Correlation between systolic transvalvular flow and proximal aortic wall changes in bicuspid aortic valve stenosis

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Abstract

OBJECTIVES: The purpose of this study was to analyse the correlation between preoperative systolic transvalvular flow patterns and proximal aortic wall lesions in patients undergoing surgery for bicuspid aortic valve (BAV) stenosis.

METHODS: A total of 48 consecutive patients with BAV stenosis (mean age 58 ± 9 years, 65% male) underwent aortic valve replacement (AVR) ± proximal aortic surgery from January 2012 through February 2013. Preoperative cardiac phase-contrast cine magnetic resonance imaging (MRI) assessment was performed in all patients in order to detect the area of maximal flow-induced stress in the proximal aorta. Based on these MRI data, two aortic wall samples (i.e. area of the maximal stress (jet sample) and the opposite aortic wall (control sample)) were collected during AVR surgery. Aortic wall changes were graded based on a summation of seven histological criteria (each scored from 0 to 3). Histological sum score (0–21) was separately calculated and compared between the two aortic samples (i.e. jet sample vs control sample).

RESULTS: An eccentric transvalvular flow jet hitting the proximal aortic wall could be identified in all 48 (100%) patients. The mean histological sum score was significantly higher in the jet sample vs control sample areas of the aorta (i.e. 4.1 ± 1.8 vs 2.2 ± 1.5, respectively) (P = 0.02). None of the patients had a higher sum score value in the control sample.

CONCLUSIONS: Our study demonstrates a strong correlation between the systolic pattern of the transvalvular flow jet and asymmetric proximal aortic wall changes in patients undergoing AVR for BAV stenosis.

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

INTRODUCTION

The optimal treatment of patients with bicuspid aortic valve (BAV) disease and ascending aortic dilatation is still controversial. The widely accepted theory that BAV disease is a congenital disorder of vascular connective tissue [1, 2] has led to aggressive treatment recommendations of the proximal aorta in such patients, approaching aortic management recommendations for patients with Marfan syndrome [3, 4]. However, recent clinical evidence does not support such an aggressive surgical approach to BAV patients [5, 6]. It is widely accepted that BAV is a heterogeneous disease with markedly different types of BAV-associated aortopathy (i.e. so-called BAV phenotypes) [7, 8]. Individual BAV phenotypes may be caused by unique pathogenetic mechanisms and may require tailored surgical approaches [9]. Recent in vitro and in vivo studies have provided major insight into the pathogenesis of the different phenotypes of BAV disease [10–12].

In the current study, we focused on one of the most common groups of BAV patients, namely those with BAV stenosis. Haemodynamic factors have been proposed to play a major role in the development of aortopathy in patients with BAV stenosis [8, 13]. However, such a haemodynamic hypothesis has been mostly based on indirect observational data and definitive clinical evidence is lacking. The aim of this study was to, therefore, prospectively evaluate systolic transvalvular flow patterns and associated proximal aortic wall lesions in patients undergoing surgery for BAV stenosis.

MATERIALS AND METHODS

We prospectively evaluated all patients with BAV stenosis who underwent aortic valve replacement (AVR) with or without concomitant
proximal aortic replacement at Central Hospital, Bad Berka, Germany from January 2012 through February 2013. Study approval was obtained from our local ethics committee and all patients gave written informed consent.

A total of 70 patients with BAV disease underwent elective AVR surgery with or without concomitant proximal aortic replacement at our institution during the study period. BAV patients with predominant aortic valve insufficiency (n = 18) were excluded from this analysis. Moreover, 4 BAV patients who had contraindications for preoperative magnetic resonance imaging (MRI) examination (i.e. claustrophobia or implanted cardiac pacemaker/defibrillator) were excluded. Other exclusion criteria included the presence of Marfan syndrome and those undergoing urgent or emergent surgery. Based on these inclusion criteria, a total of 48 consecutive patients with BAV stenosis (mean age 58 ± 9 years, 65% male) were identified and served as a focus of the current study.

