Aortopathy in patients with bicuspid aortic valve stenosis: role of aortic root functional parameters

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OBJECTIVES: We prospectively examined functional characteristics of the aortic root and transvalvular hemodynamic flow in order to define factors associated with the severity of aortopathy in patients undergoing surgery for bicuspid aortic valve (BAV) stenosis.

METHODS: A total of 103 consecutive patients with BAV stenosis (mean age 61 ± 9 years, 66% male) underwent aortic valve replacement ± concomitant aortic surgery from January 2012 through March 2014. All patients underwent preoperative cardiac magnetic resonance imaging (MRI) in order to evaluate the systolic transvalvular flow and the following functional parameters: (i) angulation between the left ventricular outflow axis and the aortic root, (ii) geometrical orientation of residual aortic valve orifice and (iii) BAV cusp fusion pattern. MRI data were used to guide sampling of the ascending aorta during surgery [i.e. jet-sample from the area where the flow-jet impacts on the aortic wall and control sample from the opposite aortic wall (obtained from the aortotomy site)]. Aortopathy was quantified by means of a histological sum-score (0 to 21+) in each sample.

RESULTS: A significant correlation was found between histological sum-score in the jet-sample and the angle between the LV outflow axis and the aortic root (r = 0.6, P = 0.007). Moreover, there was a linear correlation between proximal aortic diameter and the angle between systolic flow-jet and ascending aortic wall (r = 0.5, P = 0.006). Logistic regression identified the angle between the LV outflow axis and the aortic root (OR 1.1, P = 0.04) and the angle between the flow-jet and the aortic wall (OR 1.2, P = 0.001) as independent predictors of an indexed proximal aortic diameter ≥22 mm/m².

CONCLUSIONS: Functional parameters of the aortic root may be used to predict the severity of aortopathy in patients with BAV stenosis, and may be useful in predicting future risk of aortic disease in such patients.

Keywords: Bicuspid aortic valve • Aorta • Aortic aneurysm • Aortopathy

INTRODUCTION

As evidenced by a recent survey of the cardiac surgical community, the treatment of patients with bicuspid aortic valve (BAV)-associated aortopathy is inconsistent and mostly based on the preference of the individual surgeon or institutional policy [1]. Guidelines are currently lacking for the surgical strategy of bicuspid aortic valve surgery. Aortic root functional parameters may be useful in predicting future risk of aortic disease in such patients. Phenotypic heterogeneity of aortic disease in BAV has emerged as a relatively new concept in the scientific community, which has stimulated increased research in this field. BAV heterogeneity results in different types of associated aortopathy (i.e. so-called BAV phenotypes) which may be caused by distinct pathogenetic mechanisms and therefore require individualized surgical approaches [3]. Various classification systems have been proposed to stratify BAV phenotypes based on cusp fusion pattern (so-called BAV morphotype) [4], shape of the proximal aorta [5] or a combination of both factors [6]. However, the clinical relevance of these classifications is still unknown [2].

Cardiovascular MRI has the potential to integrate morphological and functional information by means of non-invasive imaging and is ideally suited for research efforts focused on BAV disease [7]. It has been established as an excellent 'one-stop' method of evaluating AV morphology, aortic root and ascending aorta dimensions and blood flow dynamics in BAV patients [8].
The current study is an extension of our previous research [9] with a focus on the most common group of BAV patients referred for aortic valve replacement (AVR) surgery, namely those with BAV stenosis. Therefore, some wording in the individual paragraphs of the Materials and Methods section is reproduced from the previous article [9]. The clinical entity of BAV stenosis has been chosen as a ‘classical’ model to analyse the role of haemodynamic factors in the development of aortopathy. Rheological factors have been proposed to play a major role in the development of this aortopathy, mostly based on observational data [10].

The aim of this study was to therefore evaluate aortic root functional characteristics and haemodynamic parameters of transvalvular flow in BAV stenosis patients, and to determine the correlation between such measures and BAV-associated aortopathy. Such information may be important to predict the presence and extent of aortopathy in patients with BAV stenosis, and therefore guide intraoperative management of the aorta.

**MATERIALS AND METHODS**

We prospectively evaluated all patients with BAV stenosis who were referred for AVR surgery with or without simultaneous replacement of the proximal thoracic aorta at Central Hospital, Bad Berka, Germany, from January 2012 through March 2014. The study was approved by our institutional ethics committee and all patients gave their written informed consent.

