Original Article

# Does the residual aorta dilate after replacement of the bicuspid aortic valve and ascending aorta?

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**Background:** Although a bicuspid aortic valve (BAV) is known to be associated with progressive ascending aortic dilatation, the fate of the residual aorta after aortic valve and ascending aorta surgery is unknown. We reviewed surgical outcomes and explored serial changes in the size of the sinus of Valsalva (SOV) and distal ascending aorta (DAAo) in 89 patients with a BAV undergoing aortic valve replacement (AVR) and graft replacement (GR) of the ascending aorta.

**Methods:** We retrospectively examined patients who underwent AVR and GR of the ascending aorta for BAV-and related disease and thoracic aortic dilatation at our institution between January 2009 and December 2018. Patients who underwent AVR alone or required intervention for the aortic root and aortic arch and patients with connective tissue diseases were excluded. Aortic diameters were examined using computed tomography (CT). Late CT more than 1 year after surgery was performed in 69 patients (78%) with a mean follow-up of 4.9±2.8 years.

**Results:** The surgical indication for aortic valve etiology was stenosis in 61 patients (69%), regurgitation in 10 (11%), and mixed in 18 (20%). Preoperative maximum short diameters of the ascending aorta, SOV, and DAAo were 47.3±4.7, 36.0±5.2, and 37.2±3.6 mm, respectively. The diameter of the SOV increased non-significantly by 0.08±0.45 mm per year [95% confidence interval (CI): −0.12 to 0.11, P=0.150], while that of the DAAo increased significantly by 0.11±0.40 mm per year (95% CI: 0.02–0.21, P=0.005). One patient required reoperation 6 years postoperatively due to a pseudo-aneurysm at the proximal anastomotic site. No patient required reoperation due to progressive dilatation of the residual aorta. According to the Kaplan-Meier analysis, the long-term survival rates were 98.9%, 98.9%, and 92.7% at 1, 5, and 10 years postoperatively, respectively.

**Conclusions:** Rapid dilatation of the residual aorta rarely occurred in patients with a BAV who underwent AVR and GR of the ascending aorta in the mid-term follow-up. For selected patients with a surgical indication for ascending aortic dilatation, simple AVR and GR of the ascending aorta may be sufficient surgical options.

**Keywords:** Aortic valve replacement (AVR); bicuspid aortic valve (BAV); ascending aortic dilatation; replacement of ascending aorta; ascending aortic diameter

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## Introduction

The bicuspid aortic valve (BAV) is the most common congenital valvular pathology with an incidence of 1–2% among the general population (1,2). BAV is known to be associated with progressive ascending aortic dilatation relative to hemodynamic and genetic factors (3-6). The abnormal shear stress acting on the aortic wall appears to underpin the cause of dilation (7-10). The presence of medial degeneration in BAV disease, characterized by apoptosis of smooth muscle cells, altered collagen content, or elastic fiber fragmentation, is considered the underlying abnormality in ascending aortic aneurysms observed among the patients (8,11,12). Therefore, isolated aortic valve replacement (AVR) fails to prevent the progressive aortic dilation in patients with a BAV (13-15). Furthermore, the dilation involves the ascending aorta and sometimes the aortic root or aortic arch; thus, preventive root and aortic arch replacements are suggested as surgical options (16). However, extended AVR surgery with root or aortic arch replacement has high mortality and morbidity, particularly in older patients (17,18). Therefore, it is important to know the effects of a simple graft replacement (GR) of the ascending aorta in combination with AVR on the residual aortic diameter, including that of the sinus of Valsalva (SOV) and the distal ascending aorta (DAAo), to determine whether an extended preventive surgery is beneficial to patients. We hypothesized that a simple GR of the ascending aorta in conjunction with an AVR would be advantageous for some cohorts in terms of survival or short- and long-term morbidity. This study aimed to review the surgical outcomes and explore serial changes in the size of the residual ascending aorta in patients with a BAV undergoing AVR and GR of the ascending aorta. We present the following article in accordance with the STROBE reporting checklist (available at https://jtd.amegroups.com/article/view/10.21037/jtd-22-1118/rc).

### Highlight box

**Key findings**

- Rapid dilatation of the residual aorta occurred rarely in patients undergoing aortic valve replacement (AVR) and ascending aortic graft replacement (GR) for bicuspid aortic valve (BAV) disease with a >45 mm ascending aorta and normal roots and arches.

**What is known and what is new?**

- The presence of medial degeneration in BAV has been linked to post-operative aortic aneurysms in patients undergoing isolated AVR. The effects of a simple GR of the ascending aorta combined with AVR on residual aortic diameters are unknown.
- Our findings contribute to the surgical strategy for patients with a BAV and ascending aortic dilatation by determining the degree of postoperative residual aortic dilatation, including the sinus of Valsalva.

**What is the implication, and what should change now?**

- Simple AVR and GR of the ascending aorta may be sufficient surgical options for selected patients with a surgical indication for ascending aortic dilatation.

## Methods

### *Patient selection*

The indications for the replacement of the aortic root, ascending aorta, and aortic arch were a maximum short diameter of ≥45, ≥45, and ≥55 mm, respectively, at the time of AVR in patients having a BAV etiology (19-21). Sixteen patients with an ascending aortic maximum short diameter <45 mm underwent GR due to their relatively young age (n=10) or malformed aortic shape (n=6), which were at risk of dilating or developing aortic complications over time. We retrospectively assessed the medical records of all patients who underwent AVR and aortic surgery for BAV-related aortic valve disease and thoracic aortic dilatation at our institution between January 2009 and December 2018. Overall, 101 patients underwent AVR and aortic surgery, of whom, 12 patients requiring aortic root and arch intervention and those with connective tissue diseases such as Marfan syndrome were excluded. The remaining 89 patients undergoing AVR and GR of the ascending aorta were examined. This study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The ethics committee of National Cerebral and Cardiovascular Center, Osaka, Japan approved this study (No. M-30-026), the need for informed consent was waived due to the retrospective nature of the study.

### *Surgery*

Median full sternotomy was performed for all patients. Cardiopulmonary bypass was established conventionally with bicaval drainage and perfusion to the proximal arch, femoral artery, or both. Cardiac arrest was achieved with a bidirectional cardioplegia infusion. GR of the ascending aorta was performed using a Dacron graft under single aortic cross-clamping. Twenty-one patients (24%)

underwent surgery under deep hypothermic circulatory arrest (DHCA) with or without cerebral perfusion. Distal anastomosis was performed at approximately 1.0 cm below the brachiocephalic artery in the open distal anastomosis or 1.5–2.0 cm below the brachiocephalic artery in aortic cross-clamping. Proximal anastomosis was performed approximately 1.0 cm above the sinotubular junction. The aortic prosthetic valve was implanted using non-everting mattress stitches in a supra-annular position. Prosthetic valves were mainly selected at the surgeon's discretion; however, biological valves were preferred for patients older than 60 years.