Definitions and measurements

The morphology and function of the aortic valve was assessed by preoperative echocardiography and cardiac MRI in all patients. BAV was suspected if two-dimensional (2D) short-axis imaging of the aortic valve demonstrated the existence of only two commissures delimiting two aortic valve cusps. The final decision regarding the bicuspidity of aortic valve was made based on the intraoperative description of valve anatomy by the surgeon. Aortic valve stenosis was defined according to published guidelines [14].

The diameter of the proximal aorta was measured preoperatively by means of transthoracic echocardiography and MRI. If the ascending aorta was <45 mm in diameter, an isolated AVR was performed.

Preoperative magnetic resonance imaging examination

Preoperative cardiac phase-contrast cine MRI examination was performed in all patients with suspected BAV stenosis in order to detect the area of maximal flow-induced stress in the proximal aorta.

A single non-contrast cardiac MRI (Avanto 1.5T scanner; Siemens, Erlangen, Germany) which included structural, functional and phase-velocity-encoded imaging of the left ventricular outflow tract (LVOT) and the proximal aorta was performed. In the first step, morphological images of the whole chest were acquired using coronal and transverse views (i.e. dark-blood technique: haste T1 in transverse view and bright-blood technique: trufi single-shot coronal) in order to visualize the geometry of the heart and the proximal aorta. Based on these images, the maximal diameter of the proximal aorta was measured as the largest observed cross-sectional diameter perpendicular to the aortic axis in a mid-vessel slice. In the next step of examination, real-time breath-hold steady-state free precession (SSFP) cine images (tfZD) were performed to detect the direction of abnormal, eccentric systolic flow jet in the proximal aorta. The quality of the systolic transvalvular jet (i.e. centric vs eccentric vs turbulent) was characterized using function sequences in the oblique coronal and the oblique sagittal LVOT views. In order to exactly localize the area where the systolic transvalvular jet contacts the aortic wall, real-time phase-contrast imaging was used in the above-mentioned views. For this purpose, the definition of flow velocity-encoded window was as close to the peak velocity of the transvalvular jet as possible (i.e. between 200 and 400 cm/s) on in-plane 2D personal computer (PC) imaging in order to minimize artefacts. A thorough analysis of function sequences and PC images was performed to detect the area maximal flow-induced stress in the proximal aorta (i.e. segment of aortic circumference that was in direct contact with the flow jet) and the exact distance (cm) between aortic valve plane and the area of maximal flow-induced stress in the proximal aorta. The circumference of proximal aorta was subdivided into six segments in order to more precisely describe the area of maximal flow-induced stress. All characteristics of the transvalvular flow jet were analysed by two study radiologists (Thorsten Scholle and Beatrix Fey). These MRI data were used to guide the sampling of aortic tissue during surgery.

Moreover, the morphology (i.e. cusp fusion pattern) and opening area of the BAV was analysed by placing a SSFP-function sequence parallel and just distal to the aortic valve annulus (i.e. at the origin of the transvalvular flow jet). Aortic valve opening area was measured directly by means of the Syngo MR B17 software (Siemens, Erlangen, Germany).

Study population

Preoperative and intraoperative variables of the study population are displayed in Table 1. Briefly, a consecutive group of relatively young, symptomatic patients with BAV stenosis underwent elective AVR surgery. The most common comorbidity was arterial hypertension (92%) and one-fourth of all the patients were smokers. All 48 patients underwent conventional AVR with or without proximal aortic surgery through a median sternotomy using standard cardiopulmonary bypass with moderate systemic hypothermia. Intraoperative management was performed using

<table>
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<th>Table 1: Preoperative/intraoperative patient variables</th>
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<tr>
<td><strong>Variable</strong></td>
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<td>Mean age (years)</td>
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<td>Mechanical valve prosthesis</td>
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<tr>
<td>Aortic root replacement</td>
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<td>Hemiarch replacement</td>
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Data presented as numbers (%) or as mean ± SD (range). BAV: bicuspid aortic valve; BSA: body surface area; COLD: chronic obstructive lung disease; CPB: cardiopulmonary bypass; NYHA: New York Heart Association.
uniform and standardized surgical and anaesthetic protocols. The stenotic aortic valve was replaced with a stented tissue valve in 54% of patients, and a mechanical valve in the remaining 46% of patients. The labeled valve prosthesis size was 21 mm in 19% of patients, 23 mm in 42%, 25 mm in 29% and 27 mm in 10%. A total of 7 patients (15%) underwent concomitant replacement of the supra-coronary ascending aorta with a tube graft for coexistent aortic aneurysm >45 mm in diameter.

