The Outcomes of Bicuspid Aortic Valve and Valve Dysfunction from Infancy to Early Adulthood

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Background: The clinical outcomes of pediatric patients with bicuspid aortic valve (BAV) are unclear. The aim of this study was to explore the short and mid-term outcomes and the risk of the progression of valve dysfunction.

Methods: We evaluated the fusion type of cusps and the valve dysfunction of 34 of 80 patients (6 of 30 screened infants and 28 of 50 outpatients) with BAV by echocardiography, from January 2009 to May 2016.

Results: Among 34 BAV patients without any complications, right-noncoronary cusp (R-N) fusion was the most common (62%) finding, followed by left-noncoronary cusp (L-N) fusion (32%). The progression of aortic regurgitation (AR) was observed in 6 patients (R-N, n = 3; L-R, n = 3). In contrast, AS progressed in one patient and improved in 6 patients. However, AR remained mild in most cases (76%) and progressed to a moderate or severe state in a few patients (19%) who were 8–20 years of age.

Conclusions: With the exception of cases involving infants with severe AS, AS remained unchanged, while AR mildly progressed in a pediatric population with BAV. It appears that the progression to a moderate or severe degree of AR typically occurs at 8 to 20 years of age.

Keywords: bicuspid aortic valve, progressive valve dysfunction, progressive aortic dilatation

Introduction

Bicuspid aortic valve (BAV), which is the most common congenital valvular anomaly, affects 0.5–2% of the general population.¹,² Although BAV is considered a benign condition, concern has been raised in recent decades about its association with the progression of valve dysfunction and progressive aortic dilatation. The large majority of studies associated with the natural history and complications of BAV have been conducted in adults.³,⁴ Although our institute could not perform complex surgery for children with congenital heart disease, the clinical outcome and the risk of progression in pediatric patients with valve dysfunction and aortic dilatation has remained unclear. The present study aimed to explore the short- and mid-term clinical outcomes and the risk of the progression of aortic valve dysfunction in pediatric patients with BAV.

Materials and Methods

Study Population

Among 11,085 inborn infants, 30 (0.27%) were diagnosed with BAV by screening echocardiography before discharge. Twenty-four of the 30 patients were excluded because follow-up was not required (n = 16), due to complications of congenital heart disease or chromosomal abnormalities (n = 3), transfer to other hospitals for catheter or surgical intervention due to progressive

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aortic stenosis \( (n = 3) \), or because they were lost to follow-up \( (n = 2) \). Thus, 6 infants and 28 of 50 outpatients with isolated BAV, and who were diagnosed during the study period were enrolled in this study (Fig. 1).

**Ethical Approval**

Formal consent is not required for this type of study because the study was practically retrospective in nature. All of the procedures involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

**Echocardiography**

All of the patients underwent a clinical evaluation and a comprehensive echocardiographic examination, which was performed by pediatric cardiologists. A diagnosis of BAV was made when only two aortic cusps were clearly identified from the parasternal short-axis view during systole. All of the patients had three raphes; none had a true bicuspid. The BAV type was divided into three groups according to the fusion of the coronary cusps. The aortic valvular annular sizes and the ascending aortic sizes of the isolated BAV patients were observed retrospectively during the study period. Aortic stenosis (AS) and regurgitation (AR) were graded using a four-level scale of severity (trivial, mild, moderate, or severe) based on a multi-parametric two-dimensional Doppler evaluation, as previously described. AS was defined as a transaortic flow velocity of \( \geq 2 \) m/s, as described elsewhere. The pediatric cardiologists used an iE33 and a SONOS 7500 (Phillips Medical Systems, Netherlands) echocardiography device with an 8–10MHz probe. Two-dimensional and pulsed-wave Doppler were performed. All echocardiographic examinations were performed during normal respiration.

**Follow-up Evaluation**

All patients were evaluated by a physical examination, electrocardiography, chest X-ray and echocardiography once per year. Echocardiography was performed by two different pediatric cardiologists either in an echo laboratory or in an outpatient clinic.

