The fate of the bicuspid valve aortopathy after aortic valve replacement

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Abstract

OBJECTIVES: The fate of the aortic dimensions in patients with a bicuspid aortic valve (BAV) after aortic valve replacement (AVR) is unclear. We investigated the evolution of aortic root and ascending aorta dimensions in patients with a BAV after AVR. To neutralize the effect of pathological transvalvular haemodynamics on aortic dimensions, we evaluated our hypotheses in patients with normal transvalvular haemodynamics after a subcoronary autograft procedure, which preserves intact the native aortic wall.

METHODS: We excluded patients operated on for endocarditis; who developed autograft insufficiency > trivial and who required autograft reoperation during the follow-up. We included 448 patients (361 with BAV; 340 males; 44.6 ± 11.4 years; mean follow-up: 7.5 ± 3.9 years). Valve phenotype was determined during surgery. Annual echocardiographic examinations (n = 3336) were performed (follow-up completeness > 98%). To allow for somatometric, gender and age influences, z-values of measurements were calculated from the general population (GP) and analysed using longitudinal methods.

RESULTS: The increase in ascending aorta did not differ from that expected in the GP (0.04 z-values/year; P = 0.06). No difference could be observed in diameter increase rates between BAV and tricuspid aortic valve patients (TAV) (0.04 vs 0.06 z-values/year; P = 0.3), as well as between BAV phenotypes. The sinus increase did not differ from that expected in the GP (0.03 z-values/year; P = 0.1), and no significant differences could be observed between BAV phenotypes. In patients undergoing aortoplasty (n = 70), no significant difference in the rates of ascending aorta and sinus increase could be observed; compared with the GP.

CONCLUSION: For the time period of this study and in patients with normal aortic root haemodynamics after AVR, ascending aorta dimensions over time are similar to that of the matched GP. Patients with a BAV did not exhibit higher rates of ascending aorta dilatation after AVR than patients with TAV. At least for the first postoperative decade, transvalvular haemodynamics appear to exhibit a greater influence than the genetic component of BAV on the development of the BAV aortopathy.

Keywords: Aorta • Ascending aorta • Aortopathy • Bicuspid aortic valve

INTRODUCTION

The bicuspid aortic valve is the most common cardiovascular malformation, with a prevalence of 1–2% in the general population (GP). The clinical presentation of BAV can vary from patients with severe valvular dysfunction and/or thoracic aortic aneurysms to asymptomatic individuals with competent valve function. Nevertheless, the presence of BAV is regarded as a risk for valve degeneration, and around 50% of patients requiring aortic valve replacement (AVR) present with a BAV [1].

In addition to valvular dysfunction, BAV has also been linked to the development of thoracic aortic aneurysms. The pathophysiology of aortic dilatation in patients with a BAV is unclear and poorly understood. It is believed that abnormal wall stress as a consequence of pathological transvalvular flow characteristics as well as cellular and extracellular abnormalities of the aortic wall in BAV patients contributes to the so-called ‘BAV aortopathy’ [2, 3].

This interplay between haemodynamics and changes on molecular level as well as their clinical implications poses a significant problem for the management of patients with a BAV requiring aortic valve surgery, especially in patients of young age. While the pathological valve function can be alleviated with successful repair or replacement of the valve, there is significant concern that the intrinsic aortic wall abnormalities in BAV patients may persist after valve replacement, and that these patients may still be at a higher risk for developing ascending aorta or root aneurysms and their associated complications. In patients with a BAV presenting for AVR, the individualized, evidence-based assessment of the risk for future aortic complications that would justify the individualized
indication for a more aggressive approach to the concomitant replacement of the ascending aorta at the time of primary valve replacement remains largely elusive.

The aim of the present study was to investigate the fate of aortic root and ascending aorta dimensions in patients with a BAV after AVR. To neutralize the effect of pathological transvalvular haemodynamics on aortic dimensions, we evaluated our hypotheses in patients with normal transvalvular haemodynamics after a subcoronary autograft procedure, which preserves intact the native aortic wall [4]. Since there is significant evidence of a continuous dynamic in aortic dimensions with age and somatometric characteristics [5], we not only analysed the absolute time course of aortic measurements of our patient population but also compared these measurements to the expected measurements of the age, gender and body surface area (BSA)-adjusted GP [5].

