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Valve Phenotype and Risk Factors of Aortic Dilatation After Aortic Valve Replacement in Japanese Patients With Bicuspid Aortic Valve

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Background: The aim of this study was to assess the risk factors for dilatation of the aorta over time in Japanese patients with bicuspid aortic valve (BAV) undergoing aortic valve replacement (AVR), focusing on the possible impact of valve fusion phenotype.

Methods and Results: Of 167 BAV patients undergoing AVR (24% of overall AVR patients, n=702), 135 patients in whom surgical intervention for the aorta was not undertaken were focused on (74 had right-left fusion and 61 non-right-left fusion type). During a mean follow up of 5.2 years, aortic growth rate (mm/year) of the ascending aorta was similar between the valve phenotype. In multivariate logistic regression, the presence of aortic regurgitation > moderate was significantly associated with a rapid dilatation of the ascending aorta, defined as >0.7 mm/year (odds ratio 2.1, 95% confidence interval 1.2–3.7, P=0.03). Independent predictors of dilatation of the aorta up to more than 45 mm were: a diameter of the ascending aorta >40 mm at the time of surgery (odds ratio 3.7, 95% confidence interval 1.2–11.4, P=0.02) and length of follow up (odds ratio 1.3-increase per year, 95% confidence interval 1.0–1.5, P=0.04).

Conclusions: The presence of aortic regurgitation and the ascending aorta of >40 mm at the time of surgery emerged as significant predictors of dilatation of the aorta after AVR but valve fusion phenotype was not. (*Circ J* 2016; **80:** 1356–1361)

Key Words: Ascending aorta aneurysm; Bicuspid aortic valve; Fusion phenotype

The Japanese clinical guideline published by the Japanese Circulation Society states that an ascending aorta in bicuspid aortic valve (BAV) patients with a diameter of >45 mm should be replaced (class I).[1] Due to lack of follow-up studies addressing this issue with Japanese patients, this guideline was formulated on the basis of clinical studies with Europeans and North Americans.[2,3] It is possible, however, that the risk of aortic events in BAV patients is different according to race. Therefore, it is critical to cumulate clinical outcomes of Japanese BAV patients and suggest a guideline specific for Japanese patients.

The postoperative management for these patients is still being debated. Phenotypic heterogeneity of BAV, including the morphology of the aortic valve and the shape of the aorta, has recently been widely recognized. A few studies have addressed the impact of phenotypic variability on postoperative growth of the aorta and aortic-related event after AVR.[4–7] In Japanese patients, however, no study has addressed this issue. The purpose of the present retrospective longitudinal study was to assess the risk factors for growth rates of the aorta over time in Japanese BAV patients undergoing AVR, focusing on the possible impact of valve fusion phenotype on dilatation of the aorta.

Methods

Among 702 consecutive Japanese patients who underwent AVR for native aortic valve stenosis or regurgitation at our institution between April 2002 and December 2012, BAV was identified in 167 patients by intraoperative direct inspection; they were then enrolled in the present study. According to cusp fusion pattern, BAV patients were further categorized as the RL group (fusion between right and left coronary cusps, n=89) or non-RL group (fusion between non-coronary and right or left coronary cusps, n=75). Three patients could not be categorized due to loss of records. Of these, we excluded 29 patients who underwent concomitant repair or replacement of the aortic root and/or ascending aorta if the maximum diameter

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Table 1. Baseline Characteristics and Operative Procedures in the RL and the Non-RL Groups

	RL group (n=72)	Non RL group (n=63)	P value
Age, years	64±12	65±11	0.72
Male gender	50 (68)	45 (74)	0.43
Body mass index, m²	1.62±0.21	1.65±0.14	0.48
NYHA class III or IV	27 (37)	25 (41)	0.59
Arterial hypertension	36 (49)	32 (53)	0.66
Diabetes mellitus	11 (15)	9 (15)	0.99
History of smoking	37 (50)	31 (51)	0.92
COPD	20 (27)	14 (23)	0.59
Aortic valve lesion			0.82
Stenosis	29 (41)	28 (45)	
Regurgitation	24 (33)	18 (28)	
Combined	19 (26)	17 (27)	
LV ejection fraction, %	60±12	57±12	0.27
LV end-diastolic dimension, mm	57±8	55±7.4	0.50
LV end-systolic dimension, mm	38±8	37±10	0.80
Left atrial dimension, mm	40±7	40±7	0.83
Mechanical prosthesis	19 (26)	19 (31)	0.67
Valve size, mm	23.8±2.0	23.6±2.1	0.76
Bioprosthesis	55 (74)	42 (69)	0.67
Valve size, mm	23.5±1.9	23.9±2.8	0.73
Concomitant procedures			
Coronary bypass grafting	12 (16)	9 (15)	0.76
Mitral valve reconstruction	5 (7)	6 (10)	0.56
Tricuspid valve reconstruction	1 (1)	1 (1.6)	0.61