A total of 140 patients with BAV disease (from 470 screened patients with aortic valve disease who were referred for aortic valve surgery) underwent elective AVR surgery with or without simultaneous proximal aortic replacement and were included in our prospective institutional BAV surgery database. BAV patients who presented with isolated/predominant aortic valve insufficiency (n = 29) were excluded from further analysis. Patients with mixed BAV disease were included only if valve stenosis was the predominant lesion (i.e. patients with severe stenosis and mild or mild-to-moderate aortic valve insufficiency). Eight BAV patients had contraindications for preoperative MRI examination (i.e. claustrophobia or previously implanted cardiac pacemaker/defibrillator) and were excluded. We excluded patients with Marfan syndrome, and those undergoing urgent/emergency surgery. Moreover, BAV patients undergoing combined cardiac surgical procedures (i.e. other than simultaneous proximal aortic surgery) were excluded. A total of 103 consecutive patients with BAV stenosis (mean age 61 ± 9 years, 66% male) met these inclusion criteria and served as a study cohort.

The primary end-point of our study was the correlation between functional characteristics of the aortic root/haemodynamic parameters of transvalvular flow and the severity of bicuspid aortopathy, defined by an indexed aortic diameter and histological sum-score.

**Definitions and measurements**

We assessed the morphology and function of the aortic valve by preoperative echocardiography and cardiac MRI in all patients. BAV was suspected if short-axis imaging of the aortic valve demonstrated the existence of only two commissures delimiting two aortic valve cusps on preoperative echocardiographic examination, and all such patients underwent subsequent MRI investigation. While transthoracic echocardiography was equivocal in 30 (29%) study patients, cardiac MRI demonstrated very high sensitivity and specificity in identifying BAV disease (i.e. 98%). The final decision regarding the bicuspidal nature was made based on the intraoperative aortic valve description by the surgeon. Published guidelines were used to define severe aortic valve stenosis [11].

The maximal diameter of the proximal aorta was measured preoperatively by means of transthoracic 2D echocardiography and cardiac MRI. Multiple end-systolic measurements of the maximal diameter of the ascending aorta were performed echocardiographically using the leading-edge convention in a parasternal long-axis view [12]. More detailed measurements of the proximal aortic diameter were accomplished by means of preoperative MRI examination (see below). If discrepancies existed between echocardiographic and MRI-derived aortic dimensions, then MRI measurements were used.

**Preoperative magnetic resonance imaging examination**

Preoperative cardiac MRI was performed in all patients with suspected BAV stenosis in order to quantify systolic transvalvular flow and functional parameters of the aortic root. The following parameters were assessed: (i) angulation between left ventricular (LV) outflow axis and aortic root, (ii) geometrical orientation of residual aortic valve orifice and (iii) BAV cusp fusion pattern. Moreover, the angle between systolic peak velocity flow-jet and the aortic segment in direct contact with the flow-jet (i.e. the angle at which the flow-jet hits the aortic wall).

A single non-contrast cardiac MRI (Avanto 1.5 T scanner; Siemens, Erlangen, Germany) included structural, functional and phase-velocity-encoded imaging of the LV and proximal thoracic aorta. First of all, morphological scans of the whole chest were acquired using coronal and transverse views (i.e. dark-blood technique: T1 HASTE in transverse view and bright-blood technique: trueFISP single coronal). The maximal diameter of the proximal aorta was measured in these views as the largest observed cross-sectional diameter perpendicular to the aortic axis in a mid-vessel slice. In the next step, standardized cardiac plan scans were acquired: vertical long-axis plane, horizontal long-axis plane and short-axis plane which were perpendicular to both long-axis planes. Based on these localizer plan scans, an LV inflow-outflow view and coronal left ventricular outflow tract (LVOT) view were modelled. Real-time breath-hold steady-state free precession (SSFP) cine images (turboFLASH 2D) in an LV inflow-outflow view and coronal LVOT view were used to detect the direction of eccentric systolic flow-jet in the proximal aorta. The quality of the transvalvular jet was characterized using function sequences and volumetric function sequences in both above-mentioned views. The ‘angulation between the LV outflow axis and aortic root (angle LV/Aorta)’ was also determined at peak systole in the LV inflow-outflow view (Fig. 1). LV outflow axis was defined as a vector connecting the LV apex and the midpoint of the LVOT, 15 mm below the aortic valve annular plane.

