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Aortic stenosis exacerbates flow aberrations related to the bicuspid aortic valve fusion pattern and the aortopathy phenotype

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Abstract

OBJECTIVES: A bicuspid aortic valve (BAV) is characterized by variable phenotypic manifestations, as well as longitudinal evolution of valve dysfunction and ascending aorta dilatation. The present study investigated the impact of severe aortic stenosis (AS) on the flow patterns and wall shear stress (WSS) distribution in BAV patients with right-left (RL) and right-non-coronary (RN) cusp fusion types, and the study aimed to reveal whether aortic dysfunction could further alter intrinsic aortic haemodynamic aberrations generated by abnormal BAV cusp fusion patterns.

METHODS: Four-dimensional flow magnetic resonance imaging was performed in 120 BAV subjects and 20 tricuspid aortic valve controls. BAV patients were evenly categorized into 4 cohorts, including RL and RN BAV with no more than mild aortic dysfunction as well as RL and RN BAV-AS with isolated severe AS.

[†]The first two authors contributed equally to this study.

RESULTS: BAV subjects exhibited eccentric outflow jets resulting in regional WSS elevation at the right-anterior position of the ascending aorta in the RL group and the right-posterior location in the RN group ($P < 0.005$). The presence of severe AS resulted in accelerated outflow jets and more prominent flow and WSS eccentricity ($P < 0.005$) by marked helical ($P = 0.014$) and vortical flow formation ($P < 0.005$), as well as increased prevalence of tubular and transverse arch dilatation. The changes to the flow jet in BAV-AS subjects blurred the differences in peak flow velocity and WSS distribution between RL and RN BAV. Differences in the phenotypes of aortopathy were associated with changes in functional haemodynamic parameters such as flow displacement and WSS eccentricity.

CONCLUSIONS: Severe AS markedly exacerbated aortic flow aberrations in BAV patients and masked the existing distinct flow features deriving from RL and RN fusion types. Longitudinal studies are needed to investigate the evolution of ascending aortic dilatation relative to the interaction between intrinsic cusp fusion types and acquired severe valve dysfunction.

Keywords: Bicuspid aortic valve • 4-dimensional flow magnetic resonance imaging • Aortic stenosis • Aortopathy

INTRODUCTION

As the most prevalent congenital heart defect affecting 1–2% of the general population, bicuspid aortic valve (BAV) is known for its heterogeneous phenotypic manifestations, including cusp fusion morphology, aortic valve dysfunction and aortic dilatation [1]. The combination of these features, as well as the longitudinal evolution of BAV valve dysfunction and ascending aortic dilatation, has conferred considerable difficulties for the investigation surrounding the underlying cause of BAV aortopathy. Emerging evidence has advocated an active role of valve-mediated haemodynamic forces, instead of genetic predisposition alone, as an important contributing factor for the progression of BAV aortopathy [2–4]. However, the current guidelines for prophylactic aortic intervention in BAV subjects are based on simple and empirical parameters such as aortic diameter and growth rate. Moreover, these cut-off values for the factors have varied substantially between conservative and aggressive strategies in recent years [5], indicating the need for additional haemodynamic metrics for patient armament.

The advent of 4-dimensional (4D) flow magnetic resonance imaging (MRI), a novel non-invasive imaging modality for *in vivo* assessment of time-resolved 3-dimensional (3D) blood flow patterns, provides an opportunity to discover and validate haemodynamic markers, to unveil rheological heterogeneity within the BAV ascending aorta and to integrate haemodynamic measures into novel risk stratification and treatment models. Previous 4D flow MRI studies have discovered that BAV cusp morphology [e.g. right-left (RL) and right-non-coronary (RN) cusp fusion] can affect the manifestation of aortopathy in the absence of aortic dysfunction via aortic haemodynamic changes [6]. A large proportion of BAV subjects will develop aortic stenosis (AS) of different extents and at different ages in their lifespan [7]. We hypothesized that such aortic dysfunction could further alter intrinsic aortic haemodynamic aberrations generated by different BAV cusp fusion patterns, and we investigated the correlation between quantitative measurements of poststenotic flow characteristics and different phenotypes of BAV aortopathy.