### *Measurements of the aortic size*

Chest computed tomography (CT) was routinely performed before surgery, approximately 1 week after surgery, and at postoperative visits, as appropriate. Aorta-related measurements were examined using CT with the DAAo measured just proximal to the brachiocephalic artery; the maximum short diameter was reported as the final size. The largest sinus-to-sinus measurements of the three values were used for the Valsalva sinusoidal diameter. During the follow-up period, hospital death occurred in one patient, another patient underwent reoperation 2 months after the surgery due to prosthetic valve endocarditis, and the remaining 18 patients were lost to follow-up. Mid-term CT scans were obtained for 69 patients (follow-up rate 78%) more than 1 year after surgery, with a mean duration of CT follow-up from surgery of 4.9±2.8 years (1.0–10.6 years). The latest measurements were adopted as a diameter of SOV or DAAo at the most recent follow-up.

### *Postoperative management and follow-up*

All patients were administered antiplatelet and anticoagulation therapy with aspirin and warfarin once adequate hemostasis was achieved. Patients with mechanical valves received warfarin permanently, with the dose adjusted as needed to achieve a target international normalized ratio (INR) of 2.0–2.5. In contrast, patients with biological valves received warfarin for only the first 3 months with a target INR of 1.5–2.0. Additionally, all patients, regardless of the valve type, were permanently on aspirin maintenance at a dose of 100 mg daily.

Follow-up data after the operation were obtained by reviewing patient medical records and telephone or postal mail interviews. The mean follow-up period was 6.1±2.7 years (0.6–11.2 years).

### *Definitions and study endpoints*

Cystic medial necrosis (CMN) of the excised aortic wall was evaluated by pathological examination and graded from 0 to 3, with 3 being the most severe (3). All cardiac and non-cardiac events, including death, were recorded. Early mortality was defined as in-hospital mortality, and late mortality was defined as death occurring beyond this period. Major adverse cardiac and cerebrovascular events (MACCEs) were defined as cardiac-related death, reoperation, myocardial infarction, aorta-related major complications such as aortic dissection, and cerebrovascular accidents. The primary endpoints were changes in the diameter of the residual aorta assessed on late follow-up CT. In the subgroup analysis, serial changes in the diameters of the SOV and DAAo were evaluated by stratifying several potential risk factors for dilatation, including age (<65 or ≥65 years), sex, existence of chronic obstructive pulmonary disorder (COPD), BAV phenotype, pathological CMN grade, SOV and DAAo diameters at baseline (<40 or ≥40 mm), aortic valve etiology, prosthetic valve type, and graft size. Secondary endpoints were survival rate and MACCEs-free survival.

### *Statistical analysis*

Continuous variables are presented as mean ± standard deviation; categorical variables are summarized as frequencies and percentages. Preoperative and postoperative data were compared using paired *t*-tests. Group differences were evaluated using *t*-test and the Wilcoxon test. A Kaplan-Meier analysis was performed to assess survival, freedom from MACCEs, reoperation, and aorta-related disease. Time-scale multilevel regression model was examined to assess the interactional effect of (risk factors at baseline) × (time follow-up) on the developing aortic diameter after the survey. Random effect was assigned in both intercept and slope. Moreover, the pattern of change in the aortic diameter over time was examined with latent class trajectory analyses. This statistical approach objectivity prepares the optimal and major trajectory patterns with a statistical justification to facilitate causal inference when ransom assignment is not possible in given observational datasets (22). The analysis was repeated step-by-step,

**Table 1** Patient characteristics

| Patient characteristics | Number (n=89) |
|---|---|
| Age (years), mean ± SD [min–max] | 62±11 [30–85] |
| Female sex | 38 (43%) |
| Body surface area ($m^2$) | 1.64±0.20 |
| Hypertension | 55 (62%) |
| Dyslipidemia | 33 (37%) |
| Diabetes mellitus | 10 (11%) |
| Chronic kidney disease | 9 (10%) |
| Chronic obstructive pulmonary disorder | 14 (16%) |
| Peripheral artery disease | 1 (1%) |
| New York Heart Association class | |
| I | 15 (17%) |
| II | 64 (72%) |
| III | 9 (10%) |
| IV | 1 (1%) |
| Left ventricular ejection fraction | |
| >50% | 76 (85%) |
| 30–50% | 8 (9%) |
| <30% | 5 (6%) |
| Aortic valve etiology | |
| AS | 61 (69%) |
| AR | 10 (11%) |
| ASR | 18 (20%) |
| Phenotype of bicuspid aortic valve | |
| Type 0 | 32 (36%) |
| AS/AR/ASR | 28/0/4 |
| Type 1 (R-L fusion) | 39 (44%) |
| AS/AR/ASR | 18/9/12 |
| Type 1 (R-N fusion) | 18 (20%) |
| AS/AR/ASR | 15/1/2 |
| Mitral regurgitation (≥ moderate) | 3 (3%) |
| Tricuspid regurgitation (≥ moderate) | 3 (3%) |
| Diameter (mm) | |
| Sinus of Valsalva, mean ± SD [min–max] | 36.0±5.2 [28–47] |
| Diameter ≥40 mm | 20 (22%) |
| Middle ascending aorta, mean ± SD [min–max] | 47.3±4.7 [38–59] |
| Distal ascending aorta, mean ± SD [min–max] | 37.2±3.6 [29–45] |
| Diameter ≥40 mm | 25 (28%) |
| EuroSCORE II, mean ± SD | 4.11±2.52 |

SD, standard deviation; AS, aortic valve stenosis, AR, aortic valve regurgitation, ASR, aortic valve stenosis and regurgitation; R-L, Right coronary cusp-Left coronary cusp; R-N, Right coronary cusp-Non coronary cusp.

starting with one group and aiming to determine the optimal number of groups; this was performed until the spectrum of maximum likelihood for the number of groups no longer converged. The largest maximum likelihood was selected to include a suitable number of groups. We corrected this trajectory analysis for age and sex. Posterior probabilities confirmed the adaptability for individual trajectories for the selected groups of all patients. Statistical analyses were performed using the JMP software version 14.2 (SAS Institute Inc., Cary, NC, USA) and R version 3.6.2. (The R Foundation for Statistical Computing, Vienna, Austria). A P value <0.05 was considered statistically significant.