The area where the systolic transvalvular flow-jet contacts the aortic wall was localized by means of real-time phase-contrast imaging in the above-mentioned views. Definition of flow-velocity-encoded window was as close to the peak transvalvular jet velocity as possible (i.e. between 200 and 400 cm/s) on in-plane 2D-phase-contrast imaging. Analysis of function sequences and phase-contrast images was performed to detect the area where the flow-jet impacts...
on the proximal aorta (i.e. segment of aortic circumference that was in direct contact with the flow-jet) and the exact distance (cm) between the aortic valve plane and the area where the flow-jet impacts on the proximal aorta. The circumference of the proximal aorta was subdivided into six segments in order to more precisely describe the aortic area in direct contact with the flow-jet. Moreover, the angle between the systolic peak-velocity flow-jet and the aortic area where the flow-jet hits the aortic wall (i.e. \( \text{angle jet/aorta} \)) was measured in the flow-velocity-encoded window. The \( \text{angle jet/aorta} \) was measured as follows: a cross-sectional line was drawn across the proximal aorta at the point where the systolic flow-jet impacts on the aortic wall (line A, Fig. 2). The second line, which is perpendicular to line A (i.e. 90° angle) and tangential to the aortic wall was drawn thereafter (line B, Fig. 2). Then, \( \text{angle jet/aorta} \) was measured between line B and the vector of the systolic transvalvular flow (angle \( \alpha \), Fig. 2).

The ‘cusp fusion pattern’ (i.e. BAV morphotype) and the opening area of the BAV were analysed by placing an SSFP-function sequence parallel and just distal to the aortic valve annulus. The ‘geometric orientation of residual aortic valve orifice’ (i.e. central versus eccentric versus slit-shaped) was analysed by means of Syngo MR B17 software (Siemens, Germany) (Fig. 3A–C). Residual valve orifice geometry was measured as follows: a turboFLASH 2D cine sequence in the LV inflow–outflow view was analysed and the parallel slice, where transvalvular flow-jet was best visible, determined. Subsequently, a cross-sectional plane positioned at the origin of the systolic flow-jet and parallel to the aortic annular plane was determined at peak systole. The resultant cross-sectional plane was used to define residual aortic valve orifice geometry.

All transvalvular flow analyses were performed by two study radiologists (Beatrix Fey and Georg Dubslaff).

**Study population**

Demographics and intraoperative variables are summarized in Table 1. The most common comorbidity was arterial hypertension and one-fourth of all patients were smokers. All 103 patients underwent elective AVR surgery with or without simultaneous aortic replacement through a median sternotomy or partial upper sternotomy.

Figure 1: Angulation between the left ventricular outflow axis and the aortic root (angle LV/Aorta), as identified by cardiac MRI. LV: left ventricle.

Figure 2: Angle between the systolic peak velocity flow-jet and the aortic area in direct contact with the flow-jet (angle jet/Aorta), as identified by cardiac MRI (flow-velocity-encoded phase-contrast imaging). (A) Cross-sectional line across the proximal aorta at the point where the systolic flow-jet impacts on the aortic wall; (B) tangential line, perpendicular to line A; \( \alpha \), angle between line B and the vector of transvalvular flow (i.e. \( \text{angle jet/aorta} \)).
During AVR surgery for each patient. The first aortic specimen (so-called ‘jet-sample’) was collected from the area where the flow-jet impacted on the proximal aortic wall, as identified by MRI analysis. The second sample (i.e. ‘control sample’) was obtained from the aortic wall lying directly opposite to the area of direct contact with the flow-jet. Aortic specimens were obtained from the aortotomy incision in 85 (82%) study patients who underwent isolated AVR only. The oblique aortotomy incision was tailored individually in order to correspond with the preoperative MRI data. The MRI-guided harvesting technique was used to successfully obtain the jet-sample in the vast majority (96%) of study patients. Owing to the oblique aortotomy incision, a control sample was harvested ~1–2 cm lower in the study patients who underwent isolated AVR only. Aortic specimens (i.e. jet-sample and control sample, respectively) were obtained from excised aortic tissue in 18 patients who underwent simultaneous proximal aortic replacement.

Both samples were fixed in 4.5% pH-buffered formalin before they were sent to the pathology institute. The aortic tissue was processed for light microscopy and embedded in paraffin, and sections were performed perpendicular to the aortic wall. Sections were stained with haematoxylin–eosin, elastica-van Gieson, Alcian blue and Masson’s trichrome stains. All specimens were evaluated by two experienced pathologists (Bernhard Theis and Iver Petersen), who were blinded to the collection site of aortic specimens (i.e. jet-sample versus control sample).

A semi-quantitative histological grading scale, described by Bechtel et al. [13], was used for the assessment of aortic wall lesions. Aortic wall alterations were graded based on seven histological criteria: fibrosis, atherosclerosis, medionecrosis, cystic medial necrosis, changes in smooth muscle cell orientation, elastic fragmentation and periaortic inflammation. Each variable was quantified from 0 (no change) to 3 (most severe change), which was based on the most injured area observed on light microscopy [13]. The values of all seven histological parameters were summed up in a histological sum-score (i.e. 0–21) for both aortic samples (i.e. jet-sample versus control sample).