METHODS

Study population

BAV patients diagnosed by transthoracic echocardiography at our institution from December 2014 to June 2017 were recruited and consecutively referred for clinical cardiac MRI assessment for aortic dimensions and flow characteristics. Patients with complex

congenital cardiac defects, infective endocarditis, acute aortic dissection and previous cardiac surgery were excluded. The study cohort consisted of 120 BAV patients evenly categorized into 4 groups according to their aortic valve cusp fusion type [8] and function as follows: RL (RL BAV group, $n = 30$) and right-non-cusp fusion BAV (RN BAV group, $n = 30$) patients with no more than mild AS or insufficiency; RL (RL BAV-AS group, $n = 30$) and RN BAV (RN BAV-AS group, $n = 30$) patients with isolated severe AS. Severe AS was defined as mean transaortic pressure gradient above 40 mmHg or aortic valve area $< 1.0 \text{ cm}^2$. Aortic size-matched tricuspid aortic valve (TAV) volunteers with no more than mild AS or insufficiency were included as controls (TAV group, $n = 20$). The present study conformed to the Declaration of Helsinki and was approved by the Ethics Committee of the Zhongshan Hospital Fudan University, Shanghai, China. Informed consent was obtained from all participants.

Magnetic resonance imaging

All subjects underwent cardiac MRI on a commercially available 3.0 Tesla system (Verio, Siemens Medical Systems, Erlangen, Germany). Dilatation of aortic segments was defined as diameter $> 40 \text{ mm}$ [9]. The phenotypes of BAV aortopathy were defined as follows: type 0, normal aorta; type 1, dilated only at the aortic root; type 2, aortic enlargement involving the tubular portion of the ascending aorta; type 3, diffuse involvement of both the entire ascending aorta and the transverse aortic arch [10].

For assessment of aortic haemodynamics, 4D flow MRI data were acquired during free breathing using respiratory and prospective electrocardiogram (ECG) gating in a sagittal oblique 3D volume covering the entire thoracic aorta. Imaging parameters and measurement planes (Fig. 1) were selected as reported previously [11]. Flow data were processed in concordance with current consensus recommendations [12]. Flow helix and vortex were semi-quantitatively evaluated in the ascending aorta using 3D particle traces and streamlines at flow systole (Supplementary Material, Appendix S1). Visualization of outflow asymmetry was created by mapping the peak systolic velocity location and the region of the upper 15th percentile of the velocities on a segmental aortic lumen map. Flow displacement was defined as the distance between vessel centroid and forward velocity-weighted centroid. Systolic wall shear stress (WSS) was calculated along the vessel lumen circumference in 8 anatomic positions (A, anterior; LA, left anterior; L, left; LP, left posterior; P, posterior; RP, right posterior; R, right; and RA, right anterior) and was averaged over the proceeding and 4 subsequent time steps after the peak systolic flow. Average systolic WSS and standard deviation (WSS-SD_{8p}) to assess WSS eccentricity were calculated across all 8 positions.

Figure 1: Representative images of the 3-dimensional streamline visualization of peak systolic flow in the thoracic aorta of an aorta size-matched TAV volunteer (**A**) and BAV subjects (**B–E**). AAo: ascending aorta; AS: aortic stenosis; BAV: bicuspid aortic valve; RL: right-left; RN: right-non-coronary; TAV: tricuspid aortic valve.