No patient died postoperatively. One patient (2%) suffered a perioperative stroke. Moreover, 1 patient developed a low cardiac output syndrome on the second postoperative day. Coronary angiography showed an acute thrombotic occlusion of the ostial circumflex artery, which was successfully treated by emergency coronary artery bypass grafting. All remaining patients had an uneventful postoperative course.

### Histological examination

Based on preoperative MRI analysis, two aortic specimens were collected during AVR surgery for each patient. The first aortic specimen (so-called ‘jet-sample’) was obtained from the area of maximal flow-induced stress as identified by MRI analysis. The second sample (i.e. ‘control-sample’) was collected from the opposite aortic wall. In a total of 41 (85%) study patients who underwent isolated AVR only, aortic specimens were obtained from the aortotomy incision. The height of aortotomy incision was tailored individually in order to correspond with the preoperative MRI data. Aortic specimens were collected from intraoperatively excised aortic tissue in the remaining 7 patients who required simultaneous ascending aortic replacement.

Both aortic samples were fixed in 4.5% pH-buffered formalin and sent to the pathology institute of the adjacent university hospital. The tissue was processed for light microscopy, embedded in paraffin and sections were performed perpendicular to the aortic wall from each specimen. 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 vs control sample).

A semi-quantitative histological grading scale, described by Bechtel et al. [15], was used for the gradation of aortic wall alterations. Briefly, aortic wall changes 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 graded from 0 (no change) to 3 (most severe change), which was based on the worst area observed at light microscopy. The values of all seven histological qualities were summarized in a histological sum score (0–21) for both aortic samples (i.e. jet sample vs 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 with range throughout the manuscript. All statistical analyses were performed with the IBM SPSS 19.0 software (IBM corp., New York, NY, USA). Histological sum score in the jet sample vs control sample was compared using the Mann-Whitney U-test. P-values of ≤0.05 were considered statistically significant.

### RESULTS

Intraoperative analysis revealed fusion of the right-left coronary cusps (i.e. BAV type 1, L/R, S) in 33 patients (69%), right-non-coronary cusps (i.e. BAV type 1, R/N, S) in 13 patients (27%) and left-non-coronary cusps (i.e. BAV type 1, N/L, S) in 2 patients (4%), according to Sievers classification system [16].

An eccentric transvalvular flow jet directed towards the proximal aortic wall could be identified in all 48 (100%) patients (Fig. 1). The area of maximal flow-induced stress, as identified by preoperative MRI, was localized at the right-lateral segment of the ascending aorta in 29 (60%) patients, at the right-posterior segment in 18 (38%) patients and at the right-anterior segment in the remaining 1 (2%) patient (Fig. 2). The mean distance between aortic valve plane and the area of maximal flow-induced stress in

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**Figure 1:** Identification of the transvalvular eccentric flow jet in the proximal aorta by cardiac magnetic resonance imaging. Eccentric flow jet directed towards the right-posterior segment of the ascending aorta in oblique sagittal view (A) and coronal view (B). Arrows show contact point between eccentric flow jet and ascending aorta.
the proximal aorta (i.e. aortic segment in direct contact with the flow jet) was 49 ± 11 mm (25–76 mm).