METHODS

Between 1994 and 2012, 596 patients underwent a subcoronary autograft procedure at our institution. Surgical details and clinical outcomes have been reported in detail previously [4, 6] and are not the focus of the present study. For the purposes of this study, we excluded patients operated on for extensive endocarditis (n = 59), patients with previous AVR (n = 24), patients with non-determinable (n = 6) or non-documented aortic valve type (n = 19), patients who were not operated on with the subcoronary technique (n = 25), and patients who developed haemodynamically relevant autograft regurgitation (n = 15). In patients who developed a haemodynamically relevant autograft regurgitation, structural valve deterioration (leaflet prolapse or leaflet tear) or endocarditis was the cause of the regurgitation development. None of these patients experienced progressive autograft regurgitation due to autograft dilatation, as seen often in patients after the root replacement technique [7]. Our standardized echocardiographic and follow-up protocol has been reported in detail previously [4, 6].

We included 448 patients (361 with BAV; 340 males; 44.6 ± 11.4 years; mean follow-up: 7.5 ± 3.9 years, 3376.12 patient × years). Detailed demographics are presented in Table 1. In all patients, the valve phenotype [8] was determined during surgery. The breakdown of the ascending aorta interventions in the BAV and tricuspid aortic valve (TAV) groups is presented in Table 2. Annual echocardiographic examinations (n = 3336) were performed in detail previously [4, 6] and follow-up was 98% complete. The distribution of the maximum patient follow-up is displayed in Fig. 1.

Statistical analysis

Simple descriptive statistics were used to summarize the data. Continuous variables are presented as mean ± standard deviation. Categorical data are described using frequencies and percentages. Regression modelling estimates are presented as mean ± standard error. The P-values of two-sided tests are reported.

The course of aortic root dimensions over time was modelled using multivariate mixed-model regression allowing for a random

| Table 1: Patient demographics and operative and postoperative characteristics |
|-----------------|-----------------|-----------------|-----------------|
| Data            | Bicuspid aortic valve | Tricuspid aortic valve | Total result |
| N               | 361              | 87              | 448            |
| Male            | 281              | 59              | 340            |
| Age (years)     | 43.98 ± 10.51    | 47.29 ± 14.44   | 44.63 ± 11.43  |
| Ascending aorta diameters |
| Normal (angiography) | 81               | 45              | 126            |
| <40 mm          | 130              | 31              | 161            |
| 40-45 mm        | 67               | 8               | 75             |
| 46-50 mm        | 39               | 3               | 39             |
| >50 mm          | 44               | 3               | 47             |
| Pure aortic regurgitation | 82              | 39              | 121            |
| Ascending aorta intervention |
| Aortoplasty     | 142              | 7               | 149            |
| Replacement     | 63               | 7               | 70             |
| Annulus (mm)    | 25.87 ± 4.71     | 23.05 ± 4.36    | 25.52 ± 4.75   |
| Sinus (mm)      | 34.29 ± 5.24     | 30.21 ± 4.66    | 33.94 ± 5.31   |
| Sinotubular junction | 30.29 ± 5.62   | 27.41 ± 6.21    | 30 ± 5.73      |
| Ascending aorta (mm) | 40.75 ± 7.85   | 34.71 ± 8.25    | 39.97 ± 8.15   |
| Valve reoperations | 9               | 3               | 12             |
| Aortic reoperations | 0               | 0               | 0              |
| Freedom from reoperation (%) |
| 5 years         | 98.2 (96.8–100)  | 98.8 (96.6–100) | 98.2 (96.8–100) |
| 10 years        | 95.6 (90.8–100)  | 97.2 (95.2–99.2) | 95.6 (90.8–100) |
| 15 years        | 93.9 (87.6–100)  | 95.6.5 (90.8–100)| 93.9 (87.6–100) |
| Survival        |
| 5 years         | 98.4 (96.9–99.8) | 96.4 (92.5–100) | 98.4 (96.9–99.8) |
| 10 years        | 96.2 (93.6–98.8) | 91.9 (85.8–98.4) | 96.2 (93.6–98.8) |
| 15 years        | 82.4 (60.8–100)  | 77.5 (66.2–90.6) | 82.4 (60.8–100) |

