magnetic resonance imaging (MRI) can be employed for the in-vivo measurement of blood flow dynamics with full 4D coverage (3D + time) of the cardiac or vascular region of interest. (1) Studies have demonstrated that 4D flow-derived blood flow visualization and flow quantification can be useful to understand normal (2) and altered aortic hemodynamics in patients with many aortic conditions including aortic dissection (3, 4), aneurysmal disease (5–7), Marfan syndrome (8), congenital heart disease including complex aortic anomalies (9–11), abnormal bicuspid aortic valves (BAV) (12–17) and aortic coarctation (18–21).

Recent studies have demonstrated that 4D flow MRI can visualize BAV-mediated changes on aortic outflow (ascending aorta (AAo) valve flow jets, accompanied by deranged helix flow patterns) and quantify associated changes in flow dynamics (net flow, peak velocity, regurgitant fraction) (22–24). However, one of the main challenges to the efficient application of 4D flow MRI is related to cumbersome and thus often time-consuming and non-standardized data analysis. Some progress has been made on the automation, efficiency, and standardization of 4D flow MRI, including automatic plane reconstruction in a short time (5–10 minutes) (1), semi-automation of plane placement in the thoracic aorta (24), and fully automated atlas-based segmentation and time frame registration (25). However, these studies are limited by their sample size (n=6 healthy volunteers (1), n=10 patients with heart failure (25)) and by their analysis efficiency (40.1 minutes per case) (24).

The purpose of this study was to test the efficiency and inter-observer reproducibility of a dedicated analysis workflow that includes data pre-processing, aortic segmentation and centerline detection, 3D flow visualization, and regional flow quantification in a cohort of 60 subjects (30 BAV patients and 30 healthy controls).

Materials and Methods

Study Cohort

Thirty BAV patients (age = 47.8 ± 11.8 years, 30% female) and 30 age-matched healthy controls (age = 48.8 ± 12.5 years, 70% female) with no history of cardiovascular disease and a normal functional tricuspid aortic valve were enrolled in the study. Patients had a clinically indicated MRI as part of routine surveillance for aortic dilatation and/or aortic valve disease and were enrolled in this study via retrospective chart review and waiver of consent. Healthy controls were prospectively recruited to undergo a research cardiovascular MRI including 4D flow. Written informed consent was obtained from all controls. Prospective enrollment

was only performed for volunteers (as per IRB approval) which included sufficient scan time for 4D flow. All subjects were included in the study according to procedures approved by the University Institutional Review Board. Patient and control demographics are summarized in Table 1.

MR Imaging

All MRI exams were performed using 1.5T and 3T MRI systems (Aera, Avanto and Skyra; Siemens Healthineers, Germany). All subjects underwent a standard-of-care thoracic cardiovascular MRI exam including 4D flow MRI of the thoracic aorta. All 30 BAV patients underwent a post-contrast enhanced 4D flow scan after a clinically indicated cardiac MRI, whereas controls underwent a similar scan protocol without contrast. The 4D flow scans were included after clinically indicated cardiac MRI scans for evaluation of left ventricular global function. At a minimum this consisted of: 1) sagittal, coronal, and transverse scout images for localizing the anatomy, 2) 2D phase contrast imaging on planes at, above, and below the aortic valve, 3) short axis cine imaging for left ventricular function assessment, 4) MR angiogram, and 5) 4D flow MRI.

Short axis cine images were acquired as 10 slices in separate end-inspiratory breath holds with spatial resolution = $1.4\text{--}2.2 \times 1.4\text{--}2.2 \times 6.0\text{--}8.0$ mm, space between slices = $10.0\text{--}13.4$ mm, slice thickness = $2.4\text{--}3.8$ mm, temporal resolution = $27.1\text{--}35.5$ ms, flip angle = $55\text{--}76^\circ$, TE/TR = $1.16\text{--}1.18/2.66\text{--}2.78$ ms. Patients received a contrast-enhanced MR angiogram with spatial resolution $1.0\text{--}1.2 \times 1.0\text{--}1.2 \times 1.4\text{--}1.6$ mm and field of view with coverage of the entire thoracic aorta. 4D flow MRI (time-resolved three-directional phase contrast MRI with three-directional velocity encoding) was acquired in a sagittal oblique 3D volume covering the thoracic aorta during free breathing using prospective ECG gating and navigator respiration control. The mean duration of the 4D flow sequences was 12.3 minutes overall (12.8 minutes for BAV patients and 11.8 minutes for healthy controls). Pulse sequence parameters were as follows: spatial resolution = $2.1\text{--}3.1 \text{ mm} \times 2.1\text{--}3.1 \text{ mm} \times 2.4\text{--}3.8$ mm, temporal resolution = $36.8\text{--}39.2$ ms, encoding velocity (venc) = $150\text{--}250$ cm/s, flip angle = $7^\circ\text{--}15^\circ$, TE/TR = $2.3\text{--}2.5/4.6\text{--}4.9$ ms. Control subjects did not receive contrast and received a trueFISP (balanced SSFP) scan with spatial resolution $1.0 \times 1.0 \times 6.0\text{--}2.2 \times 2.2 \times 8.0$ mm³, FOV = $243 \times 276 \times 150\text{--}420 \times 420 \times 170$ mm³, temporal resolution = $27.1\text{--}40.6$ ms (25–40 cardiac time points), TE/TR = $1.07\text{--}1.16/2.1\text{--}3.1$ ms, and flip angle = $30^\circ\text{--}75^\circ$.