**Statistical analysis**

Standard definitions were used for patient variables and outcomes. Categorical variables are expressed as percentages and continuous variables are expressed as mean ± SD (range) throughout the manuscript. All continuous variables were tested for normal distribution using the Shapiro–Wilk test. All statistical analyses were performed with IBM SPSS 19.0 software (IBM Corp., New York, NY, USA). A two-tailed Student’s t-test for continuous variables and χ² tests for categorical variables were used for comparisons. All statistical tests were two-tailed with a significance level of p < 0.05.
test for categorical variables were used for univariate comparisons between groups. Histological sum-score in the jet-sample versus control sample was compared using the Mann–Whitney U-test. Correlation analyses were performed using Pearson’s correlation. Multivariate logistic regression analysis was used to identify risk factors of an indexed proximal aortic diameter >22 mm/m². A cut-off value of 0.1 at the univariate selection stage was used for including candidate variables into a logistic regression model. All P values of 0.05 or less were considered statistically significant.

Intrarater reliability in angle LV/Aorta and angle jet/Aorta measurements was evaluated by duplicate measurements by the same observer. Interrater reliability was evaluated by the same measurements by two study radiologists. Reliability statistics included Lin’s concordance correlation coefficient, coefficient of variation and Bland–Altman 95% confidence interval (CI) of agreement.

RESULTS

Angulation between left ventricular outflow axis and aortic root

The mean angulation between the LV outflow axis and the aortic root (angle LV/Aorta) in our study population was 49° ± 10° (range 25°–89°) (Fig. 1). We found a significant correlation between the angle LV/Aorta and the angle jet/Aorta (r = 0.5, P < 0.01) (Fig. 4A). There was no significant correlation between the angle LV/Aorta and the distance between the aortic valve plane and the area where the flow-jet impacted on the proximal aorta (r = −0.3, P = 0.7).

Severity of aortopathy, as defined by an indexed proximal aortic diameter and histological sum-score in the jet-sample, correlated significantly with the angle LV/Aorta. In accordance with our previous publication [10], we were able to confirm a strong linear correlation between values of the histological sum-score in the jet-sample and the indexed diameter of the proximal aorta (r = 0.65, P < 0.01). There was a strong linear correlation between histological sum-score in the jet-sample and the angle LV/Aorta (r = 0.62, P = 0.007) (Fig. 4B). Furthermore, angle LV/Aorta correlated significantly with the indexed proximal aortic diameter (r = 0.47, P < 0.01).

Correlation analysis was performed between the angle LV/Aorta and the parameters of LV hypertrophy (i.e. basal septal thickness and LV posterior wall thickness) as well as maximal/mean transvalvular gradients. No significant correlation was found between the angle LV/Aorta and the parameters of LV hypertrophy (i.e. r = 0.02, P = 0.8), and between the angle LV/Aorta and transvalvular gradients (r = −0.3, P = 0.2).

The angle LV/Aorta >50° was identified in 40 (39%) study patients and was associated with a significantly larger indexed aortic diameter (21.9 ± 4 vs 19.2 ± 3 mm/m², P = 0.001), higher sum-score value in the jet-sample (4.1 ± 1.6 vs 2.5 ± 1.1, P < 0.001) and larger angle jet/Aorta (33 ± 10° vs 27 ± 7°, P = 0.002) when compared with patients with the angle LV/Aorta <50°.

Moreover, the angle jet/Aorta correlated significantly with the indexed proximal aortic diameter (r = 0.7, P < 0.01) (Fig. 4C).

Intra- and inter-rater reliability for angle LV/Aorta and angle jet/Aorta measurements are summarized in Table 2. Reproducibility of both angle measurements was good, resulting in concordance correlation coefficient values above 0.92 and the coefficient of variation ranging between 5.7 and 10.6%. Bland–Altman analysis revealed that all CIs included a zero value, which confirmed no evidence of observer-associated bias (Table 2).

Geometric orientation of residual orifice

Residual aortic valve orifice was identified to be an eccentric/asymmetric systolic opening in 31 patients (30%), slit-shaped/symmetric opening in 65 patients (63%) and centrally located residual orifice in the remaining 7 patients (7%) (Fig. 3A–C). Functional aortic root characteristics and haemodynamic parameters were compared between BAV patients with an eccentric/asymmetric opening versus slit-shaped/symmetric opening.
The cusp fusion pattern was similar in both subgroups (i.e. 72 vs 74% BAV L/R fusion, respectively). The distance between the aortic valve plane and the area where the flow-jet impacts on the proximal aorta tended to be shorter in the subgroup with an eccentric/asymmetric opening versus slit-shaped/symmetric opening (i.e. 50 ± 10 vs 58 ± 11 mm, respectively, P = 0.1). Moreover, the aortic area in direct contact with the flow-jet was localized at the right-posterior segment of the aorta more commonly in the subgroup of BAV patients with an eccentric/asymmetric opening when compared with patients with a slit-shaped/symmetric opening (i.e. 52 vs 35%, respectively, P = 0.08).