Diameters are presented as mean ± standard deviation (range); Freedom from reoperation and survival estimates are presented as % (95% confidence interval).
The assumptions of linear mixed modelling were checked and validated [9, 10]. Stepwise elimination was employed to derive the final models. Transformation of variables to restore normality was employed as appropriate. The following variables were investigated: time, patient age, presence of BAV, BAV subtype [8], preoperative haemodynamics, presence of pure aortic regurgitation and gender.

To allow a comparison of the observed measurements with those expected from the GP (Fig. 2), an increasing dynamic was observed in the ascending aorta measurements (0.25 ± 0.05 mm/year; *P* < 0.001, Fig. 3, left). There was little evidence that this increase in the ascending aorta diameters differed from that expected in the age-, gender- and BSA-matched GP (0.03 ± 0.02 z-values/year; *P* = 0.07). There was a trend towards higher initial values in the BAV population (Δintercept 1.2 ± 0.7 mm; *P* = 0.09); however, no difference could be observed in the rate of increase with time (Δslope 0.07 ± 0.07 mm/year; *P* = 0.25). Similarly, when compared with the age, gender and BSA population expected values (Fig. 3, right), there was a trend for BAV patients towards a higher initial value postoperatively (Δintercept: 0.48 ± 0.26 z-values; *P* = 0.06) but no evidence of higher initial slope (Δslope 0.02 ± 0.02).

### RESULTS

#### Clinical outcomes

Detailed clinical outcomes have been reported previously [4, 6] and are beyond the scope of the present article. Neither in the initial (596 patients) nor in this study’s population (448 patients) could a statistically significant difference be observed in terms of reoperations or survival between BAV and TAV patients. Survival of both BAV and TAV group was similar to that of the general German population. In all reoperated patients (*n* = 12, Table 1) on the autograft, autograft dysfunction due to structural valve deterioration (leaflet prolapse or leaflet tear) [11] was the primary cause of reoperation. No aortic events (aortic dissections, development of aneurysm requiring intervention) were observed, and no reoperations on the aorta were observed or were scheduled until the time of database closure (Table 1).

#### Ascending aorta diameters

As expected from the GP (Fig. 2), an increasing dynamic was observed in the ascending aorta measurements (0.25 ± 0.05 mm/year; *P* < 0.001, Fig. 3, left). There was little evidence that this increase in the ascending aorta diameters differed from that expected in the age-, gender- and BSA-matched GP (0.03 ± 0.02 z-values/year; *P* = 0.07). There was a trend towards higher initial values in the BAV population (Δintercept 1.2 ± 0.7 mm; *P* = 0.09); however, no difference could be observed in the rate of increase with time (Δslope 0.07 ± 0.07 mm/year; *P* = 0.25). Similarly, when compared with the age, gender and BSA population expected values (Fig. 3, right), there was a trend for BAV patients towards a higher initial value postoperatively (Δintercept: 0.48 ± 0.26 z-values; *P* = 0.06) but no evidence of higher initial slope (Δslope 0.02 ± 0.02).
Figure 2: Fifth and 95th percentiles of the ascending aorta (left) and sinus of Valsalva (right) in males (solid line) and females (dotted line) without cardiac abnormalities, connective tissue disorders and BAV. Each line represents a BSA-specific curve. Adapted from ref. [5] with permission. BSA: body surface area.

Figure 3: Evolution of absolute (left) and relative (right) ascending aorta diameters in our patient population. The solid lines depict the evolution of a 49-year old male with 1.9 m² BSA and a tricuspid aortic valve (TAV) (blue line) or a bicuspid aortic valve (BAV) (red line). No difference in the slope of increase of ascending aorta diameters with time could be observed.
No significant influence of gender, preoperative haemodynamics or presence of pure aortic regurgitation could be observed on the slope of the absolute diameters or z-value diameters. Patients who underwent an aortoplasty did not experience higher rates of ascending aorta diameter or z-value increase (Fig. 4).