Data Analysis

Data analysis was performed on a software prototype (Circle Cardiovascular Imaging, Calgary, Canada). For all 60 subjects, two independent observers (with 1 (**) and 2 (**) years of experience with 4D flow analysis) conducted aortic 4D flow analysis based on a 5-step analysis workflow (Figure 1): 1) Pre-processing, 2) Segmentation, 3) Aortic centerline generation, 4) Flow visualization and 5) Flow quantification.

Pre-processing involved noise masking, corrections for eddy current induced phase offset errors and velocity aliasing (25, 26). Thresholding and 3D segmentation of the aorta is based on an automatically derived 3D phase contrast (PC)-MR angiogram. Creation of an aortic centerline using a semi-automated centerline tracing tool is used to help place 2D analysis

planes. 3D flow visualization using 3D streamlines and velocity maximum intensity projections (MIP) is used for flow grading. 3D blood flow visualization using streamlines at peak systole was used to grade the presence of valve flow jets which persisted after the original velocity threshold was increased. The extent of AAo helical flow was also assessed using a 3-point scale (trivial $< 360^\circ$ rotation; $360^\circ < \text{moderate} < 720^\circ$ rotation; severe $> 720^\circ$ rotation). Quantification of net flow, peak velocity, and regurgitation fraction was analyzed in four 2D planes at defined anatomic locations (level of AAo peak velocity identified in peak velocity MIP, mid AAo, aortic arch, descending aorta (DAo)).

Timing of the analysis workflow for each case began when the data was loaded into the 4D flow analysis program and ended once all 4 analysis planes were placed and the flow visualization and grading was performed. The total analysis time (5-step analysis protocol + flow pattern grading) was independently recorded for each case and each observer.

To mitigate bias in inter-observer variability, the 5-step analysis protocol was practiced on a subset of separate aortic 4D flow cases ($n=10$) by both observers to standardize the placement of the 4 analysis planes and flow visualization grading.

Statistical analysis

Continuous variables are reported as mean $\pm$ standard deviation. A Shapiro-Wilk test was used to test for statistical normality. Levene's test was used to test for homogeneity of variance. Statistical significance between BAV patient and healthy control demographics and hemodynamics was calculated using unpaired two-tailed t-tests for normally distributed data and using unpaired Mann-Whitney tests for data that did not have normal distribution. Agreement between observers was assessed using intraclass correlation coefficient (ICC) and 95% confidence intervals (CI) based on absolute-agreement, two-way mixed-effects models and Bland-Altman analysis (27) to determine limits of agreement (LOA) and bias for net flow, peak velocity, and regurgitant fraction in all four analysis planes (LOA; % difference ± 1.96 SD). A 5% threshold was applied to regurgitant fraction Bland Altman analysis because regurgitant values less than 5% can reasonably be considered not clinically significant. P-values < 0.05 were considered statistically significant.

Results

Study Cohort

As summarized in Table 1, heart rate was significantly different between BAV patients (73.3 ± 13.1 bpm) compared to healthy controls (66.6 ± 8.4 bpm, $p = 0.04$). BAV patients were age matched to healthy controls but there were significantly more males in the BAV patient cohort (70% male, $p < 0.001$) than the healthy control cohort (30% male).

Analysis Time

The time needed to complete the 5-step 4D flow data analysis workflow was 5.0 ± 1.4 minutes (average over both observers and all 60 subjects). Total analysis time was significantly different between observers (observer 1 average= 4.3 ± 1.1 min, range=3–7 min; observer 2 average= 5.6 ± 1.4 min, range= 3–10 min; $p < 0.001$) but remained < 10 minutes

(range 3–10 minutes). Analysis time comparing BAV patients to controls was significantly different for both observers (observer 1 BAV patients (average=5.0±0.8 min, range=3–7 min) vs. controls (average=3.7±1.0 min, range=3–7 min) $p<0.001$; observer 2 BAV patients (average=6.1±1.3 min, range=4–8 min) vs. controls (average=5.0±1.3 min, range=3–10 min) $p=0.002$).