Statistical analysis

Data were reported as mean $\pm$ SD or medians (interquartile ranges) for continuous variables and as frequencies (percentages) for categorical variables. The Shapiro–Wilk test was used to evaluate the normal distribution of continuous parameters. The differences among the 5 groups were assessed by one-way ANOVA (Gaussian distribution) or Kruskal–Wallis H analysis (non-Gaussian distribution). If the parameter was significantly different between groups ($P < 0.05$), multiple comparisons were analysed using the Student's t -test (Gaussian distribution) or the Mann–Whitney U -test (non-Gaussian distribution). Differences in percentages were evaluated using the χ^2 test when no cell had an expected value < 1 and no more than 20% of the cells had expected values of < 5 ; otherwise, we used the Fisher's exact test. Statistical significance was defined as 2-sided $P < 0.05$. When multiple pairwise comparisons were performed between 4 study groups and 1 control group, the level of statistical significance was adjusted using the Bonferroni correction. An analysis was performed with SPSS 15.0 software (Chicago, IL, USA).

RESULTS

Study cohort

The demographics of all subjects are summarized in Table 1. Aortic valve features in non-stenotic BAV patients (RL and RN BAV groups) were similar to the TAV control group, while BAV patients with severe AS had markedly higher peak aortic transvalvular velocity and mean gradient (both $P < 0.001$), reflecting a marked reduction in the aortic valve area. BAV patients with severe AS were older than their non-stenotic counterparts (RL BAV versus RL BAV-AS: $P < 0.001$; RN BAV versus RN BAV-AS: $P = 0.001$).

BAV patients with a dilated ascending aorta, including type 2 and type 3 aortopathy, increased from 56.7% (34/60) in non-stenotic BAV patients to 65.0% (39/60) in stenotic subjects. The diffuse involvement of both the ascending aorta and the transverse aortic arch (type 3) was more prevalent in patients with the RN fusion type than their RL counterparts with severe AS [63.2% (12/19) vs 25.0% (5/20), $P = 0.016$] or without AS [58.8% (10/17) vs 17.6% (3/17), $P = 0.013$].

Three-dimensional blood flow visualization and interpretation

Figure 1 shows representative images of 4D flow-derived systolic 3D blood flow streamlines in the thoracic aorta. In contrast to cohesive streamlines parallel to the vessel wall of the ascending aorta found in TAV controls, the aortic outflow patterns in BAV subjects were altered to demonstrate the eccentric outflow jet impinging at the right-anterior position of the ascending aorta in RL fusion morphology and at the right-posterior position in the RN fusion type. Severe AS further accelerated the outflow jets and led to more prominent flow eccentricity and complexity.

Grading of helical and vortical flow and mapping of peak systolic velocity locations were utilized to interpret the distinct differences in flow characteristics between valve morphologies and function. For non-stenotic BAV patients, helical flow scores were significantly higher for the RL fusion type compared to the TAV control group (Fig. 2, $P = 0.002$), whereas RN BAV patients presented with increased vortical flow scores (Fig. 2, $P = 0.027$). RL BAV patients exhibited peak systolic flow jet along the right-anterior wall at the proximal ascending aorta towards the left anterior wall at the supra-aortic level, whereas RN BAV patients demonstrated localized outflow jet from the right-posterior wall of the proximal ascending aorta (Fig. 3). On the other hand, severe AS introduced pronounced helical (RL BAV versus RL BAV-AS: $P = 0.014$) and vortical flow formations (RL BAV versus RL BAV-AS: $P = 0.001$) in BAV patients, especially for patients with the RN fusion pattern (Fig. 2, helical flow: $P < 0.001$; vortical flow: $P = 0.003$) and altered the flow jet direction towards the right-anterior wall at the mid-ascending aorta in RN BAV-AS patients. Notably, differences in peak flow velocity distributions between RL and RN BAV patients at the level of the mid-ascending aorta were no longer evident for patients with severe AS (Fig. 3). Flow displacement measurements also demonstrated marked eccentricity in BAV patients compared with TAV controls, which was even more prominent in BAV subjects with severe AS (Table 2).