The clinical endpoints were cardiac death, aortic complications \((e.g.,\text{ dissection or rupture})\), and the need for surgery or percutaneous balloon valvuloplasty. The echocardiographic endpoint was the progression of AS or AR, which was defined by an increase of \( >1 \) grade from baseline in a follow-up evaluation. The aortic valvular annular size was examined using the nomograms reported by Gautier. Significant progressive aortic dilation and progressive aortic dilation were defined as a Z-score of \( \geq 2 \) at baseline, as previously described.

**Statistical Analysis**

Normally distributed values were presented as the mean \( \pm \) standard deviation. Non-normally distributed values were presented as the median and interquartile range. The differences from baseline to the end of the follow-up period were explored using a paired \( t \)-test and Fisher’s exact test. All analyses were performed with the JMP® statistical software package (ver. 9.0.2, SAS Insti-

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Fig. 1 The enrollment and follow-up of patients
The chart shows the proportion of patients who were followed at the outpatient department during the follow-up period.

30 neonates and 50 outpatients were assessed for eligibility

22 outpatients had congenital heart disease and chromosomal anomaly

16 neonates had no follow-up

3 neonates had severe AS and transferred

3 neonates had major shunts and chromosomal anomaly

2 neonates moved and had follow-up at other hospitals

34 outpatients were assessed at the end of follow-up
tute Inc., Tokyo, Japan). $p$ values of $<0.05$ were considered to indicate statistical significance.

**Results**

**Baseline Characteristics of the Study Population**

A total of 34 patients with isolated BAV: 6 of 30 infants (from a total of 11,085 who underwent screening) and 28 of 50 outpatients were followed up during the study period. The enrollment and follow-up of patients are described in Fig. 1. The general characteristics of the study population at the first observation are shown in Table 1.

| Table 1 General characteristics of the patients at the initial check up (n = 34) |
|---------------------------------|-----------------|----------------|----------------|----------------|----------------|----------------|----------------|----------------|----------------|----------------|----------------|----------------|----------------|----------------|----------------|----------------|
| Male gender (n)                | 23              | 68%            |                |                |                |                |                |                |                |                |                |                |                |                |                |                |
| Age (years)                    | 5.8 (0.2–25)    |                |                |                |                |                |                |                |                |                |                |                |                |                |                |                |
| BSA (m²)                       | 0.78 (0.2–1.73) |                |                |                |                |                |                |                |                |                |                |                |                |                |                |                |
| Annular size (mm)              | 13.9 (7.81–27.8) |                |                |                |                |                |                |                |                |                |                |                |                |                |                |                |
| Ascending aortic size (mm)     | 20.8 (7.2–29.2) |                |                |                |                |                |                |                |                |                |                |                |                |                |                |                |
| Spatial orientation            |                |                |                |                |                |                |                |                |                |                |                |                |                |                |                |                |
| L-R fusion                     | 11              | 32%            |                |                |                |                |                |                |                |                |                |                |                |                |                |                |
| R-N fusion                     | 21              | 62%            |                |                |                |                |                |                |                |                |                |                |                |                |                |                |
| L-N fusion                     | 2               | 6%             |                |                |                |                |                |                |                |                |                |                |                |                |                |                |
| AR                             | 15              | 44%            |                |                |                |                |                |                |                |                |                |                |                |                |                |                |
| AS                             | 11              | 32%            |                |                |                |                |                |                |                |                |                |                |                |                |                |                |

L-R fusion: left-right coronary cusp fusion
R-N fusion: right-noncoronary cusp fusion
L-N fusion: left-noncoronary cusp fusion
AR: Aortic regurgitation
AS: Aortic stenosis

**Progression of Aortic Valvular Annular Size**

The data on the aortic valvular annular sizes according to the fusion site of BAV are shown in Fig. 2. The Z-score of the average valvular size of all patients with right-non coronary cusp fusion (R-N fusion) (n = 21; average follow-up period, 5.39 years) increased from 0.038 to 0.34 (Fig. 2). The valvular size increased from 0.059 to 0.80 in those with left coronary and right coronary cusp fusion (L-R fusion) (n = 11; average follow-up period, 5.8 years) and from 0.25 to 0.50 in those with left-noncoronary cusp fusion (L-N fusion) (n = 2; average follow-up period, 4.5 years). However, significant differences were noted between the initial and final checkup findings among all fusion types, and there were 5 patients (L-R, n = 3; R-N fusion, n = 2) whose annular size was enlarged (Z > 2) at the final checkup. Four of them had AR (mild, n = 2; moderate, n = 2). One patient had a small Z (< −2) valvular size and AS (transaortic flow velocity = 3.7 m/s). The valvular size in all patients with simple BAV increased significantly, but no marked changes in the annular size were observed between the initial and final checkup among patients with progressive AR or AS.