## Results

### *Patient characteristics*

Baseline patient characteristics are summarized in *Table 1*. The mean age was 62±11 years, and 43% of patients were female. The mean EuroSCORE II was 4.11±2.52. The surgical indication for aortic valve etiology was stenosis in 61 patients (69%), regurgitation in 10 (11%), and mixed in 18 (20%). The phenotypes of BAV were type 0 in 32 patients (36%), Right coronary cusp-Left coronary cusp (R-L) fusion type 1 in 39 (44%), and Right coronary cusp-Non coronary cusp (R-N) fusion type 1 in 18 (20%). Preoperative maximum short diameters of the ascending aorta, SOV, and DAAo were 47.3±4.7, 36.0±5.2, and 37.2±3.6 mm, respectively with a mean follow-up of 5.8±2.4 and 4.1±2.6 years.

**Table 2** Intraoperative results

| Intraoperative results | Number (n=89) |
|---|---|
| Size of aortic valve prosthesis (mm) | |
| 17 | 1 (1%) |
| 19 | 9 (10%) |
| 20 | 1 (1%) |
| 21 | 24 (27%) |
| 22 | 4 (4%) |
| 23 | 28 (31%) |
| 25 | 12 (13%) |
| 26 | 1 (1%) |
| 27 | 9 (10%) |
| Type of aortic valve prosthesis | |
| Mechanical | 13 (15%) |
| Biological | 76 (85%) |
| Size of ascending aortic graft (mm) | |
| 22 | 2 (2%) |
| 24 | 9 (10%) |
| 26 | 34 (38%) |
| 28 | 27 (30%) |
| 30 | 17 (19%) |
| Concomitant procedure | |
| Coronary artery bypass grafting | 3 (3%) |
| Mitral valve repair | 2 (2%) |
| Tricuspid valve repair | 3 (3%) |
| Maze procedure | 3 (3%) |
| Myectomy | 2 (2%) |
| Operation time (min), mean ± SD | 317±80 |
| Cardiopulmonary bypass time (min), mean ± SD | 150±39 |
| Aortic cross-clamp time (min), mean ± SD | 108±26 |
| Pathology | |
| Cystic medial necrosis grade | |
| 0 | 8 (10%) |
| 1 | 34 (41%) |
| 2 | 27 (33%) |
| 3 | 14 (17%) |

### *Intra- and postoperative early and long-term clinical outcomes*

The intraoperative results are detailed in *Table 2*. Biological valves were implanted in 76 patients (85%). The most utilized prosthetic valve and graft sizes were 23 mm (n=28, 31%) and 26 mm (n=34, 38%), respectively. In-hospital mortality occurred in one patient (1%) because of pulmonary embolism and subsequent major pulmonary bleeding. One patient developed aortic dissection at the distal anastomosis site as confirmed by postoperative CT 7 days after the operation. The patient was carefully followed, and no aggravation of the dissection was observed. During follow-up, one late mortality occurred because of pneumonia 104 months after the operation. According to the Kaplan-Meier analysis, at 1, 5, and 10 years post operation, the survival rates were 98.9%, 98.9%, and 92.7%, respectively (*Figure 1A*), and the rates for freedom from MACCEs were 95.5%, 89.8%, and 72.0%, respectively (*Figure 1B*). Among the MACCEs, five patients (6%) required reoperation during follow-up because of coincidental detection of pseudo-aneurysm at the proximal anastomotic site 6 years post operation (n=1); structural valve deterioration at 4, 7, and 10 years after the operation (n=3); and prosthetic valve endocarditis 2 months after the operation (n=2). According to the Kaplan-Meier analysis, at 1, 5, and 10 years postoperatively, the rates of freedom from reoperation were 98.9%, 97.2%, and 78.5%, respectively (*Figure 1C*), and the rates of freedom from aorta-related events were 98.9%, 98.9%, and 95.2%, respectively (*Figure 1D*). Details of early and long-term postoperative clinical outcomes are presented in *Table 3*.

### *Serial changes in the diameter of the SOV and DAAo*

Serial changes in the diameters of the SOV and DAAo are presented in *Table 4*, and time-dependent changes are shown in *Figure 2*. In all patients, the diameter of SOV increased by 0.08±0.45 mm per year; however, this was not statistically significant (95% CI: −0.12 to 0.11, P=0.150) and did not correlate with the change in diameter over time (r=0.189 P=0.124; *Figure 2A*). In contrast, DAAo significantly increased by 0.11±0.40 mm per year (95% CI: 0.02–0.21, P=0.005) and was weakly correlated (r=0.325 P=0.006; *Figure 2B*) with time. The dilatation rate of some patients was higher than average. Using cut-off values