Ascending aortic wall shear stress

In comparison with the TAV control group, average systolic WSS and WSS eccentricity parameter WSS-SD_{8p} were found to be elevated in all 4 BAV groups at 3 analysis planes along the ascending

Table 1: Demographic and clinical characteristics

	Control	Study group				P-value
	TAV (n = 20)	RL BAV (n = 30)	RN BAV (n = 30)	RL BAV-AS (n = 30)	RN BAV-AS (n = 30)	
Gender (male/female)	13/7	21/9	17/13	19/11	18/12	0.862
Age (years)	54 ± 10	49 ± 11	50 ± 10	59 ± 7 ^a	56 ± 8 ^a	<0.001
Body surface area (m ²)	1.77 ± 0.11	1.79 ± 0.11	1.79 ± 0.15	1.76 ± 0.12	1.76 ± 0.16	0.805
Comorbid conditions						
Hypertension	5 (25.0)	4 (13.3)	3 (10.0)	5 (16.7)	6 (20.0)	0.648 ^b
Diabetes	1 (5.0)	1 (3.3)	2 (6.7)	3 (10.0)	2 (6.7)	0.941 ^b
History of CAD	1 (5.0)	0	0	2 (6.7)	1 (3.3)	0.500 ^b
SBP (mmHg)	123 ± 12	125 ± 12	124 ± 14	127 ± 10	121 ± 13	0.460
DBP (mmHg)	77 ± 10	77 ± 8	78 ± 7	77 ± 8	76 ± 8	0.862
Beta-blocker therapy	2 (10.0)	4 (13.3)	3 (10.0)	4 (13.3)	4 (13.3)	1.000 ^b
ACEI/ARB therapy	1 (5.0)	0	0	3 (10.0)	2 (6.7)	0.200 ^b
LV ejection fraction (%)	62.9 ± 4.1	63.2 ± 3.8	62.2 ± 3.4	64.0 ± 3.5	63.7 ± 4.3	0.390
Aortic valve features						
Aortic valve area (cm ²)	2.5 (2.3–2.8)	2.4 (2.2–2.7)	2.3 (2.2–2.7)	0.8 (0.7–0.9) ^{a,c}	0.8 (0.7–0.9) ^{a,c}	<0.001
Peak velocity (m/s)	1.6 ± 0.2	1.7 ± 0.3	1.8 ± 0.4	4.6 ± 0.5 ^{a,c}	4.8 ± 0.5 ^{a,c}	<0.001
Mean gradient (mmHg)	5.4 (4.1–6.4)	6.1 (5.2–8.0)	6.9 (5.0–8.1)	45.7 (41.6–54.6) ^{a,c}	50.6 (43.1–57.8) ^{a,c}	<0.001
Stroke volume (ml)	54.9 ± 8.0	54.4 ± 8.1	54.3 ± 10.7	56.6 ± 11.1	57.0 ± 10.0	0.752
Aortic diameters (mm)						
Aortic sinus	34.3 ± 3.9	35.5 ± 4.1	33.7 ± 4.5	34.3 ± 4.2	33.7 ± 4.1	0.448
Mid-ascending aorta	39.5 ± 4.5	40.0 ± 5.4	41.3 ± 5.8	42.1 ± 4.9	41.6 ± 4.3	0.309
Aortopathy						
Type 0/1	10 (50.0)	13 (43.3)	13 (43.3)	10 (33.3)	11 (36.7)	0.779
Type 2	8 (40.0)	14 (46.7)	7 (23.4)	15 (50.0)	7 (23.4)	0.081
Type 3	2 (10.0)	3 (10.0)	10 (33.3)	5 (16.7)	12 (40.0)	0.016

All continuous data are presented as mean ± standard deviation or as median (interquartile range).

^aP < 0.005 between non-stenotic and stenotic BAV patients with the same fusion type.

^bP obtained from the Fisher's exact test.

^cP < 0.005 compared with TAV controls.