**Sinus of Valsalva diameters**

Sinus of Valsalva dimensions increased at a rate of $0.13 \pm 0.04$ mm/year ($P < 0.001$) (Fig. 5, left). There was no evidence that this increase in the diameters differed from that expected in the...
age-, gender- and BSA-matched GP (0.02 ± 0.02 z-values/year; \( P = 0.22 \)). No difference in the initial diameters (Δintercept 0.6 ± 0.5 mm; \( P = 0.2 \)) or the rate of increase with time (Δslope 0.08 ± 0.05 mm/year; \( P = 0.12 \)) between BAV and TAV could be observed. Patient age, male gender and presence of pure aortic regurgitation led to increased initial diameters (\( P < 0.01 \) for all); however, this did not influence the rate of increase with time. In a similar fashion to the absolute diameters, no significant difference between TAV and BAV could be observed in the initial z-values or the rate of their increase (Fig. 5, right).

**Aortic annulus**

An increase in annulus diameters with time could be observed (\( P = 0.001 \)) (Fig. 6, left); however, the rate of increase was significantly influenced by the patients' age and the slope flattened as age increases (from 0.22 mm/year at 40 years of age to 0.14 mm/year at 60 years of age; \( P < 0.001 \) for the interaction between age and time). Increased BSA, male gender and presence of pure aortic regurgitation led to increased initial diameters (\( P < 0.01 \) for all). Patients with a BAV had a slight, albeit statistically significantly higher initial diameters (Δintercept 1.2 ± 0.04 mm; \( P < 0.01 \), Fig. 6, left); however, no difference in the slope of increase between BAV and TAV could be observed (Δslope 0.02 mm/year; \( P = 0.59 \), Fig. 6, left). No influence of somatometric characteristics, gender or presence of pure aortic regurgitation on the slope of increase could be observed.

**Sinotubular junction**

Similarly, an increase in sinotubular junction (STJ) diameters could be observed with time (\( P < 0.001 \)) with a slope varying with patient age (from 0.34 mm/year at 40 years to 0.20 mm/year at 60 years of age; \( P < 0.02 \) for the interaction). Male gender, larger BSA and presence of pure aortic regurgitation were associated with statistically significant higher diameters (\( P < 0.001 \) for all). Patients with a BAV had a slightly higher initial STJ diameter (Δintercept 1.2 mm; \( P < 0.03 \), Fig. 6, right); however, no difference in the rate of increase could be observed (Δslope 0.08 mm/year; \( P < 0.10 \), Fig. 6, right). Somatometric characteristics and the presence of pure aortic regurgitation had no influence on the slope of increase with time. Patients who underwent an aortoplasty did not experience higher rates of diameter increase.

**DISCUSSION**

Our work adds to a significant body of evidence that has surfaced recently [12–15], altogether challenging the clinical significance of BAV aortopathy after correction of the valve lesion and the necessity for an aggressive strategy in patients with a BAV undergoing isolated aortic valve interventions. No aortic events were observed, nor any clinically significant development of aortic root or ascending aorta aneurysms. In the 12 patients who required a reoperation, structural valve deterioration or endocarditis was the sole indication, and in no patients was an intervention on the
ascending aorta necessary. In addition, this work may provide some insights on the interplay between genetics and haemodynamics as causes for the dilatation observed in many patients with a BAV. In patients with normal aortic haemodynamics after the subcoronary autograft procedure, which preserves the native aortic wall and restores ‘normal tricuspid transvalvular flow’ [16], we could not observe evidence of a higher increase in aortic root and ascending aorta diameters in patients with a BAV compared with those with a TAV for up to 15 years postoperatively. Additionally, during a considerable 3376 years of cumulative follow-up and at least for the first postoperative decade, we were unable to observe any indications of higher dilatation rates in either BAV or TAV patients in comparison with the age-, gender- and BSA-adjusted diameters of the GP.