Data are presented as frequency (percentage) or mean±standard deviation. COPD, chronic obstructive pulmonary disease; RL, fusion between right and left coronary cusps; LV, left ventricular; NYHA, New York Heart Association.

exceeded 45 mm (17 in the RL group, 12 in the non-RL group). Aortic root replacement was indicated mainly in patients with significant dilatation of the Valsalva sinus (>45 mm in diameter). Of the remaining 135 patients who were not candidates for concomitant aortic surgery, both pre- and post-operative computed tomography scans were performed in 47 patients (29 in the RL group, 18 in the non-RL group). Written informed consent from all patients and approval from the local research ethics committee at our institution were obtained.

Outcomes

Aortic growth rate was defined as the difference between the diameter at the time of surgery and the diameter at postoperative follow up, divided by the follow-up time interval in years. A rapid progression was defined as a growth rate falling within the third tertile of distribution of the growth rate variable. Estimated survival free from postoperative dilatation of the aorta up to more than 45 mm during the follow up was calculated by using the Kaplan-Meier method. The diameters of Valsalva sinus and sinotubular junction were measured twice (inner-edge to inner-edge method) by 2-dimensional echocardiography in parasternal long-axis views at their maximal diameters. The size of the ascending aorta was quantified by cross-sectional dimensions in the transverse plane of multidetector CT scans. As secondary endpoints, death, aortic event defined as aortic dissection, or aortic surgery were assessed. Death was classified as cardiovascular death related to aortic dissection, sudden death, non-cardiovascular death, or death of an unknown cause. Sudden death was defined as a sudden unexpected pulseless condition. If unwitnessed, sudden deaths were those in which the patient was found dead within 24 h of having last been seen alive and in a normal state of health. Documentation of the cause of death was based on information obtained from witnesses, family members, death certificates, hospital records, and autopsy records. Collection of baseline clinical information was conducted through hospital charts or database review. Follow-up data were mainly collected through annual outpatient visits, a review of hospital charts, or contact with patients, relatives, and/or referring physicians using mail with questions regarding survival, symptoms, and subsequent hospitalizations. The mean duration of the observation period was 5.2±3.1 years in the RL group and 5.1±3.0 years in the non-RL group. No contact details were available for 15 of 139 patients (98.5% completeness of data).

Statistical Analysis

Descriptive statistics are presented as mean ± SD or frequency (percentage). Bivariate comparisons of pre- and post-operative data were performed with the paired t-test. Unpaired t-test and χ^2 analysis were used to compare continuous and categorical variables, respectively. Analysis of time-dependent occurrences was presented graphically with Kaplan-Meier plots, and analyzed statistically by using the log-rank test. Multivariate logistic regression models were developed with the forward stepwise method to predict a rapid growth at the ascending and root level separately and postoperative dilatation of the aorta up to more than 45 mm. The valve phenotype and all the other baseline variables listed in Table 1 were tested by bivariate association with the above dependent variables, and variables showing significant association were entered as

Table 2. Temporal Changes of Aortic Diameters

Valve phenotype	BAV patients			
	RL group		Non RL group	
	Baseline	Follow	Baseline	Follow
No. of patients	29		18	
Annulus, mm	22.1±3.2	24.0±2.7	21.0±3.5	23.8±3.2
Valsalva, mm	34.1±5.2	34.9±4.5	34.7±4.8	36.6±5.0
ST junction, mm	28.7±4.9	28.5±3.9	29.2±5.7	29.8±3.6
Ascending aorta, mm	37.9±4.3	40.5±5.3*	38.9±4.0	42.2±4.2*

Data are presented as mean±standard deviation. BAV, bicuspid aortic valve; ST, sinotubular. Other abbreviations as in Table 1. *P<0.05 vs. baseline.