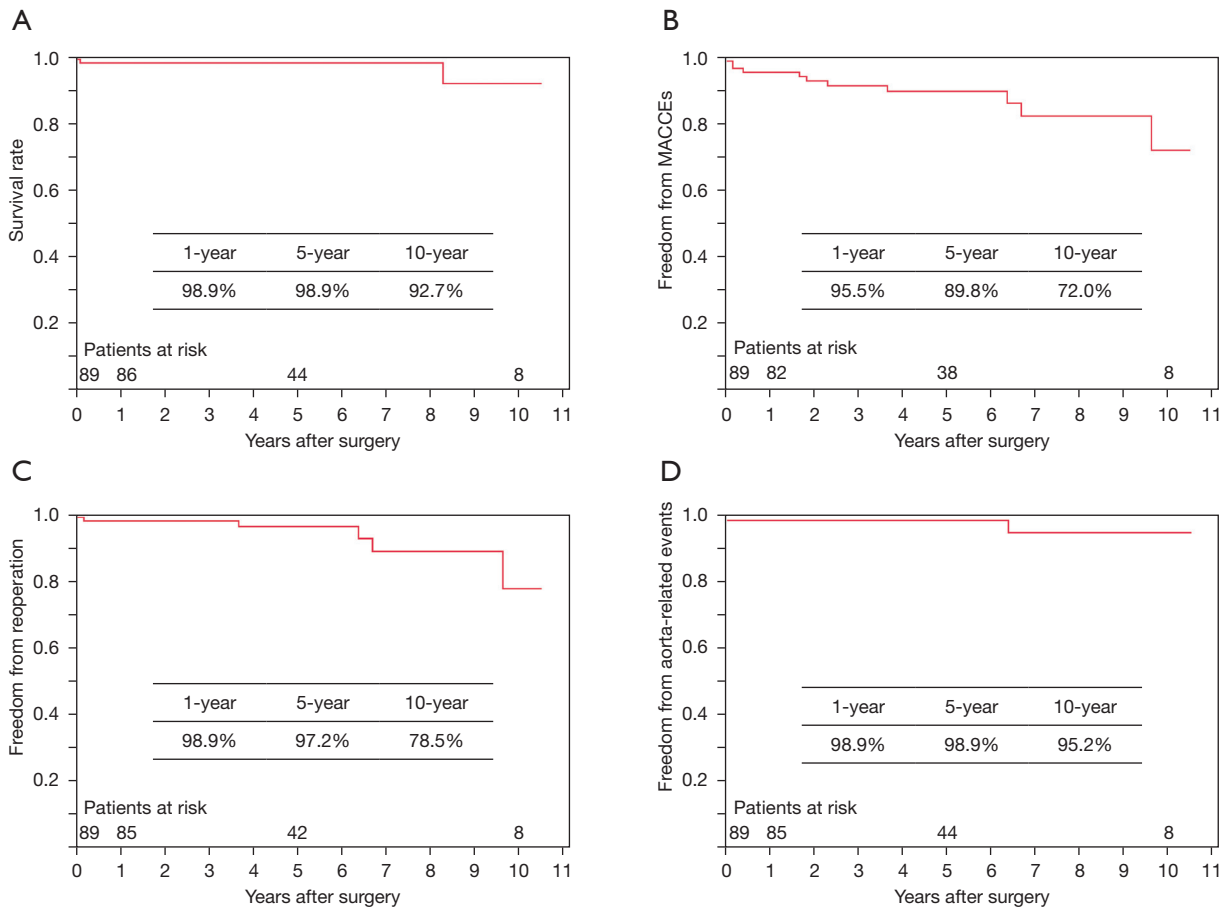


**Figure 1** Kaplan-Meier analysis. (A) Survival rate; (B) freedom from MACCEs; (C) freedom from reoperation; and (D) freedom from aorta-related events. MACCEs, major adverse cardiac or cerebrovascular events.

with an average dilatation, higher expansion cohorts were detected in 26 (38%) patients with SOV and 29 (42%) with DAAo. Except for the baseline SOV diameter, there were no significant differences in SOV preoperative parameters and intraoperative or postoperative outcomes. Patients with a lower SOV at baseline had a greater expansion rate (*Table 5*). In contrast, patients with a larger DAAo expansion had a higher CMN grade, prevalence rate of MACCEs, reoperation rates, and a smaller DAAo diameter at baseline (*Table 6*). On stratification with baseline SOV or DAAo, 20 (22%) patients presented with an SOV diameter >40 mm at baseline, with fewer female patients, larger body surface area, and a higher prevalence of aortic regurgitation etiology; however, postoperative outcomes were comparable to those of patients with SOV diameter ≤40 mm, except for SOV diameter at late follow-up. SOV diameter >40 mm at baseline was higher at late follow-up (Table S1). Fourteen patients (16%) had DAAo >40 mm at baseline. Preoperative, intraoperative, and postoperative results were similar, except for the late follow-up diameter and DAAo expansion rate. Similar to SOV, patients with DAAo >40 mm at baseline had an elevated DAAo at late follow-up. Patients with DAAo ≤40 mm had a greater expansion rate (Table S2).

### *Time-based interaction with potential modifying factors of progressive dilatation of the residual aorta*

The generalized linear estimate showed that baseline variables such as sex, SOV <40 *vs.* ≥40 mm, aortic valve etiology, and aortic graft size had a significant correlation with the SOV diameter at late follow-up. Moreover, only baseline DAAo <40 *vs.* ≥40 mm had a significant correlation with the diameter of the DAAo at late follow-up (Table S3). Furthermore, the time-scaled multilevel analysis in which

**Table 3** Early and late outcomes

| Outcomes | Number |
|---|---|
| Early outcomes | |
| In-hospital mortality | 1 (1%) |
| Reoperation for bleeding | 4 (4%) |
| Permanent pacemaker implantation | 1 (1%) |
| Atrial fibrillation | 15 (17%) |
| Aortic dissection | 1 (1%) |
| Ventilation time (hour), mean ± SD | 11±10 |
| ICU stay (day), mean ± SD | 3±2 |
| Hospital stay (day), mean ± SD | 15±7 |
| Late outcomes | |
| Follow-up (years), mean ± SD [min–max] | 6.1±2.7 [0.6–11.2] |
| Late mortality | 1 (1%) |
| MACCEs | 9 (10%) |
| Reoperation | 5 (6%) |
| Pseudo-aneurysm | 1 (1%) |
| Structural valve deterioration | 3 (3%) |
| Prosthetic valve endocarditis | 1 (1%) |
| Ischemic stroke | 3 (3%) |
| Heart failure | 1 (1%) |
| Diameter at late follow-up (mm), mean ± SD [min–max] | |
| Sinus of Valsalva | 36.5±4.8 [28–50] |
| Distal ascending aorta | 37.7±3.3 [29–45] |

SD, standard deviation; ICU, intensive care unit, MACCEs, major adverse cardiac and cerebrovascular events.

**Table 4** Diameter of the SOV and DAAo at baseline and late follow-up

| All patients (n=89) | Baseline, mm | At late follow, mm | Expansion rate (mm/year) | P value |
|---|---|---|---|---|
| SOV | 36.3±5.1 | 36.5±4.8 | 0.08±0.45 | 0.150 |
| DAAo | 37.0±3.5 | 37.7±3.3 | 0.11±0.40 | 0.005 |

SOV, sinus of Valsalva; DAAo, distal ascending aorta.

the concept of time is considered showed no significant association of dilatation of the SOV and the DAAo with potential modifying factors (*Table* 7). In the trajectory analysis, a total of four trajectory patterns were identified as optimal classifications in the SOV and DAAo (Table S4).