The aortic segment in direct contact with the transvalvular flow jet was located at the right-lateral wall of the proximal aorta most commonly in BAV patients with the right-left coronary cusp fusion (i.e. 65%). In contrast, a transvalvular flow jet hitting the right-posterior segment of the proximal aorta was seen more commonly in BAV patients with the right-non-coronary cusp fusion vs BAV patients with the right-left coronary cusp fusion (i.e. 58 vs 35%, \( P < 0.01 \)).

Mean histological sum score was significantly higher in the jet sample vs control sample (i.e. 4.1 ± 1.8 vs 2.2 ± 1.5, respectively) (\( P = 0.02 \)). Moreover, none of the study patients had a higher histological sum score value in the control sample when compared with the jet sample.

Difference in the sum score in jet sample vs control sample was even higher in the subgroup of study patients (\( n = 18 \)) with a proximal aortic diameter of >40 mm (i.e. 5.0 ± 1.4 vs 2.4 ± 1.5, respectively) (\( P < 0.01 \)). The cut-off value of 40 mm was used on the basis of our previous retrospective studies [6, 8]. Moreover, there was a strong linear correlation between histological sum score in the jet sample and the diameter of the proximal aorta (\( r = 0.7, P = 0.01 \)). There was only mild correlation between sum score in the control sample and the diameter of the proximal aorta (\( r = 0.3, P = 0.04 \)) (Fig. 3A and B).

**DISCUSSION**

The optimal surgical treatment of patients with BAV disease and concomitant dilatation of the ascending aorta remains controversial. A full spectrum of surgical methods has been advocated for the treatment of BAV-associated aortopathy ranging from the most conservative approach (i.e. leaving the aortic dilatation untreated in the absence of a large aneurysm) to a very aggressive procedure (i.e. routine composite graft replacement of the aortic root [17] and total aortic arch replacement in the majority of BAV patients [4]). However, such strategies are mostly based on indirect observational data and clinical evidence to support one specific treatment strategy over another is insufficient.

BAV disease has been shown to be a very heterogeneous disorder with markedly different types of BAV-associated aortopathy (i.e. so-called BAV phenotypes) [7, 8]. Individual BAV phenotypes may be caused by unique pathogenetic mechanisms and may require tailored surgical approaches [9, 13]. Novel in vitro and in vivo studies have provided some insight into the pathogenesis of the different phenotypes of BAV disease [10–12]. Of particular interest, Hope et al. [10] used four-dimensional flow MRI to convincingly show abnormal helical systolic flow patterns, even in the absence of relevant BAV stenosis or coexistent aortic aneurysm. However, there are only limited data on the clinical outcomes of individual BAV phenotypes.

In the current study, we focused on the most common and homogeneous subgroup of BAV patients, namely those with BAV stenosis. Our previous data [8] and those from others [13] indicate that haemodynamic factors play a larger role in the pathogenesis of aortopathy in the patients with BAV stenosis than previously acknowledged. Based on recently published haemodynamic...
studies of BAV disease [18], we prospectively evaluated systolic transvalvular flow patterns and the associated proximal aortic wall lesions in the patients with BAV stenosis. Our results clearly demonstrate more severe histological lesions in the area of the proximal aorta where maximal flow-induced stress occurs, as identified by preoperative cardiac MRI analysis. The mean histological sum score within patients was significantly higher in the jet sample vs control sample (i.e. 4.1 ± 1.8 vs 2.2 ± 1.5), which is the most important finding of this study. These data indicate a strong correlation between the systolic transvalvular flow pattern and histological changes in the proximal aorta in the patients with BAV stenosis, further supporting the haemodynamic theory of BAV-associated aortopathy and refuting the genetic theory in such patients. The mean histological sum score values were relatively low in both samples (i.e. sum score ranged from 0 to 21), which is indicative of rather mild histological lesions in the aortic wall texture. The reason for this finding may be a small number of patients with significant aortic dilatation in our study (i.e. only 15% patients underwent simultaneous supracoronary ascending aortic replacement). In support of this argumentation, we also found a linear correlation between histological sum score in the jet sample and the diameter of the proximal aorta in our study. Moreover, this finding supports the clinical relevance of histological grading model [15], which was used for the assessment of proximal aortopathy in our study.