It seems that the most important contributing factor to the development of aortic dilatation in BAV patients is the haemodynamic wall stress as a consequence of pathological transvalvular flow characteristics [17]. Our findings seem at first hand to be in contrast to other studies published that show that BAV patients with a ‘non-dysfunctional’ BAV have a higher expansion rate than the GP [18, 19]. However, evidences have recently surfaced that even ‘non-dysfunctional’ BAV may result in abnormal flow characteristics [20–22], which may still pose significant and continuous stress to the ascending aorta. Furthermore, it is unknown whether the characteristics of the control group in the previously mentioned trials have been thoroughly investigated and modelled for factors influencing aortic dimensions as in recent reports [5] or compared with the expected population values. Recent studies have verified that BAV patients after AVR, even with milder-to-moderate ascending aortic dilatation, have a considerably low risk for adverse aortic events [14, 15].

Although we were unable to find a difference in dilatation rates between patients with BAV or TAV, it must be noted that our approach to the ascending aorta of diameter measuring between 40 and 50 mm was relatively aggressive. Of the total 114 patients with an ascending aorta diameter between 40 and 50 mm (Table 2), 38 underwent an aortoplasty and 36 underwent a replacement, while in 40 patients, no intervention was performed. The decision to replace the ascending aorta in these patients was subjective, less well documented and included factors such as the quality and thickness of the aortic wall, the macroscopic configuration of the ascending aorta, the subtype of the BAV phenotype as well as the patient’s age and somatometric characteristics.

In 70 patients overall, an aortoplasty was performed (Tables 1 and 2), either to reduce a dilated ascending aorta in patients who had abnormal dimensions or to restore an abnormal configuration of the ascending aorta to a more normal shape. Our technique of aortoplasty is to exclude a portion of the ascending aorta between two Teflon stripes, without implanting foreign material in the vessel lumen, thus preserving the tissue characteristics of the native aortic wall. This intervention was more frequently performed in patients with a BAV than with a TAV (P = 0.04), as was an ascending aorta replacement (P < 0.01) (Tables 1 and 2). Patients who underwent an aortoplasty did not experience higher rates of dilatation, between the BAV or TAV group, or in comparison with the GP (Fig. 4).

The aim of a ‘prophylactic’ ascending aorta replacement at the time of aortic valve procedures is to prevent future aortic complications and events such as dilatation, development of aneurysms or aortic dissection. Although current knowledge suggests that the aortic diameters play an important role in the evaluation of the risk for aortic events, there is a significant and worrisome lack of evidence in the literature regarding the accurate, precise and patient-specific definition of ‘normal’ or ‘expected’ aortic diameters. Decisions in the everyday clinical practice are mostly based on an arbitrary, universally accepted lower limit of the abnormal diameters (50 mm), which alone cannot always predict the risk of aortic events [23] and might not be applicable to all individuals with the same diameter. Several attempts to integrate somatometric characteristics into the decision process have been proposed [24, 25]; however, their adoption and applicability is neither unanimous nor widespread. Most recommendations define abnormal diameters as diameters >50–55 mm, and denote a grey zone between 40 and 50 mm; however, recent evidence regarding ascending aorta diameters in patients without pathological cardiovascular manifestations indicates that the relationship between normal (‘expected’), the abnormal (‘unexpected/rare’) and the ‘pathological’ is more complicated [5] and several factors such as somatometric characteristics and age define the expected ascending aorta diameters. Although in a pure mechanistic evaluation, the aortic wall tension according to Laplace’s equation depends only on the diameter, wall thickness and pressure difference, evidence from clinical trials shows that the risk for catastrophic aortic events cannot be entirely explained by the aortic diameter [23]. In the IRAD registry, almost 40% of patients presenting with acute Type A dissection had aortic diameters of <40 mm and 60% had a diameter of <55 mm. Furthermore, 50% of all Type A dissections in patients with normal aortic diameters (<40 mm) occurred in the absence of every known risk factor (hypertension, Marfan and BAV) [23].