ACEI: angiotensin-converting enzyme inhibitor; ARB: angiotensin receptor blocker; AS: aortic stenosis; BAV: bicuspid aortic valve; CAD: coronary artery disease; DBP: diastolic blood pressure; LV: left ventricle; RL: right and left cusp fusion type; RN: right and non-coronary cusp fusion type; SBP: systolic blood pressure; TAV: tricuspid aortic valve.

aorta ($P < 0.005$), except for the distal ascending aortic plane in the RL BAV group (average systolic WSS, $P = 0.093$; WSS-SD_{8P}, $P = 0.333$) (Table 2). The asymmetrical position of the WSS peak was found to be shifted from the right to the right-anterior position and then to the left-anterior position along the proximal to the distal ascending aortic planes in both the RL BAV and RL BAV-AS groups (Fig. 4). Consistent with the eccentric systolic outflow jet distributions (Fig. 3), the location of regional increased WSS in RN BAV patients was detected at the right-posterior and posterior positions of the proximal ascending aorta, which was different from the right and right-anterior positions in RL BAV subjects, with no difference in the presence of severe AS. At the level of the mid-ascending aorta, peak WSS locations remained at the right-posterior position in RN BAV patients but switched to right-anterior in RN BAV-AS subjects (Fig. 4). For the level of the distal ascending aorta, both stenotic and non-stenotic RN BAV patients demonstrated marked elevation of average systolic WSS (RL BAV versus RN BAV: $P = 0.002$; RL BAV-AS versus RN BAV-AS: $P = 0.004$) and flow displacement (RL BAV versus RN BAV: $P = 0.001$; RL BAV-AS versus RN BAV-AS: $P < 0.001$) compared with their RL counterparts.

Haemodynamic parameters in bicuspid aortic valve aortopathy

Comparisons of haemodynamic parameters among the 3 BAV aortopathy phenotypes revealed significant differences for flow

displacement and WSS-SD_{8P} (one-way ANOVA and Kruskal-Wallis H analysis, $P < 0.001$), except for average systolic WSS ($P > 0.10$) in non-stenotic BAV patients. When severe AS was present, flow displacement provided better discrimination among phenotypes of BAV aortopathy ($P < 0.001$). Flow displacement and WSS-SD_{8P} as parameters to differentiate aortopathy phenotype are depicted in Fig. 5. In non-stenotic BAV patients, flow displacement and WSS-SD_{8P} were markedly elevated at the level of the mid- and distal ascending aorta among those with type 3 aortopathy and reduced at the level of proximal and mid-ascending aorta among those with type 1 aortopathy, compared to those with type 2 aortopathy. Interestingly, differences in WSS-SD_{8P} among aortopathy phenotypes were no longer detectable when severe AS was introduced. These findings indicated the potential value of haemodynamic parameters other than WSS for the illustration of BAV aortopathy, especially in the presence of severe AS, which introduced increased patient-to-patient variability into the WSS assessment.

DISCUSSION

The present study showed that severe AS could alter individual systolic outflow patterns arising from various BAV cusp fusion types by introducing novel abnormal flow patterns, increasing flow eccentricity and elevating regional WSS. Functional haemodynamic parameters in association with the expression of

Figure 2: Qualitative evaluation of the flow helix and vortex were displayed by stacked bar plot (upper) and bar chart (mean $\pm$ standard deviation, lower). Significantly higher helical and vortical flow scores were found in BAV patients compared to TAV controls. Severe AS further introduced pronounced helical and vortical flow formations compared with their non-stenotic counterparts. AS: aortic stenosis; BAV: bicuspid aortic valve; RL: right-left; RN: right-non-coronary; TAV: tricuspid aortic valve.

aortopathy need to be carefully evaluated because poststenotic aortic haemodynamic alterations could mask, even assimilate the existing flow patterns related to the cusp fusion type.