The area of maximal flow-induced stress, as identified by preoperative MRI, was localized at the lateral and/or posterior wall of the greater curvature of the ascending aorta in 98% of our study patients (Fig. 2). In addition, the area of contact between eccentric flow jet and the aortic wall was located in the proximal ascending aorta in the majority of study patients (i.e. on average 50 mm above aortic valve plane). These findings support the phenotypic association between BAV stenosis and asymmetric dilatation of the tubular ascending aorta, as described by Cotrufo et al. [13].

Only minor differences in the propagation pattern of the transvalvular flow jet were found between BAV patients with the right-left coronary cusp fusion vs right-non-coronary cusp fusion. The systolic transvalvular flow jet was directed more right-laterally in BAV patients with the right-left coronary cusp fusion, whereas BAV patients with the right-non-coronary cusp fusion showed flow jet towards the posterior segment of the greater curvature more frequently. However, we failed to find a difference in the dilatation pattern of the proximal aorta between these two subgroups of patients. Indeed, we found only asymmetric dilatation at the convexity of the tubular ascending aorta in all patients. This finding is in contrast with the previously published data by Russo et al. [19]. However, Russo et al. analysed a mixed BAV population (i.e. patients with BAV stenosis and BAV insufficiency, which were almost equally distributed in the study cohort).

Another interesting finding in our study is that transvalvular flow characteristics were not uniform in BAV patients with the same cusp fusion pattern (e.g., 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). This finding may be explained by differences in the exact geometrical orientation of the residual aortic valve orifice, which could be shown by preoperative cardiac MRI analysis. Another possible explanation for this phenomenon could be a variable angulation between the LVOT and the aortic root, as described previously by den Reijer et al. [11]. These additional factors may have influenced the propagation of flow jet in the proximal aorta.

**Study limitations**

The current study has some limitations, starting with the limited study sample size. However, our goal was to focus on a homogeneous subgroup of BAV patients who underwent elective isolated AVR surgery with/without concomitant proximal aortic replacement, thereby limiting the size of the potential patient group. The lack of comparison with a representative tricuspid aortic valve (TAV) group is another limitation of our study. Our plan is to perform such a comparison (i.e. BAV vs TAV) in a following study.

**Conclusions**

Our study demonstrates a strong correlation between the systolic pattern of the transvalvular flow jet and the asymmetric proximal aortic wall changes in patients with BAV stenosis. The present data further support the hypothesis that BAV-associated aortopathy in patients with BAV stenosis represents a predominantly haemodynamic-induced phenomenon. Such an observation has clinical implications in the approach to the ascending aorta in patients with BAV stenosis.

**Conflict of interest:** none declared.

**REFERENCES**


APPENDIX. CONFERENCE DISCUSSION

Dr M. Misfeld (Leipzig, Germany): Dilation of the ascending aorta occurs frequently in patients with bicuspid aortic valves. Since aortic valves and the ascending aorta originate from the same embryonic cells, viz., the neural crest cells, pathologies of both structures may be genetically linked. On the other hand, it has been shown in numerous studies that both pathologies are also closely associated with each other because certain haemodynamic changes occur in bicuspid aortic valves, including specific flow patterns in the ascending aorta. In addition, it has been demonstrated that there are various regional iterations of endothelial nitric oxide synthase in ascending aortic aneurysm, variations in activities at the protein level, as well as changes at the microstructural level with regard to collagenous and elastic fibres, fibroblasts and smooth muscle cells.

Since we see different types of bicuspid aortic valves and a variety of ascending aortic aneurysms, from symmetric ones to saccular dilations, commonly affecting the convexity of the ascending aorta, there might be unknown pathologies and hypotheses which could explain the relationship between the presence of bicuspid aortic valves and the development of ascending aortic aneurysms. This may also be true because some patients with bicuspid aortic valves develop aneurysms and some do not.