Flow Grading

Examples of 3D blood flow visualization for a BAV patient and a healthy control by both observers are shown in Figure 2. Compared to healthy controls, BAV patients presented with marked aortic valve outflow jets impinging on the outer AAo curvature accompanied by adjacent helical flow patterns, successfully reproduced by both observers. Flow pattern grading (Table 2) revealed clearly visible valve outflow jets in all 30 BAV patients and moderate to severe flow derangement (helical flow) in all 30 BAV patients (100% for both observers).

Blood Flow Quantification

Results of regional blood flow quantification for both observers (net flow, peak velocity and regurgitant fraction) are summarized in Figure 3. Both observers found that net flow, peak velocity, and regurgitant fraction was significantly elevated for BAV patients compared to controls ($p < 0.05$ for all planes and both observers (except plane 4 for regurgitant fraction)). In addition, ICC demonstrated excellent inter-observer agreement for all flow metrics (net flow: 0.979 [95% CI: 0.972–0.984], peak velocity: 0.931 [95% CI: 0.912–0.946] and regurgitant fraction: 0.928 [95% CI: 0.906–0.945]). Finally, Bland-Altman analysis (Figure 4.A–C) revealed excellent inter-observer reproducibility for aorta net flow and peak velocities with minimal bias for all metrics (net flow: –1.7ml/s; peak velocity: 1.0cm/s; regurgitant fraction: –1.4%) and good to moderate limits of agreement (increased LOA for regurgitant fraction).

Discussion

Our study demonstrates the potential of an efficient data analysis workflow to perform standardized 4D flow MRI processing in under 10 minutes, and with good-to-excellent reproducibility for flow and velocity quantification. Previous studies employed similar data analysis workflow methods or full automation to perform the analysis (1, 28, 29). However, these studies had a limited cohort size which impedes on the generalization of analysis times, and reduced efficiency (longer analysis times). For example, in a retrospective study of 20 patients with congenitally altered aortic valve, Schnell et al. reported an average analysis time of 40.1 minutes. There were additional studies that were also limited by sample size ($n=6$ healthy volunteers (1), $n=10$ patients with heart failure (25)).

A 4D flow analysis protocol was developed by both observers to promote the standardization and efficiency of the workflow. Practicing pre-processing, aortic plane placement, and vessel contouring based on anatomic landmarks and time points during the cardiac cycle on 10 cases was important to the reproducibility of the results.

BAV patients demonstrated significantly elevated net flow, peak velocity and regurgitation fraction compared to the control group for both observers throughout most planes. BAV patients also demonstrated marked aortic valve outflow jets accompanied by moderate to severe aortic flow derangement. Only three of the BAV patients (zero controls) were scanned at 3 T. Both observers indicated that the three BAV patients scanned at 3T were of similar image quality to the rest of the 1.5 T cases. Imaging at 3T will provide improved signal to noise ratio (SNR) and thus improved image quality but possibly also increased susceptibility and field homogeneity artifacts. Perhaps the reason why the observers did not indicate SNR differences between the 1.5 T and 3 T cases was because of how few cases there were at 3 T. Other studies demonstrated that greater flow derangements contributed to aortic dilation leading to aneurysm development. These flow derangements were found to normalize after aortic valve replacement surgery (13, 15, 17, 19). Statistically significant net flow differences ($p < 0.05$) between males and females in the BAV cohort may explain why elevated net flow values in the BAV patient cohort were observed (male vs. female net flow (ml/s) $\pm$ standard deviation for all four planes: 92.7 ± 29.9 vs 64.3 ± 12.6 , $p < 0.001$; 91.8 ± 20.7 vs 68.5 ± 14.5 , $p = 0.002$; 74.9 ± 15.2 vs 58.5 ± 15.2 , $p = 0.02$; 63.7 ± 13.4 vs 49.7 ± 10.3 , $p = 0.005$) Wheatley et al. found significantly increased cardiac index for a group of 30 males compared to 30 females at rest which could explain our observed differences in net flow in the predominantly male patient group compared to the control group (30).