Early interpretations of BAV aortopathy in the setting of AS have attributed poststenosis dilatation to aortic flow disturbances caused by the stenotic valve in a way similar to that of tricuspid valves [13]. However, it should be noted that a bicuspid valve was congenitally malfunctional. Before AS developed, the intrinsic flow patterns derived from the RL and RN cusp fusion produced distinct WSS hot zones on the thoracic aorta of BAV patients. The development of severe AS could exacerbate the flow disturbance with more helical and vortical formation, as well as increased flow eccentricity and regional WSS. The most curious finding of the present study was the tendency towards unified peak velocity and WSS distribution pattern from the mid-ascending aorta and above between the originally distinct RL and RN subjects when severe AS had developed. To elaborate, the flow retained its individual traits derived from RL and RN fusions at the aortic root and the proximal ascending aorta when the outflow jet was restricted by the diminished valve area; it became more similar to each other along the aorta from the mid-ascending plane. This

gradual metamorphosis of aortic haemodynamic alterations might provide a potential explanation for the high prevalence of type 3 aortopathy in BAV RN patients when severe AS was present. To note, the categorization percentage of aortopathy in our cohort was similar to those reported in recent studies, including the largest published BAV aortopathy cohort by Wojnarski *et al.* [10, 14]. We speculate that BAV cusp fusion patterns laid the foundation of haemodynamic changes in aortic outflow and regional WSS. Then, prolonged exposure to stenotic valve-mediated haemodynamic alterations led to the increased prevalence of tubular and transverse arch dilatation (types 2 and 3: from 56.7% to 65.0%). Therefore, the longitudinal interaction between AS and BAV itself contributed to the evolution of ascending aortic dilatation, as the haemodynamic burden caused by valvular dysfunction or cusp fusion alone could not explain the entire spectrum of BAV aortopathy.

Accumulating evidence regarding the linkage between bicuspid morphology and aortic lesions has led to variable proposals for aortopathy classification [15, 16]. The pathogenesis of BAV aortopathy is a multifactorial process involving interactions between genetic propensity and haemodynamic burden. It is of

Figure 3: Visualization of outflow asymmetry by mapping the peak systolic velocity location (A, anterior; L, left; P, posterior; R, right) and the region of the upper 15th percentile of the velocities on the segmental aortic lumen map. Different outflow asymmetry at the proximal ascending aorta can be appreciated between BAV patients with RL and RN cusp fusion types. The existence of severe AS diminished the differences in peak flow velocity distributions between RL and RN BAV patients from the level of the mid-ascending aorta. AAO: ascending aorta; AS: aortic stenosis; BAV: bicuspid aortic valve; RL: right-left; RN: right-non-coronary; TAV: tricuspid aortic valve.