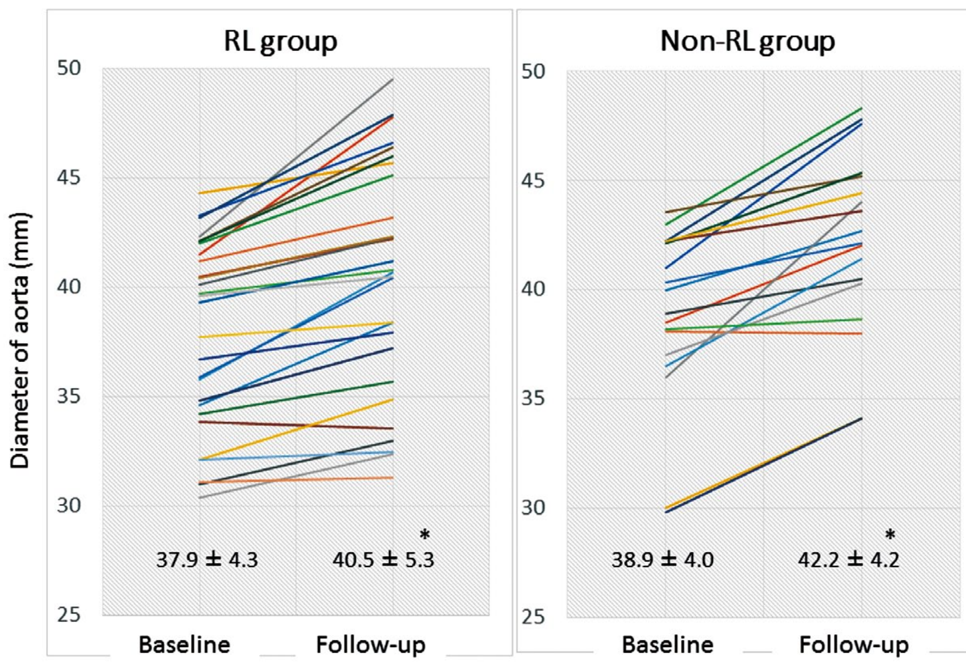

Figure 1. Temporal change of maximum diameter of the ascending aorta after surgery. Data are presented as mean±standard deviation. *P<0.05 vs. baseline (paired t-test).

multivariate models, with entry and retention set at a significance level of <0.05. All statistical testing was 2-sided. Results were considered statistically significant at a level of P<0.05. All analyses were performed with the SPSS statistical package version 20.0 (SPSS Inc, Chicago, IL, USA).

Results

Baseline Patient Characteristics

As shown in Table 1, no significant difference was found in baseline patient characteristics, LV function and dimension, and operative procedures in the RL group and the non-RL group including age, gender, prevalence of arterial hypertension, chronic obstructive pulmonary disease and diabetes mellitus, left ventricular ejection fraction and dimension, operative indication, implanted prosthesis size and concomitant procedures.

Temporal Change of Aortic Diameter

Aortic diameters at baseline and at last follow-up echocardiography are summarized in Table 2. The ascending aorta was significantly dilated during the follow-up period in both the RL group and the non-RL group, whereas no significant change was observed in diameters of the annulus, Valsalva sinus, and ST junction. Figure 1 shows temporal changes of maximum diameter of the ascending aorta after surgery. As to aortic growth rate (mm/year) of the ascending aorta, no significant difference was found between the RL group vs. the non-RL group (0.67 vs. 0.73, P=0.71). No significant difference was found between the 2 groups in terms of estimated survival free from postoperative aortic dilatation to more than 45 mm in diameter (Figure 2). During the initial 5-year postoperative period, no patient reached the primary endpoint (postoperative aortic dilatation up to 45 mm), but at the subsequent period, 14 patients reached it; 9 in the RL group and 5 in the non-RL group.