Despite having diameters of <50 mm (median: 46 mm, mean: 46 mm), 29 patients from the present population were >4 SD far from their expected diameter (probability of <3.2 × 10⁻⁵ indicating a highly rare finding for their age, gender and somatometric characteristics). Do these patients have an increased risk for aortic events? According to present knowledge, probably not. However, the rarity of their aortic dimensions might be worrisome to some. Our current knowledge on the aortic dimensions generally, and more specifically on the individualized association between risk for aortic events and aortic dimensions or patient-specific characteristics, does not allow the clinician to evaluate the degree of ‘rarity’ in the definition of the ‘pathological’.

**LIMITATIONS**

The present study is a retrospective analysis of the evaluation of aortic measurements with time in patients who underwent a subcoronary autograft procedure, which results in normal haemodynamics and tricuspid transvalvular flow and preserves the native aortic wall. Theoretically, it is unclear whether these results are applicable to patients after conventional AVR; however, our work provides an insight on the evolution of the BAV aortopathy after elimination of the haemodynamic burden. Additionally, our approach to the mildly dilated aorta was relatively aggressive (Tables 1 and 2). Owing to the retrospective nature of this study, we cannot assess the confounding influence of this fact. Although for the time period of this study and after normalization of transvalvular flow we were unable to detect a difference between BAV and TAV, the genetic component of the BAV aortopathy might require longer periods of time to exhibit its effect.

**Conflict of interest:** none declared.
REFERENCES


APPENDIX. CONFERENCE DISCUSSION

Dr P. Vallabhajosyula (Philadelphia, PA, USA): In summary, this study attempts to ask a very important question in bicuspid aortic valve syndrome: basically, how do you tease apart aortopathy that is native to the aorta itself, versus aortopathy that is secondary to a primary valve problem, an issue which you address in patients undergoing aortic valve replacement. The authors conclude that in bicuspid patients without significant aortic aneurysm disease to start with, and who did not undergo any major ascending aortic replacement at the time of aortic valve replacement, it is safe to follow these patients out without resecting that ascending aorta. This study attests to some of the other reports, including those by Dr Tirona David, who studied this issue. I basically have two questions.

One question relates to the subselection of patients. There were patients who underwent aortoplasty with aortic diameters between 40 to 50 mm in the studies that were followed through to look for ascending aortic dilatation. I was wondering, what is the aortoplasty that you do and would you not expect the suture line to affect future ascending aortic dilatation?

My second question is more of a general one regarding your practice. The study includes patients from 1994 to 2012. Nowadays, clearly there is mounting evidence that valve-sparing root replacement provides excellent results. In your study there were 121 patients who presented with pure aortic insufficiency preoperatively. What is the current practice at your institution regarding performing a Ross operation as opposed to considering valve repair/root reimplantation or root remodelling in these patients?

Dr Charitos: I will start with the second question, if I may. We perform the Ross procedure in patients in whom we cannot repair or preserve the aortic valve. Our strategy is, first, to try to repair the valve or perform a valve-sparing procedure. If the valve cannot be salvaged, for example, in aortic valve stenosis or severely malformed cuff, we perform the Ross procedure. The Ross procedure is the third step in our strategy, the first two being the attempt to reconstruct the valve and perform valve-sparing surgery.

Regarding your first question, the technique is that we exclude part of the ascending aorta between two Teflon strips. We feel that this preserves the native tissue and the native tissue characteristics. We haven’t seen any adverse events from the aortoplasty throughout our experience. The reason we included these patients in this modelling strategy is that we feel the aortoplasty has a very small, if any, effect on the compliance characteristics of the aorta. We contemplated removing these patients, but we feel that since we are not implanting any foreign material within the lumen or are not changing the compliance characteristics, it might be better to include these patients in this study; however, we present their data separately.

Dr H.-H. Sievers (Lübeck, Germany): I am the senior author and I only want to make a little comment. This study gives the impression that genetics may not have as much of an influence as I personally had felt; maybe other colleagues also expected this, or that the haemodynamics have a greater influence. We did not observe larger diameters in those patients with bicuspid aortic valves. But if you look at the P-values after 10 years (it was a mean follow-up of seven years), this was 0.06. So there is a trend. And it may be that if we wait 10 years more, we will find a significance.

So, this study is only a view over 10 years and not a view over the lifespan of these patients, and we have to be careful when drawing final conclusions from this observation.