Table 2: Haemodynamic quantification at measurement planes

	Control TAV (n = 20)	Study group				P-value
		RL BAV (n = 30)	RN BAV (n = 30)	RL BAV-AS (n = 30)	RN BAV-AS (n = 30)	
Flow displacement <i>d</i> (mm)						
Proximal ascending aorta	4.08 ± 2.66	7.45 ± 1.89 ^a	6.89 ± 2.44 ^a	8.64 ± 1.91 ^a	8.24 ± 2.29 ^a	<0.001
Mid-ascending aorta	4.28 ± 1.93	6.11 ± 2.39 ^a	6.70 ± 2.45 ^a	8.23 ± 2.10 ^{a,b}	8.40 ± 2.16 ^{a,b}	<0.001
Distal ascending aorta	2.69 ± 1.54	3.17 ± 1.25	4.70 ± 2.13 ^{a,c}	4.81 ± 1.61 ^{a,b}	6.86 ± 2.24 ^{a,b,c}	<0.001
Average systolic WSS (N/m ²)						
Proximal ascending aorta	0.43 ± 0.12	0.54 ± 0.14 ^a	0.52 ± 0.16 ^a	0.69 ± 0.18 ^{a,b}	0.71 ± 0.16 ^{a,b}	<0.001
Mid-ascending aorta	0.45 ± 0.12	0.57 ± 0.13 ^a	0.63 ± 0.16 ^a	0.74 ± 0.18 ^{a,b}	0.84 ± 0.17 ^{a,b}	<0.001
Distal ascending aorta	0.41 ± 0.08	0.47 ± 0.12	0.59 ± 0.12 ^{a,c}	0.60 ± 0.15 ^{a,b}	0.72 ± 0.14 ^{a,b,c}	<0.001
Systolic WSS-SD _{8P} (N/m ²)						
Proximal ascending aorta	0.08 ± 0.03	0.14 ± 0.04 ^a	0.14 ± 0.04 ^a	0.22 ± 0.06 ^{a,b}	0.22 ± 0.06 ^{a,b}	<0.001
Mid-ascending aorta	0.08 ± 0.02	0.14 ± 0.05 ^a	0.14 ± 0.04 ^a	0.23 ± 0.07 ^{a,b}	0.23 ± 0.06 ^{a,b}	<0.001
Distal ascending aorta	0.05 ± 0.01	0.06 ± 0.02	0.08 ± 0.03 ^{a,c}	0.16 ± 0.04 ^{a,b}	0.19 ± 0.06 ^{a,b}	<0.001

All continuous data are presented as mean ± standard deviation or as median (interquartile range).

^a*P* < 0.005 compared with TAV controls.

^b*P* < 0.005 between non-stenotic and stenotic BAV patients with the same fusion type.

^c*P* < 0.005 between RL and RN BAV patients with the same aortic dysfunction status.

AS: aortic stenosis; BAV: bicuspid aortic valve; RL: right and left cusp fusion type; RN: right and non-coronary cusp fusion type; TAV: tricuspid aortic valve; WSS: wall shear stress; WSS-SD_{8P}: standard deviation of circumferential wall shear stress across 8 anatomic positions.

grave importance to have a categorization scheme harbouring a surgical rationale as well as capable of indicating the weighing of either genetic or haemodynamic factors when applying to an individual patient [17]. In the present study, BAV aortopathy has

been categorized into isolated root dilatation (type 1), tubular ascending aortic dilatation (type 2) and diffuse dilatation involving aortic arch (type 3). This categorization was recommended by Verma and Siu [1] in a recent review on the guidance of

Figure 4: Segmental systolic WSS measurements were displayed across 8 anatomic positions (A: anterior; LA: left anterior; L: left; LP: left posterior; P: posterior; RP: right posterior; R: right; and RA: right anterior). The position of peak systolic velocity corresponded to the position of peak WSS (blue circle). Error bars represented the standard deviation of individual WSS variation. *Statistical significance for BAV patients and TAV controls ($P < 0.005$); †Statistical significance between BAV patients with RL and RN cusp fusion types ($P < 0.005$). AAO: ascending aorta; AS: aortic stenosis; BAV: bicuspid aortic valve; RL: right-left; RN: right-non-coronary; TAV: tricuspid aortic valve; WSS: wall shear stress.

determining the extent of resection in patients requiring surgical intervention. It was further proved to be in accordance with the clinical findings that, cases with a dilated ascending aorta, including ascending (type 2) and arch phenotypes (type 3), might be viewed as two closely related phenotypes on one spectrum inclined to possess a deeper haemodynamic underpinning, in contrast to root phenotype which has been acknowledged to have stronger genetic susceptibility [18, 19]. We indicated that functional haemodynamic parameters could reflect the morphometric differences of the ascending aorta, as well as discern ascending and arch phenotypes in dilated cases. Interestingly, the choice of the most sensitive functional haemodynamic parameter and its optimal cut-off value would be different when the post-stenotic flow pattern overlaps and somehow overrides the BAV flow pattern. Thus, the present study offered a unique vantage point over the real-world scenario of BAV aortopathy and advocated the spectral composition of type 2 and 3 aortopathy via haemodynamic parameters.