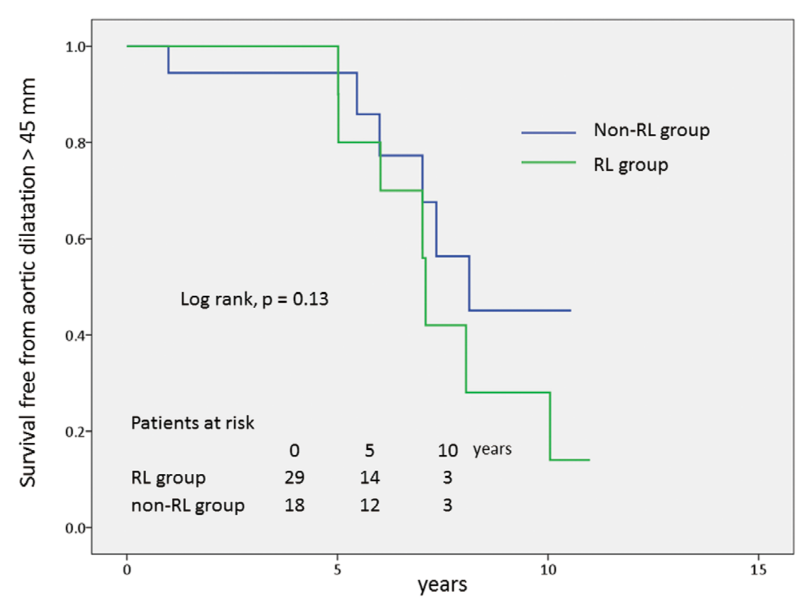

Figure 2. Survival free from ascending aorta dilatation to more than 45 mm in diameter.

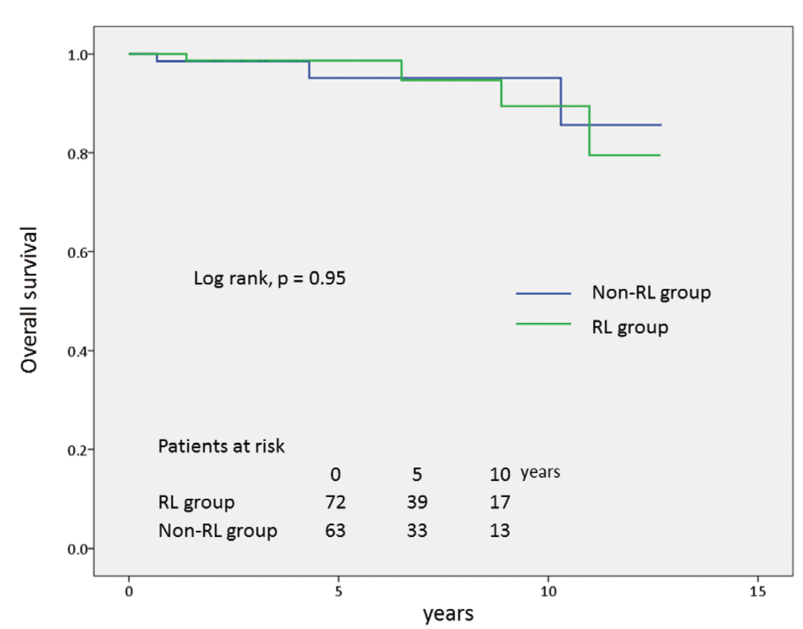

Figure 3. Survival rates in the fusion between right and left coronary cusps (RL) and the non-RL groups.

Predictors of Rapid Progression of Aortic Diameter and Postoperative Dilatation >45 mm

A rapid progressing aortic diameter was defined as a growth rate falling within the third tertile of growth rates distribution: >0.7 mm/year for the ascending aorta. The dilatation of the annulus, Valsalva sinus, and ST junction level was insignificant; therefore, no analysis of predictors was performed for these levels. In multivariate logistic regression models, only the presence of aortic regurgitation > moderate was significantly associated with a rapid dilatation of the ascending aorta (odds ratio 2.1, 95% confidence interval 1.2–3.7, P=0.03). Independent predictors of dilatation of the aorta up to more than 45 mm were: a diameter of the ascending aorta >40 mm at the time of surgery (odds ratio 3.7, 95% confidence interval 1.2–11.4, P=0.02) and length of follow up was the only (odds ratio 1.3-increase per year, 95% confidence interval 1.0–1.5, P=0.04). Valve phenotype did not emerge as a significant predictor of a rapid progression of aortic diameter and postoperative dilatation >45 mm.

Secondary Endpoint

A total of 7 patients (3 in the RL group and 4 in the non-RL group) died during the follow-up period (**Figure 3**). As to in-hospital outcomes, 30-day mortality was 0%. Respective rates

Table 3. Secondary Endpoint

	RL	Non RL
No. of patients	72	63
Overall death	4	3
Cardiovascular-related	2	2
Acute myocardial infarction	0	0
Heart failure	1	1
Cerebral hemorrhage	1	1
Sudden death	0	0
Non-cardiovascular-related	2	1
Infection	1	1
Malignancy	1	0
Hepatic failure	0	0
Pulmonary failure	0	0
Unknown cause	0	0
Aortic events	1	1
Aortic dissection	0	0
Aortic surgery	1	1
Ascending	1	0
Arch	0	1
Descending	0	0

Data are presented as frequency (percentage). RL, fusion between right and left coronary cusps.

of stroke and acute kidney injury requiring dialysis were 2.2% and 0.7%. Table 3 shows details of mortality and aortic events. Four of 7 mortalities were cardiovascular-related, but neither sudden death, death from an unknown cause, nor aortic dissection was documented. The distribution of causes of death was almost equal between the RL and the non-RL groups. Aortic surgery was required in 2 patients, and this included ascending aorta replacement in the non-RL group 10 years after AVR because its diameter progressively dilated and reached more than 50 mm. Similarly, 1 patient from the RL group underwent replacement of the ascending and arch aorta 10 years after AVR.