Proximal aortic diameters and histological sum-score values were comparable between both subgroups of patients and showed only a weak tendency towards more severe aortopathy in the patient subgroup with an eccentric/asymmetric opening (i.e. indexed aortic diameter 20.8 ± 4 vs 19.9 ± 3 mm/m² in the subgroup with a slit-shaped/symmetric opening, P = 0.3). After combining the variables of eccentric/asymmetric opening with the angle LV/aorta >50° (resulting in a total of 9 patients), we observed a statistically significant difference in the prevalence of an indexed aortic diameter ≥22 mm/m² between groups (i.e. 67 vs 23%, P < 0.01). In contrast, the combination of slit-shaped/symmetric opening with the angle LV/aorta <50° (a total of 40 patients) was associated with a low prevalence of an indexed aortic diameter ≥22 mm/m² (i.e. 13 vs 37%, P = 0.02).

## Cusp fusion pattern

Based on preoperative MRI analysis and intraoperative inspection, fusion of the right-left coronary cusps (i.e. BAV type 1, L/R, S) was identified in 75 patients (73%), and right-non-coronary cusps (i.e. BAV type 1, R/N, S) in 26 patients (25%) [14]. Two remaining patients had a symmetrical BAV without evidence of raphe (i.e. BAV type 0).

An eccentric systolic transvalvular flow-jet directed towards the proximal aortic wall could be identified in 102 (99%) patients. One patient with a BAV type 0 valve had a centrally located systolic flow-jet without any direct contact with the proximal aortic wall. The mean distance between aortic valve plane and aortic segment in direct contact with the flow-jet was comparable between patients with the two BAV cusp fusion patterns (i.e. 53 ± 9 mm in the BAV L/R group vs 56 ± 12 mm in the BAV R/N group, P = 0.2). Moreover, the angle jet/Aorta was comparable between the two groups of cusp fusion (i.e. 30° ± 9° in the BAV L/R group vs 27° ± 9° in the BAV R/N group, P = 0.1). Only the aortic segment in direct contact with the transvalvular flow-jet was located at the right lateral wall of the proximal aorta more commonly in BAV patients with the L/R fusion versus BAV patients with the R/N fusion (i.e. 67 vs 46%, P = 0.04). In contrast, a transvalvular flow-jet hitting the right-posterior segment of the proximal aorta was seen more commonly in BAV patients with the R/N cusp fusion versus BAV patients with L/R cusp fusion (i.e. 54 vs 33%, P < 0.01).

There was no significant difference in the severity of aortopathy between the two BAV fused-cusp subgroups, as defined by an indexed maximal aortic diameter and histological sum-score. The mean histological sum-score in the jet-sample was comparable between both cusp fusion patterns (i.e. 3.2 ± 1.8 in the BAV L/R group vs 2.6 ± 1.4 in the BAV R/N group, P = 0.3). Although not statistically significant, histological differences were predominantly observed in the subcategories of medionecrosis, cystic medial necrosis and elastic fragmentation. The maximal proximal aortic diameter was 41 ± 7 mm in the BAV L/R group vs 39 ± 6 mm in the BAV R/N group (P = 0.2). Moreover, there was no significant difference in the indexed aortic diameter between both cusp fusion patterns (i.e. 20.8 ± 4.0 in the BAV L/R group vs 19.6 ± 4 in the BAV R/N group, P = 0.2).

Logistic regression analysis was performed in order to identify the predictors of an indexed proximal aortic diameter ≥22 mm/m². All variables with a cut-off P ≤ 0.1 in the univariate analysis and those known to have an effect on aortic dilatation were included; namely: age, arterial hypertension, smoking and chronic pulmonary disease. Furthermore, we included parameters of LV hypertrophy (i.e. basal septal thickness) and preoperative transvalvular gradients in the multivariate analysis. The angle between the LV outflow axis and the aortic root (OR 1.1, P = 0.04) and the angle between the systolic peak velocity flow-jet and the aortic wall (OR 1.2, P = 0.001) were identified as the only independent predictors of an indexed proximal aortic diameter ≥22 mm/m² (Table 3).