Limitations

A limitation of this study is a focus on standard regional flow quantification in the aorta. Other hemodynamic parameters such as wall shear stress, pulse-wave velocity or pressure gradients which are frequently analyzed in 4D flow MRI studies were not tested, nor was 4D flow evaluation applied to pulmonary arteries or veins. Future studies are warranted to test the inclusion of these advanced hemodynamic metrics in a similarly efficient and standardized manner. Because BAV disease affects males predominantly, matching BAV patients and healthy controls based on age limited our gender matching capabilities (31). This limitation could restrict our understanding of gender differences in terms of BAV disease. Another limitation of this study was no comparison to other software solutions. Future studies should employ a similar workflow on multiple software solutions to validate findings. Finally, the absence of image quality assessment on results was a limitation of this study. For example, no comparison between gadolinium-based contrast-enhanced MRIs and non-contrast scans were assessed. Additionally, there was no scan-rescan reproducibility test for this study. However, various other scan-rescan studies have shown 4D flow MRI to be reproducible for flow and peak velocity measurements (32, 33). Four-dimensional flow observer training was also not rigorously tested before 4D flow analysis. The difference in processing times between observers may be attributed to differing levels of experience with the post-processing tool. These factors could limit the degree of reproducibility of our results compared to other groups doing similar reproducibility testing.

Conclusion

The findings of this study suggest that a standardized 4D flow MRI analysis workflow can efficiently assess aortic hemodynamics in less than 10 minutes and identify BAV patients compared to a control cohort.

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Figure 1:

5-step 4D flow Data analysis workflow 1) Pre-processing with noise masking, corrections for eddy current induced phase offset errors and velocity aliasing; 2) thresholding and 3D segmentation of the aorta based on an automatically derived 3D PC-MR angiogram; 3) creation of an aortic centerline; 4) 3D flow visualization using 3D streamlines and velocity maximum intensity projections (MIP); and 5) quantification of net flow, peak velocity, and regurgitation fraction in 4 analysis planes at defined anatomic locations (level of AAO peak velocity identified in peak velocity MIP, mid AAO, aortic arch, descending aorta).

Figure 2:
3D blood flow visualization based on systolic 3D streamlines with a velocity threshold of 0–1.6m/s for a patient with BAV (A,B) and a healthy control (C,D) analyzed by both observers (observer 1: A,C; observer 2: B,D). BAV mediated marked valve outflow jets and helical flow in the AAo can be clearly identified for the patient for both observers (red arrows in A,B). No valve outflow jets or helical flow can be identified for the control for both observers (C,D). Images were compared during the same systolic cardiac phase.

Figure 3:

Differences in BAV patients vs. controls for net flow, peak velocity, and regurgitant fraction for both observers. Both observers found that net flow, peak velocity, and regurgitant fraction was significantly elevated ($p < 0.05$ for all planes and both observers (except plane 4 for regurgitant fraction)). Error bars indicate standard error.

Figure 4:

Bland-Altman analysis (A-C) of inter-observer variability for the quantification of aortic net flow, systolic peak velocity, and regurgitant fraction. Bland-Altman analysis present data from all 60 subjects and all 4 analysis planes i.e. 240 data points for all analyses (except for the regurgitant fraction Bland-Altman analysis which contains 80 data points due to the 5% threshold).

Table 1:

Demographics

Demographics	BAV Patients	Healthy Controls	p-value
Age (years)	47.8 ± 11.8	48.8 ± 12.5	0.66
Male (N)	21	9	0.001
Female (N)	9	21	0.001
Height (cm)	176.8 ± 8.1	168.7 ± 8.1	<0.001
Weight (lbs)	83.8 ± 14.8	79.8 ± 20.7	0.33
BMI (kg/m ²)	26.8 ± 4.6	28.1 ± 7.0	0.40
Heart rate (bpm)	73.3 ± 13.1	66.6 ± 8.4	0.04
Systolic blood pressure (mmHg)	122.0 ± 15.1	129.5 ± 20.9	0.14
Diastolic blood pressure (mmHg)	77.0 ± 10.2	78.4 ± 11.6	0.56

Cohort of 30 bicuspid aortic valve (BAV) patients and 30 healthy controls used by both observers to analyze 4D flow.

Table 2:

Flow Pattern Grading

BAV Patients		
Flow Pattern Grading	Observer 1	Observer 2
Trivial helical flow	n=0	n=0
Moderate helical flow	n=3	n=12
Severe helical flow	n=27	n=18
Aortic valve flow jets	n=30	n=30
Healthy Controls		
Flow Pattern Grading	Observer 1	Observer 2
Trivial helical flow	n=27	n=29
Moderate helical flow	n=3	n=1
Severe helical flow	n=0	n=0
Aortic valve flow jets	n=2	n=2

Cohort of 30 bicuspid aortic valve (BAV) patients and 30 healthy controls; trivial < 360° rotation of blood flow; 360° < moderate < 720° rotation; Severe > 720° rotation.