**Progression of Aortic Valve Dysfunction**

Figs. 3, 4 show that AS remained unchanged or was improved in six patients during the follow-up period across all types of fusion. The average transaortic flow velocity did not change to a significant extent (Fig. 2).

![Fig. 2 The changes in the aortic annular size, ascending aortic size, and transaortic flow velocity for each type of fusion](image-url)

The blue line indicates RCC–NCC fusion, the orange line indicates LCC–RCC fusion, and the grey line indicates LCC–RCC fusion. The data are shown as the mean and range. The changes were not statistically significant. The characteristics of valve dysfunction are also shown. The degree of AR was mostly mild (the light blue line indicates moderate, the blue line indicates mild, and the blue-black line indicates trivial).
shows the changes in AS in patients with the different types of fusion: among patients with R-N fusion, AS improved in 4 patients; among patients with L-R fusion, AS improved in one patient and progressed in one patient; among patients with L-N fusion, AS improved in one patient and remained unchanged in one patient.

In contrast to our findings with AS, the outcomes of AR were aggravated. Once AR was detected, the degree progressed or remained unchanged in most cases. Fig. 3, 4 show that AR tended to progress gradually. At the final checkup, AR was observed in 14 patients (67%) with R-N fusion, 6 patients (55%) with L-R fusion, and 1 patient (50%) with L-N fusion. Among 21 patients with AR at the final checkup, the degree of AR was mild in 16 patients (76%), moderate in 3 patients (14%), and severe in 1 patient (5%). There were four patients (R-N fusion, n = 3; L-R fusion, n = 1) whose state of AR was moderate or severe. AR was aggravated from mild, to moderate or severe in patients of 8–20 years of age (Fig. 5).

Fig. 3  The changes in the valve dysfunction for each type of fusion
The blue line indicates RCC-NCC fusion, the orange line indicates LCC-RCC fusion, and the grey line indicates LCC-RCC fusion.

Fig. 4  The changes in the degree of AR for each type of fusion
The degree of AR was mostly mild (the checkered pattern indicates trivial, the dotted pattern indicates mild, the diamond pattern indicates moderate, and the black pattern indicates severe).

Fig. 5  The progression of AR
Four patients progressed to moderate or severe AR. All patients were followed from 1 year of age, and their valve dysfunction was recorded in their medical charts. The graph shows when the AR progressed in each patient. The progression was observed at between 8 and 20 years of age.
Ascending aortic dilation was detected in six patients (R-N fusion, n = 3; L-R fusion, n = 2; L-N fusion, n = 1); however, the valve dysfunction was mild or moderate in these patients. One patient had no valve dysfunction, and 3 had mild AR (velocity of the ascending aorta: 1.59 m/s, 1.83 m/s, and 2.42 m/s, respectively). Among these 3 patients, 2 had moderate AR and mild AS (velocity of the ascending aorta: 2.52 m/s and 2.85 m/s, respectively), and the other had moderate AR but mild AS (velocity of the ascending aorta: 2.85 m/s). The ascending aortic size did not change significantly in any of the fusion types (Figs. 2–4).

Clinical Follow-up Examinations

All patients remained alive at the end of the follow-up period. Three infants reached a clinical endpoint. All 3 patients had AS, which showed immediate progression (within one week), which necessitated elective balloon valvuloplasty (n = 1) or surgical valvotomy (n = 1) for severe AS. One patient was transferred to another institute for intervention because the pressure gradient estimated by echocardiography was >50 mmHg. With the exception of the three infants with severe AS, none of the patients with isolated BAV required surgical or medical treatment. None of the spatial orientations led to a statistically significant difference in the R-N, L-R and L-N fusion types.