## DISCUSSION

Aortic management of patients with BAV-associated aortopathy remains controversial. Phenotypic heterogeneity of BAV-associated aortic disease and inconsistency of published follow-up data [15] have resulted in a broad spectrum of surgical methods in the treatment of bicuspid aortopathy, ranging from the most conservative approach to a very aggressive aortic resection procedure. Such strategies are mostly based on the preference of individual surgeons or institutional policy [1]; however, data to support one specific treatment strategy over another are incomplete.

Although the concept of BAV heterogeneity has gained increasing acceptance in the last few years, there are only limited data on individual BAV phenotypes [2]. In the current study, we focused on the most common subgroup of BAV patients who are referred for AVR surgery, namely those with BAV stenosis. This clinical entity was selected intentionally as a ‘classical’ model in order to analyse haemodynamic factors in the development of aortopathy. Our previous data [16] and those from other groups [10] indicate that haemodynamic factors may play a major role in the development of aortopathy in patients with BAV stenosis. Nonetheless, the contributing effect of congenital aortic wall weakness may not be completely excluded as recently demonstrated in a bio-molecular study of aortic wall immaturity by Grewal et al. [17].
In-depth analysis of BAV phenotypes requires a better understanding of the correlation between morphological features and functional characteristics of the aortic root with transvalvular blood flow patterns. Cardiovascular MRI has the potential to integrate morphological and functional information obtained by non-invasive imaging and is ideally suited for research efforts focused on BAV disease [7]. In recent years, a number of rheological studies using novel imaging and analysis techniques such as flow-sensitive 4D cardiac MRI provided valuable insights into the transvalvular haemodynamics of BAV patients [8, 18].

Cusp fusion pattern in BAV disease has been reported to have a major impact on the severity of transvalvular flow abnormalities, a factor that might influence the expression of aortopathy [8, 18]. BAV patients with L/R fusion have significantly larger aortic root diameters and more severe histological changes in the proximal aorta, when compared with BAV patients with R/N fusion [5, 6]. However, published follow-up data on progression of aortopathy in different cusp fusion patterns are inconsistent. Some authors found BAV patients with L/R fusion at an increased risk of rapid aortic dilatation [19], while others reported the same findings in patients with R/N fusion [20]. One possible explanation for this discrepancy may be the co-existence of other rheological characteristics that also contribute to the development of BAV aortopathy. In our previous analysis, we found that transvalvular flow propagation in the proximal aorta was not uniform in BAV patients with the same cusp fusion pattern (e.g. the flow-jet was located at the right-lateral aortic wall in 65% and in the right-posterior wall in 35% of type I L/R BAV patients) [9]. Therefore, we prospectively examined additional functional characteristics of aortic root/parameters of transvalvular blood flow in the current study, in order to better define aortopathy in a consecutive group of BAV stenosis patients. Cardiac MRI analysis was performed with a special focus on (i) angulation between the LV outflow axis and the aortic root. Previously, den Reijer et al. quantified the deflection of systolic transvalvular flow by calculating the angle between the flow-jet direction vector and the aortic-LVOT channel axis at systole [21]; (ii) geometrical orientation of residual aortic valve orifice [22]; and (iii) angle between the systolic peak velocity flow-jet and the aortic segment in direct contact with the flow-jet. The effect of this angulation on the magnitude of systolic wall shear stress and progression of aneurysmal disease has been demonstrated in vitro and in vivo [18].

In the current study, the severity of bicuspid aortopathy was measured by an indexed proximal aortic diameter and histological sum-score in the jet-sample. This quantification was based on a previously demonstrated strong linear correlation between histological sum-score in the jet-sample and proximal aortic dimensions [9], a finding that could be confirmed in our current analysis. The sum-score of control samples demonstrated only a weak correlation with haemodynamic parameters of transvalvular blood flow and the diameters of the proximal aorta [9]. Therefore, we focused on the sum-score in the jet-sample as a better marker of the severity of aortopathy.

Our results demonstrate that the angle between the LV outflow axis and the aortic root (angle LV/Aorta) and the angle between the systolic peak velocity flow-jet and the aortic segment in direct contact with the flow-jet (angle jet/Aorta) correlated significantly with the severity of bicuspid aortopathy (Fig. 4A–C and Table 3). The geometric orientation of residual aortic valve orifice and the cusp fusion pattern failed to reach significant correlation with the indexed proximal aortic diameter and histological sum-score.