Flow displacement and WSS eccentricity, reflecting outflow asymmetry and regional WSS increment, worked better in discerning the phenotype of aortopathy than segmental average systolic WSS, which corresponded to previous findings that the elevation of regional WSS was associated with changes in regional aortic wall histology and proteolytic events [3, 4]. To move a step forward and take AS into the picture, WSS eccentricity would be more susceptible to poststenotic haemodynamic changes, and it increased in correlation with the accelerated

peak transvalvular flow velocity [11], which left flow displacement as the only reliable parameter.

Recent 4D flow MRI improvements and postprocessing pipelines have allowed more comprehensive access to WSS distribution by permitting the calculation of 3D WSS along the entire great vessel lumen surface [20]. The locations of significantly elevated systolic WSS in comparison with TAV controls along the ascending aorta in each BAV group, based on manual placement on 2-dimensional planes in our study, were similar to the results from 3D WSS atlas [21]. However, there were discrepancies in the magnitude of regional systolic WSS between the 3D WSS atlas and our study, because 3D WSS atlas provided an averaged WSS magnitude of the region of interest instead of local anatomical positions. This approach was more sensitive to the difference of WSS within the indicated analytical plane, thus enabling us to demonstrate higher segmental average WSS in the distal ascending aorta of RN fusion type than RL fusion type, which eluded statistical approval by the 3D WSS approach. By prevailing over the current methodology, the 3D WSS could provide a vivid heatmap allowing cardiovascular surgeons to determine the extent of at-risk tissue exposed to an abnormally high WSS and to optimize the resection and reconstruction strategy if WSS indices were to be validated by a more extensive investigation for predicting disease progression [22]. It should be noted that time-averaged 3D WSS required a robust time-resolved segmentation, which was difficult to achieve, given the constant movement of the ascending aorta. This problem was largely overcome in our

Figure 5: Flow displacement and WSS-SD_{8P} as haemodynamic parameters to discern aortopathy phenotypes in BAV patients without (left) or with severe AS (right). Red lines indicate mean value. AAO: ascending aorta; AS: aortic stenosis; BAV: bicuspid aortic valve; RL: right-left; RN: right-non-coronary; TAV: tricuspid aortic valve; WSS: wall shear stress.

study via the segmenting contour for all time frames to get time-averaged WSS, which mitigated measurement noise as well as limited the interference of the vessel movement on WSS calculation. As promising haemodynamic parameters, flow displacement and WSS eccentricity correlated well with BAV aortopathy and might be worth adding to the 3D WSS analyses in the future.

Limitations

As a cross-sectional investigation, the present study provided observational, instead of causative, evidences for the pathogenesis of BAV aortopathy. To include age-matched AS and non-AS BAV

subjects or to perform covariate adjustment for age might be unnecessary, because the development of severe AS usually took years and demonstrated higher prevalence in the elderly BAV population, and the age-related effects could not be appropriately reflected by either approach. We did not include the TAV AS group as well, for TAV was not a disease entity and the variation in the aetiology for TAV stenosis could introduce unpredictable bias into the study. The gradual shift of flow patterns might be appreciated if BAV patients with various degrees of AS were included. Nonetheless, further well-designed longitudinal studies could provide valuable information on whether and how the development of AS would change aortic WSS and other flow features in a series of clinical, imaging and perhaps molecular surveys.

CONCLUSION

The appearance of severe AS markedly exacerbated aortic flow aberrations in BAV patients and masked the existing distinct flow features related to RL and RN fusion types. The real-world scenario of BAV aortopathy should be considered in the context of a time-consuming interaction between intrinsic cusp fusion types and acquired valve dysfunction, and functional haemodynamic parameters derived from 4D flow MRI analysis might be promising indicators for flow-mediated aortopathy during its evolving process.

SUPPLEMENTARY MATERIAL

Supplementary material is available at *EJCTS* online.

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