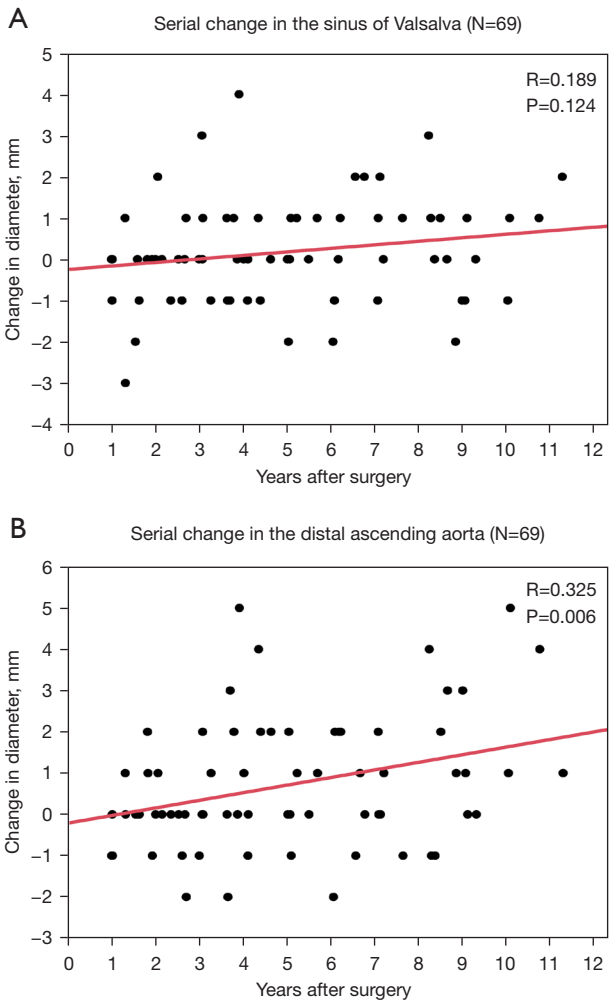


**Figure 2** Time course change in (A) the sinus of Valsalva and (B) the distal ascending aorta in all patients.

Posterior probabilities for individual classification of the SOV and DAAo were both high (SOV: 0.91±0.13; DAAo: 0.92±0.11). The majority pattern was class 2 in the SOV (n=36) and class 3 in the DAAo (n=35). For both the SOV and DAAo, the aortic diameter size at baseline remained stable over time in all four classifications. Notably, even in patients under class 4, with a dilated SOV and DAAo >40 mm, the diameters never showed significant growth and remained clinically negligible (*Figure 3*). Model probably showed from 0.91–0.97 (Table S5).

## Discussion

In patients with a BAV who undergo AVR and GR of the ascending aorta., the postoperative increase is negligible

**Table 5** Comparison of higher and lower expansion of the SOV

| Variables | Higher expansion of SOV (n=26) | Lower expansion of SOV (n=43) | P value |
|---|---|---|---|
| Preoperative characteristics | | | |
| Age (years) | 62±10 | 61±13 | 0.887 |
| Female sex | 13 (50%) | 12 (28%) | 0.066 |
| Body surface area ($m^2$) | 1.61±0.20 | 1.65±0.19 | 0.356 |
| Hypertension | 18 (69%) | 23 (53%) | 0.193 |
| Chronic obstructive pulmonary disorder | 3 (12%) | 9 (21%) | 0.307 |
| Aortic valve etiology | | | 0.565 |
| Stenosis | 19 (73%) | 28 (65%) | |
| Regurgitation | 2 (8%) | 7 (16%) | |
| Mixed | 5 (19%) | 8 (19%) | |
| Phenotype of bicuspid aortic valve | | | 0.365 |
| Type 0 | 8 (31%) | 16 (37%) | |
| Type 1 (R-L fusion) | 14 (54%) | 16 (37%) | |
| Type 1 (R-N fusion) | 4 (15%) | 11 (26%) | |
| Diameter (mm) | | | |
| Sinus of Valsalva | 34.5±4.0 | 37.6±5.4 | 0.021 |
| Middle ascending aorta | 47.9±5.2 | 46.8±4.2 | 0.495 |
| Distal ascending aorta | 36.5±3.7 | 37.3±3.4 | 0.422 |
| EuroSCORE II | 1.87±1.49 | 2.30±2.45 | 0.569 |
| Intraoperative results | | | |
| Operation time (min) | 340±85 | 321±73 | 0.432 |
| Cardiopulmonary bypass time (min) | 154±33 | 157±42 | 0.906 |
| Aortic cross-clamp time (min) | 109±19 | 113±27 | 0.642 |
| Cystic medial necrosis grade | | | 0.623 |
| 0 | 4 (16%) | 3 (7%) | |
| 1 | 9 (36%) | 20 (47%) | |
| 2 | 8 (32%) | 12 (28%) | |
| 3 | 4 (16%) | 8 (19%) | |
| Postoperative outcomes | | | |
| In-hospital mortality | 0 | 0 | N/A |
| Reoperation for bleeding | 1 (4%) | 3 (7%) | 0.579 |
| Atrial fibrillation | 6 (23%) | 6 (14%) | 0.338 |
| Aortic dissection | 0 | 1 (2%) | 0.329 |
| Ventilation time (hour) | 13±11 | 12±12 | 0.115 |
| ICU stay (day) | 3±1 | 3±1 | 0.612 |

**Table 5** (*continued*)

**Table 5** (*continued*)

| Variables | Higher expansion of SOV (n=26) | Lower expansion of SOV (n=43) | P value |
|---|---|---|---|
| Hospital stay (day) | 18±10 | 15±5 | 0.208 |
| Follow-up (years) | 7.9±2.5 | 6.5±2.7 | 0.035 |
| Late mortality | 0 | 1 (2%) | 0.329 |
| MACCEs | 5 (19%) | 7 (16%) | 0.106 |
| Reoperation | | | 0.123 |
| Pseudo-aneurysm at sinus of Valsalva | 1 (4%) | 0 | |
| Structural valve deterioration | 2 (8%) | 1 (2%) | |
| Prosthetic valve endocarditis | 0 | 0 | |
| Expansion rate (mm/year) | | | |
| Sinus of Valsalva | 0.37±0.34 | −0.21±0.44 | <0.0001 |
| Distal ascending aorta | 0.20±0.41 | 0.06±0.40 | 0.286 |

Data are presented as mean ± SD or n (%). SOV, sinus of Valsalva; R-L, Right coronary cusp-Left coronary cusp; R-N, Right coronary cusp-Non coronary cusp; ICU, intensive care unit; MACCEs, major adverse cardiac and cerebrovascular events; N/A, not applicable.

**Table 6** Comparison of higher and lower expansion of the DAAo

| Variables | Higher expansion of DAAo (n=29) | Lower expansion of DAAo (n=40) | P value |
|---|---|---|---|
| Preoperative characteristics | | | |
| Age (years) | 62±10 | 61±13 | 0.794 |
| Female sex | 13 (45%) | 12 (30%) | 0.207 |
| Body surface area ($m^2$) | 1.64±0.17 | 1.64±0.21 | 0.995 |
| Hypertension | 19 (66%) | 22 (55%) | 0.378 |
| Chronic obstructive pulmonary disorder | 5 (17%) | 7 (18%) | 0.978 |
| Aortic valve etiology | | | 0.259 |
| Stenosis | 20 (69%) | 27 (68%) | |
| Regurgitation | 4 (14%) | 5 (13%) | |
| Mixed | 5 (17%) | 8 (20%) | |
| Phenotype of bicuspid aortic valve | | | 0.676 |
| Type 0 | 10 (34%) | 14 (35%) | |
| Type 1 (R-L fusion) | 12 (41%) | 18 (45%) | |
| Type 1 (R-N fusion) | 7 (24%) | 8 (20%) | |
| Diameter (mm) | | | |
| Sinus of Valsalva | 36.2±5.6 | 36.6±4.8 | 0.550 |
| Middle ascending aorta | 45.7±4.0 | 48.3±4.8 | 0.012 |
| Distal ascending aorta | 35.3±2.7 | 38.2±3.5 | 0.001 |
| EuroSCORE II | 1.40±1.00 | 2.91±2.71 | 0.051 |