There might be several explanations for our finding that angle LV/Aorta is a strong correlate of the severity of bicuspid aortopathy. From a bio-mechanical point of view, the angle LV/Aorta may be considered as a first ‘obstacle’ in the way of a high-velocity forward flow-jet generated during LV systole which propagates along the outflow axis. Therefore, a large angle LV/Aorta may initiate a significant axial deflection of systolic forward flow which impacts with high-energy on the adjacent aortic wall. Secondly, there are some data in the literature indicating that angle LV/Aorta may have a major impact on transvalvular pressure gradients across mechanical aortic valve prostheses [23] and may aggravate dynamic LVOT obstruction in hypertrophic obstructive cardiomyopathy [24].

The causes of individual variability of angle LV/Aorta have still to be identified. No longitudinal MRI data are available to date and we cannot therefore exclude the possibility that this angulation may change over time, as aortic stenosis and LV remodelling progress. Nonetheless, we found no significant correlation between the angle LV/Aorta and parameters of LV hypertrophy (i.e. $r = 0.02, P = 0.8$ and transvalvular gradients $r = -0.3, P = 0.2$). Moreover, it remains to be clarified if this angulation is specific for BAV disease and if it is influenced by the changing shape of a progressively enlarging aorta.

We were able to identify at least two typical combinations of aortic root functional characteristics and resultant rheological parameters (i.e. haemodynamic profiles). The first haemodynamic profile (Fig. 5A) may be characterized by a large angle between the LV outflow axis and the aortic root (i.e. angle LV/Aorta >50°) in combination with an eccentric/asymmetric residual opening. The resultant systolic transvalvular flow-jet propagates very eccentrically and hits at a short distance and very steep angle (i.e. angle jet/ Aorta >30°) against the right-posterior segment of the aortic root. This constellation of functional/rheological parameters was associated with a 67% prevalence of bicuspid aortopathy in our study and may be summarized as a ‘deleterious’ haemodynamic profile. The second form (Fig. 5B) is characterized by a small angle between the LV outflow axis and the aortic root (i.e. angle LV/Aorta <50°) in combination with a symmetric/slit-shaped residual opening. The resultant systolic jet is centrally located and propagates a relatively long distance along the aortic axis before it contacts the right-lateral segment of the mid-ascending aorta in a tangential fashion (i.e.
angle jet/Aorta <30°). This combination of functional/rheological characteristics was associated with a low prevalence of aortopathy (i.e. 13%) in our study and therefore may be considered a 'benign' haemodynamic profile. We are aware of the fact that other forms of BAV-associated haemodynamic profiles may also exist.

We conclude that a specific combination of structural/functional aortic root parameters in patients with BAV stenosis (i.e. angle LV/Aorta in combination with geometric orientation of residual valve orifice) may result in a specific haemodynamic profile of systolic transvalvular flow, which in turn predicts the extent of associated aortopathy.

Study limitations

The current study has some limitations. Only patients with severe/symptomatic BAV stenosis referred for AVR surgery were included in this study. This clinical entity represents a typical surgical population and our findings may therefore not be generalizable to the whole BAV population. Moreover, we have no longitudinal MRI data on the development of BAV disease in our study group. Therefore, we may not exclude the possibility that the transvalvular flow pattern changes over time and worsening aortic valve stenosis may transform the flow. Furthermore, we may not exclude the fact that the progressively enlarging aorta simultaneously elongates and causes horizontalization of the heart so that the angle LV/Aorta widens as a secondary effect. Nevertheless, we found a total of 19 study patients with a large angle LV/Aorta (i.e. angle LV/Aorta >50°) and an indexed aortic diameter that was <22 mm/m². Only a longitudinal MRI study of BAV patients with a normally sized aorta would be able to address this issue.

The lack of comparison with a representative tricuspid aortic valve (TAV) group is another limitation of our study. Comparison of functional haemodynamic parameters between patients with BAV versus TAV stenosis will be an issue of ongoing prospective study.

CONCLUSIONS

Our study demonstrates a strong correlation between the functional characteristics of the aortic root/haemodynamic parameters of transvalvular flow and the severity of bicuspid aortopathy. Functional parameters of the aortic root may be used to predict the severity of aortopathy in patients with BAV stenosis, and may
be useful in determining intraoperative management of the ascending aorta and future risk of aortic disease in such patients.

**Conflict of interest:** none declared.

**REFERENCES**


**APPENDIX. CONFERENCE DISCUSSION**

Dr A. Della Corte (Naples, Italy): The fact that the flow is skewed and hits the aortic wall in an abnormal fashion is already acquired knowledge, but you put it in relation with the degree of aortic wall degeneration, which is a very good idea.

I have a couple of questions, and I will start by stimulating some insights from you. What is the possible explanation for the left ventricle to aorta angle predicting the dilatation and the degree of degeneration of the aortic wall? By what mechanism could this angle influence aortic wall degeneration, and what are the determinants of this angle in bicuspid patients?

