Bicuspid Valve Morphology Determines the Position of Elevated Velocity and WSS: 4D Flow MRI in 202 Subjects

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Introduction: Bicuspid aortic valve (BAV) disease occurs in 1-2% of all newborns and is associated with elevated incidence of aortopathy such as dissection, dilation, and aneurysm formation. In particular, BAV subjects are known to express two dominant patterns of aortic dilation, that is: a 'type 1' pattern in which the dilation involves the root and proximal portion of the tubular ascending aorta (AAo); or a 'type 2' in which the distal AAo and arch are dilated[2]. Acknowledging the possibility for intrinsic tissue abnormalities in the BAV aorta, there is also recent evidence that aortopathy may be related to hemodynamic changes (i.e. outflow patterns and wall shear stress [WSS]) due to the orientation of the valve leaflets[3]. Specifically, recent studies showed that different BAV valve morphologies (RL and RN fusion patterns) resulted in significantly altered systolic aortic outflow patterns and WSS[4,5,6]. Moreover, hemodynamic changes were associated with expression of BAV aortopathy suggesting a physiologic mechanism by which BAV morphology can influence expression of aortopathy[4,5,6]. However, these studies have been limited to small subject numbers and regional WSS analysis in individual analysis planes. In order to improve on these limitations, this study uses a volumetric technique to investigate the valve morphology and hemodynamic hypothesis in a cohort of 202 4D flow MRI exams.

Table 1. Subject demographics

BAV type	Number of subjects	Age (years)	SOV (cm)	MAA (cm)
Sievers0 AP	27M, 6W	40±13	4.0±0.6	3.7±0.8
Sievers0 LAT	6M, 10W	39±9	3.9±0.6	3.9±0.7
Sievers1 RL	65M, 21W	42±13	3.9±0.5	3.8±0.7
Sievers1 RN	3M, 2W	42±7	4.0±0.3	3.8±0.5
Controls	42M, 20W	44±12	N/A	N/A

AP=Anterior-Posterior, LAT=Lateral, RL=Right-Left, RN=Right-Non-coronary, M=Man, W=Woman, SOV=Sinus of Valsalva diameter, MAA = Mid-Ascending Aorta diameter, N/A=Not Applicable

Methods: ECG and respiratory navigator gated 4D flow MRI exams were performed in 140 BAV patients and 62 healthy controls on 1.5 and 3T MAGNETOM Avanto, Espree, Aera and Skyra MRI systems (Siemens Healthcare, Erlangen, Germany). The BAV morphology was assessed on balanced steady state free precession images at the level of the valve and classified according to the Sievers scheme, with Sievers type 0 AP and LAT indicating BAV with no raphe, and opening in anterior-posterior and lateral direction, respectively. Sievers type 1 RL and RN indicate BAV with a raphe, with fusion of the right-left coronary valve (and opening in AP direction) and fusion of the right-non-coronary valve (and opening in LAT direction), respectively. Spatial resolution was 1.7-3.6x1.8–2.4x2.2–3.0 mm^3; temporal resolution was 37–42 ms resulting in 14 to 25 time frames; TE/TR/FA was 2.2-2.8 ms/4.6-5.3 ms/7-15^0 and the VENC was 1.5–4.5 m/s. All 4D flow MRI data were corrected for eddy currents, Maxwell terms, and velocity aliasing using in-house built software in Matlab (Natick, The Mathworks, USA)[7]. 3D Phase contrast (PC) magnetic resonance angiography (MRA) images were created by voxel-wise multiplication of the magnitude data with absolute velocities averaged over all cardiac time frames[7]. The thoracic aorta was semi-automatically segmented using a commercial software package (Mimics, Materialise, Leuven, Belgium). The time frame with the maximum average absolute velocity in the segmentation was defined as peak systole. Peak velocity was assessed in a velocity Maximum Intensity Projection (MIP) to determine that all subjects had no stenosis (peak velocity <2m/s). Sinus of Valsalva (SOV) and mid-ascending aortic (MAA) diameters were measured from contrast-enhanced MRA data. For comparison with the BAV patients, three age-categorized cohort-averaged velocity and WSS maps were created of the control data (19-40 years old, n=24; 41-50 years old, n=19; 51-78 years old, n=19). Two methods were used to determine the difference in peak systolic aortic velocity and WSS between different BAV morphology configurations: 1) cohort-averaged velocity and WSS maps using a previously published methodology[8], and 2) *P*-value maps[8] delineating significantly higher or lower velocity and WSS (Wilcoxon rank sum test, $P<0.05$ was considered significant) for all patient cohorts, as compared to the healthy age-matched control groups.