**Table 6** (*continued*)

**Table 6** (*continued*)

| Variables | Higher expansion of DAAo (n=29) | Lower expansion of DAAo (n=40) | P value |
|---|---|---|---|
| Intraoperative results | | | |
| Operation time (min) | 326±77 | 330±79 | 0.808 |
| Cardiopulmonary bypass time (min) | 145±36 | 164±39 | 0.032 |
| Aortic cross-clamp time (min) | 106±24 | 115±24 | 0.107 |
| Cystic medial necrosis grade | | | 0.021 |
| 0 | 3 (10%) | 4 (10%) | |
| 1 | 11 (38%) | 18 (46%) | |
| 2 | 7 (24%) | 13 (33%) | |
| 3 | 8 (28%) | 4 (10%) | |
| Postoperative outcomes | | | |
| In-hospital mortality | 0 | 0 | N/A |
| Reoperation for bleeding | 1 (3%) | 3 (8%) | 0.464 |
| Atrial fibrillation | 8 (28%) | 4 (10%) | 0.058 |
| Aortic dissection | 0 | 1 (3%) | 0.294 |
| Ventilation time (hour) | 16±18 | 10±5 | 0.081 |
| ICU stay (day) | 3±1 | 3±1 | 0.923 |
| Hospital stay (day) | 14±5 | 17±8 | 0.037 |
| Follow-up (years) | 7.6±2.4 | 6.6±2.9 | 0.115 |
| Late mortality | 1 (3%) | 0 | 0.185 |
| MACCEs | 9 (31%) | 3 (8%) | 0.011 |
| Reoperation | | | 0.008 |
| Pseudo-aneurysm at sinus of Valsalva | 1 (3%) | 0 | |
| Structural valve deterioration | 3 (10%) | 0 | |
| Prosthetic valve endocarditis | 0 | 0 | |
| Expansion rate (mm/year) | | | |
| Sinus of Valsalva | 0.14±0.42 | −0.08±0.53 | 0.348 |
| Distal ascending aorta | 0.46±0.29 | −0.14±0.28 | <0.0001 |

Data are presented as mean ± SD or n (%). DAAo, distal ascending aorta; R-L, Right coronary cusp-Left coronary cusp; R-N, Right coronary cusp-Non coronary cusp; ICU, intensive care unit; MACCEs, major adverse cardiac and cerebrovascular events; N/A, not applicable.

in the SOV but showed significant enlargement in the DAAo. Nonetheless, postoperative survival rates and rates of freedom from aorta-related events at 1, 5, and 10 years after the operation remain high and over 90%, with no aorta-related death in our cohort study. Furthermore, we did not observe any effect of modifying factors in dilatation such as age (<65 or ≥65 years), sex, existence of COPD, BAV phenotype, pathological CMN grade, SOV and DAAo diameters at baseline (<40 or ≥40 mm), aortic valve etiology, prosthetic valve type, and graft size. To treat ascending aortic dilatation owing to a BAV, some may consider that prophylactic root or arch replacement should be performed if any dilatation is present in the SOV or DAAo (23). However, aortic arch surgery leads

**Table 7** Time-scaled multilevel analysis for dilatation of the SOV and DAAo

| Variables | Coefficient | SE | P value |
|---|---|---|---|
| Time interaction for SOV | | | |
| Years | 0.039 | 0.137 | 0.778 |
| Age × years | –0.026 | 0.122 | 0.832 |
| Sex × years | 0.230 | 0.233 | 0.326 |
| COPD × years | 0.045 | 0.394 | 0.908 |
| Hypertension × years | 0.366 | 0.452 | 0.425 |
| BAV phenotype × years | –0.179 | 0.187 | 0.340 |
| CMN grade × years | 0.114 | 0.139 | 0.414 |
| SOV <40 *vs.* ≥40 × years | 0.030 | 0.183 | 0.872 |
| Aortic valve etiology × years | –0.022 | 0.283 | 0.937 |
| Prosthetic valve type × years | 0.001 | 0.322 | 0.998 |
| Aortic graft size × years | 0.024 | 0.062 | 0.701 |
| Time interaction for DAAo | | | |
| Years | 0.096 | 0.089 | 0.283 |
| Age × years | –0.016 | 0.079 | 0.836 |
| Sex × years | 0.039 | 0.199 | 0.844 |
| COPD × years | –0.082 | 0.258 | 0.751 |
| Hypertension × years | –0.191 | 0.281 | 0.498 |
| BAV phenotype × years | 0.026 | 0.122 | 0.835 |
| CMN grade × years | –0.043 | 0.089 | 0.633 |
| DAAo <40 *vs.* ≥40 × years | –0.121 | 0.164 | 0.462 |
| Aortic valve etiology × years | –0.011 | 0.196 | 0.955 |
| Prosthetic valve type × years | –0.126 | 0.218 | 0.564 |
| Aortic graft size × years | 0.022 | 0.042 | 0.603 |

SOB, sinus of Valsalva; DAAo, distal ascending aorta; COPD, chronic obstructive pulmonary disorder; BAV, bicuspid aortic valve; CMN, cystic medial necrosis; SE, standard error.

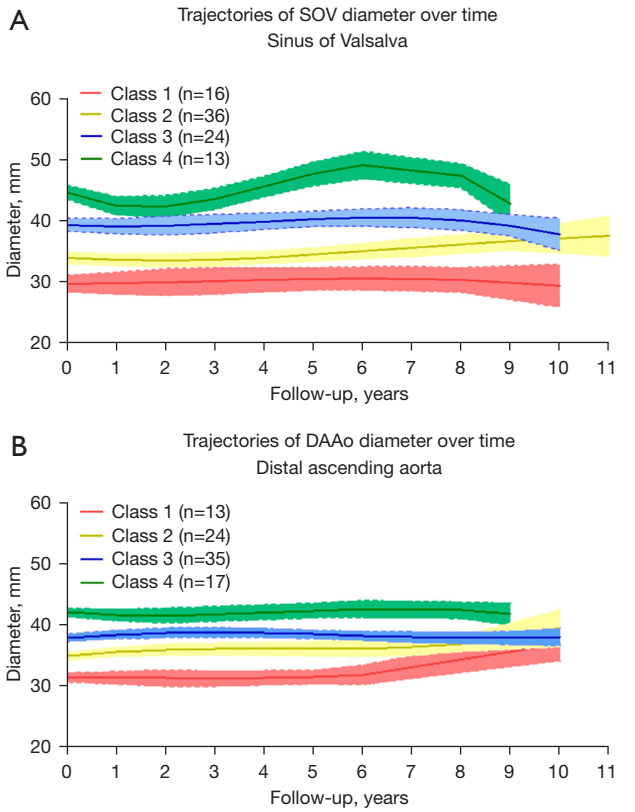


**Figure 3** Trajectories for the sinus of Valsalva and distal ascending aorta diameter overtime. SOV, sinus of Valsalva; DAAo, distal ascending aorta.