Discussion

In the present study, isolated AVR surgery for BAV patients with the root and/or ascending aorta <45 mm in diameter provided excellent results, with low hospital morbidity and mortality, low rate of reoperation and aortic events, and survival at a mean follow-up period of 5.1±3.0 years. In contrast, postoperative aortic dilatation was observed at the ascending level but not at the Valsalva sinus and ST junction. Aortic growth rate after AVR was similar between the 2 valve phenotypes (RL type vs. non-RL type). Among 47 patients in whom both pre- and post-operative computed tomography scans were performed, however, diameters of the ascending aorta exceeded 45 mm in 14 patients (30%) after 5 years of AVR surgery. Patients with an ascending aorta of 40–45 mm in diameter at the time of surgery were at 3-fold increased risk of aortic dilatation up to >45 mm after 5 years of AVR surgery. The presence of aortic regurgitation > moderate was only a predictor for a rapid postoperative dilatation (>0.7 mm/year) of the ascending aorta.

The 2014 AHA/ACC guideline recommends replacement of the ascending aorta in BAV patients who are undergoing AVR because of severe aortic stenosis or regurgitation if the diameter of the ascending aorta is greater than 4.5 cm.[3] The present study again raised a question about how we should treat BAV patients with a borderline diameter of the ascending aorta at AVR surgery. Aortic events after isolated AVR surgery in patients with BAV disease has become the center of discussion due to a limited number of follow-up studies addressing this issue and discordant results.[8–13] Considering the relatively long life expectancy of BAV patients undergoing AVR surgery, not only aortic diameters but also the patient's age should be included in the decision-making process for BAV patients. Because the natural history of BAV aortopathy in the Japanese population is still unclear, and the incidence of aortic events in BAV patients might be different according to race, it is also important to know the long-term results of Japanese patients when deciding on the strategies used to treat the dilated aorta. Although only limited data are available on BAV aortopathy after AVR in Japanese patients, several investigators have shown that isolated AVR without treatment for the ascending aorta could not prevent dilation in Japanese BAV patients, but the aorta was not dilated in tricuspid aortic valve patients.[14–17] Further accumulation of data on Japanese BAV patients will be required to establish a guideline that is specific for Japanese patients.

The type of BAV disease (ie, valve function or phenotype) has been reported to influence the natural history of aortopathy in BAV patients. Recently, growing evidence shows that cusp fusion phenotype can impact aortic blood flow and wall shear stress. Hemodynamic forces exerted on the ascending aorta wall may help to complement the static information for aortic dimensions and to facilitate more individualized patient management.[18] The RL BAV fusion is associated with significantly elevated wall shear stress at focal regions in the ascending aorta.[19] The direction of helical flow differs according to BAV phenotype, with right-handed helical flow as the predominant pattern in BAV RL type, and left-handed helical flow in BAV non-RL type.[18] Longitudinal follow up is needed to determine whether an abnormal helical flow pattern correlates with bicuspid aortopathy.

The present study has a number of potential limitations. First, it was a retrospective study and enrolled only patients at a single center, which limited the generality of the findings. Second, the mean follow-up period was relatively short at 5.2 years, and only 22% of patients (n=139) were followed up for >10 years. Third, insufficient statistical power due to the small number of patients and the low incidence of the events did not allow us to precisely assess the impact of valve fusion phenotype on dilation of the aorta. Fourth, we were unable to perform enhanced CT and measure the aortic dimension of each level of the aorta, which might help to more accurately understand the difference of aortic dilatation pattern and natural course of aortopathy after AVR. Finally, there was no available data on medications after discharge, which could have affected outcomes, because the patients received postoperative treatment from different hospitals.

In conclusion, the presence of aortic regurgitation and an ascending aorta of >40 mm at the time of surgery are significant predictors of dilatation of the aorta after AVR but valve fusion phenotype was not.

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