Discussion

This study found that in a pediatric population with BAV, although the short and mid-term clinical outcome was favorable, AR was aggravated from mild to moderate or severe at 8–20 years of age. As previous studies have shown, with the exception of infants in whom AS immediately progressed within one week, the progression of valve dysfunction was relatively slow—especially in AS. Although BAV is usually considered to be a benign condition, it is reported to be a considerable risk factor for the progression of valve dysfunction, particularly after the fourth decade of life.

In the neonatal period, L-R fusion was the most frequent type of fusion among patients with BAV, followed by R-N. On the other hand, R-N fusion was the most frequent type of fusion in childhood, followed by L-R fusion. In the previous studies, L-R fusion was reported to be more common than other types of fusion. The results of our study were different, in part due to the small population. In addition, R-N fusion is reported to be associated with a high risk of valve dysfunction. This would be the reason for the continuation of follow-up in pediatric BAV patients with R-N fusion.

In our study, R-N fusion was the most common type of fusion in both AR and AS. The prevalence of R-N fusion was highest among patients with AS, and the prevalence of L-R fusion was the highest among patients with AR. The difference might have been—in part—due to the small study population.

McNally et al. reported that the hemodynamics of L-R fusion generates a skewed orifice jet, possibly suggesting stenosis in L-R fusion. Cao et al. found that L-N fusion generated the most markedly abnormal jet angle, but the most substantial anomalies in flow displacement were achieved by L-R fusion in the proximal ascending aorta and R-N fusion in the middle ascending aorta. Those authors concluded that eccentricity, skewness, peak velocity and helicity did not exhibit strong specificity to a given BAV morphotype in a non-dilated aorta. They also reported that the flow angle and displacement were slightly affected by the leaflet fusion pattern. Youssefi et al. reported that the helicity was greater in AS-BAV (L-R fusion) and that the wall shear stress was great in AS-BAV (R-N fusion). Our study showed that patients with R-N and L-R fusion had valve dysfunction as well as both AS and AR; however, the relationship between the cusp fusion type and valve dysfunction should be investigated in greater detail.

We found that the progression to a moderate or severe degree of AR occurred at between 8 and 20 years of age. Although the valve disease in BAV progress after the fourth decade of life, our data suggest that the valve dysfunction progresses, even during adolescence. In particular, R-N fusion was associated with a high risk of intervention and both AS and AR progressed rapidly. Some BAV patients require aortic valve replacement (AS, 17%; AR, 35.4%). In BAV patients with R-N fusion, jet was observed at the level of the aortic valve; this finding suggests—to some degree—that AS may occur more frequently in patients with R-N fusion than in those with other types of fusion.

In line with the results of previous study, the present study showed that ascending aortic enlargement is not related to the severity of valve dysfunction. Two patients had ascending aorta enlargement (AAE); both had...
severe valve dysfunction. Although children with BAV should be observed closely, the results suggest that their prognosis is not so severe. It was recently reported that the 25-year survival rate of children with BAV was not significantly different from that of the general population.\(^1\) The rate of infectious endocarditis was only 2% and fatal events such as aortic dissection and rupture were rare (0.5% per 25 years).\(^2\)

**Limitations**

The present study was associated with some limitations. The study was retrospective in nature and was performed in a single institute.

We examine all newborn infants using echocardiography; however, in the present study, the occurrence of BAV was 0.27%. The difference between our study and previous studies might depend on the size of the aortic valve. It might sometimes be difficult to identify whether or not the raphe is fused in the small neonatal aortic valve. Some of the raphes that were diagnosed as not being fused during the neonatal period were found to be fused when the patients were older. Thus, the rate of BAV might have been underestimated.

**Conclusion**

In our study, L-R fusion was most common during the neonatal period, while valve dysfunction was mostly observed in patients with R-N cusp fusion. AR progresses during adolescence but AS remains unchanged (with the exception of infants with severe AS who require intervention during the neonatal period). Further prospective studies should be performed in larger cohorts in order to clarify the characteristics of children with BAV as they transition to adulthood.

**Conflicts of Interest**

The authors declare no conflicts of interest in association with the present study.

**References**