to prolonged cardiopulmonary bypass and aortic cross-clamp time, resulting in poor early and late outcomes compared with GR of the ascending aorta (24). In addition, compared with clamped and DHCA, the freedom from repeat aortic arch surgery and survival are reportedly similar in patients undergoing GR of the ascending aorta, but longer cardiopulmonary bypass and aortic cross-clamp times and an increased risk of blood transfusion were obtained with DHCA (25). Moreover, intervention in the cervical vessels obviously increases the risk of mortality and stroke (26,27). Therefore, prophylactic arch surgery would be preferably avoided in the absence of aortic arch dilation. Vendramin *et al.* recommended untouched root surgery to minimize surgical risks. In addition, they showed that the mean diameters of the aortic root at 6 years of follow-up were significantly smaller than the preoperative diameters because GR of the ascending aorta influences the reverse remodeling of the aortic root (17). In this study, we demonstrated that the slight increase in SOV did not correlate with the time lapsed after surgery, and the increase in the DAAo, although significant, is clinically trivial, with the maximum expansion of the DAAo being 0.11±0.40 mm per year. In general, recent studies have suggested that aortic stenosis is associated with ascending aorta phenotype, while aortic regurgitation is associated with root phenotype (8). In the case of the former, root dilatation after AVR has

already been shown to be uncommon. The low prevalence of aortic valve regurgitation in this study might affect the small occurrence of SOV dilatation, and the combination of AVR and GR of the ascending aorta may be sufficient to prevent further dilatation of the residual aorta in the absence of aorta-related events and surgeries owing to pathological aortic dilatation. This combination provided excellent mid-term survival and freedom from MACCEs. Our results are consistent with those of several reports, demonstrating rare arch dilatation following GR of the ascending aorta at late follow-up (18,23,28,29). Furthermore, when this cohort study was divided into two groups with clamped or DHCA without cross-clamp, we observed prolonged operation, cardiopulmonary bypass, and aortic cross-clamp time; more frequent reoperation for bleeding; and longer hospital stay in the latter group (Table S6), similar to previous reports (25,28). Although clamped GR of the ascending aorta was recommended, when possible, the cut-off diameter of the DAAo could not be determined in this study. The patients with a high surgical risk had a poor operative outcome following AVR and GR of the ascending aorta; therefore, it is imperative that minimal surgery, such as the wrapping technique, be considered for these patients. For patients with a moderately dilated ascending aorta, this technique should be simple and safe, and it could be an alternative treatment option (30,31).

Although the natural expansion rate of the ascending aorta is reportedly 0.2–1.9 mm/year in a BAV (8,11,32), the postoperative expansion rate was much lower. On stratification with higher and lower expansion rate, the baseline diameters were substantially linked with diameters at late follow-up as indicated by the generalized linear estimate, but the time-scaled multilevel analysis could not discover any time-dependent dilatation. We considered that the operation changed the eccentric jet and as such, reduced the shear stress on the aortic wall (8,33,34). We also investigated the impact of CMN grade on the change in the residual aortic diameter and revealed that patients with a larger DAAo expansion had a higher CMN grade, but did not observe any association between high-grade CMN and progression of the SOV and DAAo dilatation. Valve replacement reduces the shear stress on the aortic wall while reducing the adverse effects of abnormal regulatory pathway activation in the vascular smooth muscle cells; however, details of the possible underlying mechanisms remain unclear.

We used trajectory analysis to identify modifying factors of progressive dilatation of the residual aorta. Scatter maps and the relevant correlation analysis are not suitable to clarify individual time-dependent aortic changes. In contrast, trajectory analysis calculates the optimal number and frequency of variation patterns mathematically and detects the groups with a similar pattern of aortic changes by generalizing individual trajectories. As a result, we could divide this cohort study into four groups, which had stable aortic diameter over time. Based on the current study findings, we believe that our simple GR of the ascending aorta is an effective treatment method with a very low risk of residual aortic dilatation in patients with a BAV at the time of AVR.

This study had several limitations. First, this was a single-center retrospective study with a limited number of patients, which may influence its statistical power. In the Kaplan-Meier analysis, there were only eight patients remaining at 10 years after the operation; thus, longer follow-up period and a larger number of patients are necessary to validate our conclusions. Second, patients in this series had relatively small ascending aortas because most were undergoing surgery for valvular reasons. Therefore, in this cohort study, patients with a primary indication for thoracic aneurysm and secondary indication for moderately degenerated aortic valve disease were not included. Third, CT follow-up data were incomplete (follow-up rate 78%). Fourth, all patients had only the baseline and a single follow-up measurement and not multiple follow-up measurements. However, we used two time-scale points: (I) time at follow-up measurements was random for both investigators and patients and (II) validation study for model probability in trajectory analyses revealed that it was universally high (Table S2). We concluded, therefore, that this limitation would not have a substantial impact on the overall principal results and conclusion. Fifth, although it was not presented, it might be interesting to see if there was a correlation between the aortic dilatation rate before and after the operation. Finally, we did not have access to detailed information concerning the blood pressure or prescribed medication during the follow-up, which might have affected our findings.

## Conclusions

In selected patients with a BAV with a >45 mm ascending aorta and normal roots and arches, the GR of the ascending aorta without concomitant root and arch procedure

produced excellent survival rates, freedom from MACCEs, and fewer reoperation and aorta-related events in the mid-term follow-up. Rapid dilatation of the residual aorta rarely occurred in patients with a BAV who had undergone AVR and GR of the ascending aorta. For selected patients with a surgical indication for ascending aortic dilatation, simple AVR and GR of the ascending aorta may be sufficient surgical options.

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## Footnote

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*Conflicts of Interest:* All authors have completed the ICMJE uniform disclosure form (available at https://jtd.amegroups.com/article/view/10.21037/jtd-22-1118/coif). The authors have no conflicts of interest to declare.

*Ethical Statement:* The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of ant part of the work are appropriately investigated and resolved. This study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The ethics committee of National Cerebral and Cardiovascular Center, Osaka, Japan approved this study (No. M-30-026); the need for informed consent was waived due to the retrospective nature of the study.