Dr Girdauskas and co-workers analysed 48 consecutive patients with bicuspid aortic valve stenosis using MRI imaging and identified the areas of maximal wall stress in the ascending aorta where the flow jet hits the aortic wall. These regions were further analysed histologically using a specific histological sum score and compared to aortic tissue samples without increased wall stress. In the majority of cases, histological changes as judged by the sum score were more severe in the area of the ascending aorta where the flow jet hits the aortic wall, indicating cellular damage. The authors conclude that there is a strong relation between the systolic pattern of transvalvular flow jets and asymmetric changes in the ascending aorta.

Dr Girdauskas and his colleagues are to be commended for the excellent idea of analysing and correlating MRI images with histological changes in patients with bicuspid aortic valves and aneurysms of the ascending aorta. These findings will help to increase the knowledge of the best strategy for treating this specific group of patients having both pathologies. However, some aspects need further clarification and I would like to ask the authors to comment on the following.

First of all, how do they explain that in the most common type of bicuspid aortic valves, type I L/R following Sievers’ classification, the flow jet was located at the right lateral wall in 65% of cases and in the right posterior wall in 35% of patients, and that these flow characteristics were not more uniform? Secondly, did the authors observe different forms of aneurysms, for example, symmetric and asymmetric with dilation specifically and convexity of the ascending aorta, and how could these findings have affected the histological analysis? Thirdly, the histological sum score ranged from 0 to 21. How can a mean sum score of 4.1 in a jet sample versus 2.2 in the control sample be weighted? Do these scores correspond to mild or more severe histological tissue damage, especially because some samples with aneurysmal areas about 45 mm in the control group show sum scores above 2, and some samples without dilatation in the jet sample show sum scores under 2.

Dr Girdauskas: I would like to start with the first question regarding the flow patterns in patients with right/left coronary cusp fusion. The main finding from our study was that all these patients the right/left cusp fusion demonstrated a flow jet which was directed to the convexity of the vessel. The great majority of these patients showed propagation of the flow jet to the right lateral aortic wall. However, some of them had a flow jet directed more to the posterior wall of the great curvature. I think the reason for this, and it could be clearly demonstrated in our MRI analysis, is that the flow jet direction is not only influenced by the cusp fusion pattern but additionally by exact geometrical orientation of the residual orifice.

Another explanation for this phenomenon is the variance in the angulation between the left ventricular outflow tract and the proximal aorta. I think these are the two additional factors which influence the exact propagation of a flow jet.

Regarding your second question, we observed only asymmetric dilation in the proximal part of a tubular aorta, in the convexity of the vessel, as presented by Dr Della Corte in the form of type I dilatation. We have not seen other aortic dilatation patterns in these BAV stenosis patients.

And the last question was regarding the histological sum score values in the jet versus control samples. You are absolutely right that we saw relatively low score values in both samples, which indicates rather mild histological changes in both samples. I think the reason for this finding may be that we have a relatively low proportion of patients who have significant aortic dilatation in our study, as only 15% of them underwent an ascending aortic replacement. However, I think this fact highlights the importance of comparing the scores of the jet sample and the control sample.

Dr A. Della Corte (Naples, Italy): I have just a comment. I cannot but agree with your study because we have found similar results in our previous studies as well. What I would like to stress is that it is not so clear-cut: bicuspid stenosis patients have a haemodynamically driven aneurysm; regurgitation patients have a genetic cause of the disease. I think that both factors may coexist, and studies like yours may possibly help to find the tools to identify in the single patient, which of the two factors is predominant.

As a matter of fact, you lack a tricuspid aortic valve control group, actually. Should you find similar relation between grades of medial degeneration and patterns of flow and the wall stress in tricuspid aortic valve stenosis patients, then you could say it’s all haemodynamics; otherwise, some other factors may coexist.

Dr Girdauskas: I absolutely agree with you. Actually we included a tricuspid group in our current study. However, because of the inclusion age of less than 65, the subgroup of tricuspid patients was too small for any reasonable statistical analysis at the present time. As we are moving on with the study, the tricuspid group should become reasonable and we will probably be able to present the data next year.