Results: Subject demographics and aortic diameters are given in table 1. In Fig 1 it can be seen that results were very similar for valves opening in AP direction (Sievers 0 AP and Sievers 1 RL) and for valves opening in LAT direction (Sievers 0 LAT and Siever 1 RN). Fig 1b shows that the average outflow jet for Sievers 0 AP and Sievers 1 RL subjects is directed more towards the anterior part of the proximal aorta, whereas for Sievers 0 LAT and Sievers 1 RN, the outflow jet is directed more towards the posterior part of the proximal aorta and impinges on the outer curvature of the aorta at a more distal location. Accordingly, the velocity *P*-value maps in Fig 1c for Sievers 0 AP and Sievers 1 RL show a larger volume of significantly higher velocity in the proximal and anterior aorta than Sievers 0 LAT and Sievers 1 RN. Note the blue regions of significantly decreased velocity compared to controls, which indicate the core of helical flow found in all BAV types[9]. As a consequence of the velocity differences, the highest WSS for Sievers 0 AP and Sievers 1 RL is found at the level of the right pulmonary artery, whereas for Sievers 0 LAT and Sievers 1 RN, the highest WSS is found more distally (Fig 1c). For the *P*-value WSS maps in Fig 1d, significantly lower WSS than controls on the aortic root can be distinguished on the Sievers 0 LAT map and the Sievers 1 RN map, whereas the proximal aorta of the Sievers 0 AP map and the Sievers 1 RL map shows significantly elevated WSS compared to controls.

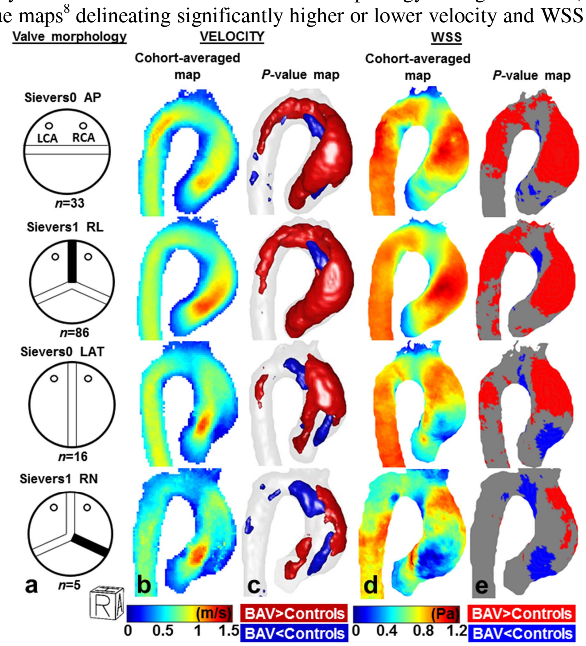

Fig 1. a) Schematic of the BAV valve types under investigation. LCA and RCA indicate the left and right coronary artery. Thick lines indicate raphes. b) Cohort-averaged velocity maps. c) P-value maps for velocity. d) Cohort-averaged WSS maps. d) P-value maps for WSS

Discussion/Conclusion: The cohort-averaged and *P*-value maps revealed important differences in aortic velocity and WSS for AP- and LAT-opening BAV patients. The difference in outflow patterns leads to higher WSS on the proximal aorta for Sievers 0 AP and Sievers 1 RL and higher WSS on the distal aorta for Sievers 0 LAT and Sievers 1 RN classified valves. It is intriguing that these WSS differences match with the reported differences in aortic dilation expression for the different BAV-fusion patterns[2]. Larger studies with longer patient follow-up (for detection of aortic growth) are necessary to evaluate the influence of outflow patterns and WSS expression on the pattern of aortic dilation.

References: [1]Hahn et al. *JACC* 1992 [2]Kang et al. *JACC Cardiovasc Imaging* 2013 [3]Verma et al. *N Engl J Med* 2014 [4]Barker et al. *Circ Cardiovasc Imaging* 2012, [5]Mahadevia et al. *Circulation* 2014 [6]Bissell et al. *Circ Cardiovasc Imaging* 2013 [7]Bock et al. ISMRM 2007 [8]van Ooij et al. *Magn Res Med* 2014 [9]Entezari et al. *J Magn Reson Imaging* 2013. **Acknowledgement:** AHA grant 14POST20460151; NIH grant K25HL119608; NIH grant R01HL115828;