Dr Girdauskas: It’s a very good question. Unfortunately, at the moment we don’t know what influences this angle between the left ventricle and the aortic root. The issue that is really important is the combination of haemodynamic factors which was shown for the residual aortic valve orifice.

At present we have no longitudinal data on these patients, and that’s a major problem because you cannot state if this angulation changes over time as aortic valve stenosis progresses. Moreover, it remains to be clarified if this angulation is influenced by the changing shape of the enlarging aorta. This might be very useful information in order to answer this question.

Dr Della Corte: So it may be either a consequence of aortic valve stenosis, as left ventricle hypertrophy and remodelling may alter also the angle of the aorta over the ventricle, or it may be a consequence of aortic dilatation. You found it in the most dilated ascending aortas in your study, didn’t you?

Dr Girdauskas: That’s right.

Dr Della Corte: Right. Then I would like to call you to some comparison with the literature because I think you give some explanation of previous apparently inconsistent findings in the literature.

You find no difference in the early wall degeneration between the two types of bicuspid aortic valve you compared, the right-left and the right-non, which is different from what has been previously reported, and I think your data are more reliable than those previously reported.

Secondly, did you confirm the correlation between the degree of medial degeneration and the aortic diameter that you found in your study?

Dr Girdauskas: Thank you. Regarding the first part of your question, I absolutely agree with your statement regarding the cusp fusion pattern and the histological changes.

Now, the histological alterations in patients with aortic stenosis depend where you collect your aortic sample. If you look at the MRI flow analysis, it’s really fascinating because you may appreciate that both cusp fusion patterns, i.e. right-noncoronary and right-left coronary, produce a different shape of systolic transvalvular flow. The aortic segment where the systolic flow jet hits the aortic wall is different. So if you collect your aortic samples at the site of maximal flow induced stress, you find the same pattern of histological changes.
Trying to overcome the ‘chicken or egg’ impasse in bicuspid aortopathy research

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A reliable parameter for measuring the severity of an aortopathy is currently lacking, probably because of the lack of knowledge of what defines the presence of an aortopathy. Is it just increased aortic diameters? Or is it the evidence, with or without dilatation, of altered mechanical properties of the aortic wall? Or presence of histological/biomolecular alterations? Most probably, different experts would answer differently to these questions, but the ‘correct’ answer is unknown.

About 10 years ago, having studied the intrinsic stenotic-like kinematics of the echocardiographically normo-functional bicuspid aortic valve (BAV) in magnetic resonance imaging (MRI) examinations, my colleagues and I looked for a method to quantify the restriction of the systolic opening motion of the fused leaflet: 2D true-Fast Imaging with Steady-state Precession (true-FISP) and phase-contrast sequences suggested that conjoint cusp hypomobility, that is, restricted motion in opening phase, was responsible for flow-jet deflection from the vessel’s axis [1]. In a small, selected cohort of patients with morphologically and functionally ‘homogeneous’ BAVs, all right-crownary-left-crownary type, all non-stenotic and non-regurgitant, the cusp opening angle (COA, between the long-axis section of the central part of the fused leaflet and the ventricular-aortic junction plane, in systole), was significantly narrower than in matched tricuspid aortic valve (TAV) of healthy subjects, showing a significant correlation with the yearly aortic growth rate in subsequent prospective follow-up [1], thus proving to be a promising tool for prognostic stratification. Since then, we have expanded that cohort, confirming the results also in the right-coronary-non-crownary type of BAV.

The study by Girdauskas et al. [2] similarly proposes novel 2D-MRI parameters to quantify flow derangement in the ascending aorta of BAV patients, but focuses on a different setting, that is, severe aortic stenosis. By choosing normally functioning BAV patients, our aim [1] was to identify early imaging markers, whereas Girdauskas’ study [2] sought to transfer the concept to the surgical decision-making process: an effective MRI predictor of aortopathy severity could help in the choice of whether to replace the ascending aorta at the time of aortic valve replacement for BAV stenosis, regardless of the diameter.

Observing a significant association, however, does not mean identifying a causal relationship. In our abovementioned study [1], the two groups of patients (BAV and TAV) were well matched for all clinical variables except ascending aorta dimensions (larger in BAV), so we wondered whether the skewed flow pattern in BAV subjects could be a consequence rather than a determinant of the aortopathy: given that differences in diameter and mechanical properties can affect flow patterns, we were faced with the typical ‘which came first the chicken or the egg’ dilemma. Thus, we used computational fluid dynamics to reproduce the flow pattern associated with BAV (restricted COA) and TAV motion (normal COA).