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## Supplementary

**Table S1** Comparison of patients with preoperative SOV >40 mm and ≤40 mm

| Comparison of patients with preoperative SOV >40 mm and ≤40 mm | SOV >40 mm (N=20) | SOV ≤40 mm (N=69) | P value |
|---|---|---|---|
| Preoperative characteristics | | | |
| Age (years) | 61±13 | 62±11 | 0.705 |
| Female sex | 2 (10%) | 36 (52%) | 0.0003 |
| Body surface area ($m^2$) | 1.73±0.16 | 1.61±0.20 | 0.017 |
| Hypertension | 13 (65%) | 42 (61%) | 0.737 |
| Chronic obstructive pulmonary disorder | 3 (15%) | 11 (16%) | 0.919 |
| Aortic valve etiology | | | 0.023 |
| Stenosis | 11 (55%) | 50 (72%) | |
| Regurgitation | 6 (30%) | 4 (6%) | |
| Mixed | 3 (15%) | 15 (22%) | |
| Phenotype of bicuspid aortic valve | | | 0.489 |
| Type 0 | 5 (25%) | 27 (39%) | |
| Type 1 (R-L fusion) | 10 (50%) | 29 (42%) | |
| Type 1 (R-N fusion) | 5 (25%) | 13 (19%) | |
| Diameter (mm) | | | |
| Sinus of Valsalva | 43.2±3.0 | 33.9±3.5 | <0.001 |
| Middle ascending aorta | 49.2±4.7 | 46.7±4.5 | 0.048 |
| Distal ascending aorta | 37.7±3.0 | 37.0±3.7 | 0.418 |
| EuroSCORE II | 2.18±1.54 | 2.14±2.13 | 0.343 |
| Intraoperative results | | | |
| Operation time (min) | 339±76 | 311±80 | 0.079 |
| Cardiopulmonary bypass time (min) | 165±38 | 146±38 | 0.035 |
| Aortic cross-clamp time (min) | 117±24 | 106±26 | 0.058 |
| Cystic medial necrosis grade | | | 0.591 |
| 0 | 2 (10%) | 6 (9%) | |
| 1 | 10 (53%) | 24 (38%) | |
| 2 | 4 (21%) | 23 (36%) | |
| 3 | 3 (16%) | 11 (17%) | |
| Postoperative outcomes | | | |
| In-hospital mortality | 0 | 1 (1%) | 0.474 |
| Reoperation for bleeding | 1 (5%) | 4 (6%) | 0.890 |
| Atrial fibrillation | 3 (15%) | 12 (18%) | 0.779 |
| Aortic dissection | 0 | 1 (1%) | 0.474 |
| Ventilation time (hour) | 14±19 | 10±8 | 0.338 |
| ICU stay (day) | 3±2 | 3±2 | 0.803 |

**Table S1** (*continued*)


https://dx.doi.org/10.21037/jtd-22-1118

**Table S1** (*continued*)

| Comparison of patients with preoperative SOV >40 mm and ≤40 mm | SOV >40 mm (N=20) | SOV ≤40 mm (N=69) | P value |
|---|---|---|---|
| Hospital stay (day) | 16±8 | 15±7 | 0.880 |
| Follow-up (years) | 6.9±2.7 | 6.0±3.0 | 0.201 |
| Late mortality | 1 (5%) | 0 | 0.082 |
| MACCEs | 3 (15%) | 11 (16%) | 0.919 |
| Reoperation | | | 0.334 |
| Pseudo-aneurysm at sinus of Valsalva | 1 (5%) | 0 (1%) | |
| Structural valve deterioration | 0 | 3 (4%) | |
| Prosthetic valve endocarditis | 0 | 1 (1%) | |
| Diameter at late follow-up (mm) | | | |
| Sinus of Valsalva | 43.1±3.4 | 34.3±3.2 | <0.0001 |
| | | 37.5±3.4 | 0.398 |
| Distal ascending aorta | 38.1±3.1 | | |
| Expansion rate (mm/year) | | | |
| Sinus of Valsalva | –0.11±0.67 | 0.05±0.41 | 0.110 |
| Distal ascending aorta | 0.11±0.40 | 0.11±0.42 | 0.832 |

ICU, intensive care unit, MACCEs, major adverse cardiac and cerebrovascular events, SOV, sinus of Valsalva.

**Table S2** Comparison of patients with preoperative DAAo >40 mm and ≤40 mm

| Comparison of patients with preoperative DAAo >40mm and ≤40mm | DAAo >40mm (N=14) | DAAo ≤40mm (N=75) | P-value |
|---|---|---|---|
| Preoperative characteristics | | | |
| Age (years) | 63±15 | 62±11 | 0.600 |
| Female sex | 5 (35%) | 33 (44%) | 0.562 |
| Body surface area ($m^2$) | 1.64±0.26 | 1.64±0.18 | 0.714 |
| Hypertension | 7 (50%) | 48 (64%) | 0.328 |
| Chronic obstructive pulmonary disorder | 2 (14%) | 12 (16%) | 0.870 |
| Aortic valve etiology | | | 0.259 |
| Stenosis | 7 (50%) | 54 (72%) | |
| Regurgitation | 3 (21%) | 7 (9%) | |
| Mixed | 4 (29%) | 14 (19%) | |
| Phenotype of bicuspid aortic valve | | | 0.676 |
| Type 0 | 5 (36%) | 27 (36%) | |
| Type 1 (R-L fusion) | 5 (36%) | 34 (45%) | |
| Type 1 (R-N fusion) | 4 (29%) | 14 (19%) | |
| Diameter (mm) | | | |
| Sinus of Valsalva | 36.9±4.7 | 35.9±5.2 | 0.478 |

**Table S2** (*continued*)


https://dx.doi.org/10.21037/jtd-22-1118

**Table S2** (*continued*)

| Comparison of patients with preoperative DAAo >40mm and ≤40mm | DAAo >40mm (N=14) | DAAo ≤40mm (N=75) | P-value |
|---|---|---|---|
| Middle ascending aorta | 50.1±4.9 | 46.7±4.5 | 0.019 |
| Distal ascending aorta | 42.7±1.4 | 36.1±2.8 | <0.0001 |
| EuroSCORE II | 4.35±4.06 | 1.85±1.40 | 0.078 |
| Intraoperative results | | | |
| Operation time (min) | 339±110 | 313±73 | 0.539 |
| Cardiopulmonary bypass time (min) | 165±52 | 148±36 | 0.255 |
| Aortic cross-clamp time (min) | 112±30 | 108±25 | 0.521 |
| Cystic medial necrosis grade | | | 0.245 |
| 0 | 0 | 8 (11%) | |
| 1 | 7 (58%) | 27 (38%) | |
| 2 | 4 (33%) | 23 (32%) | |
| 3 | 1 (8%) | 13 (18%) | |
| Postoperative outcomes | | | |
| In-hospital mortality | 0 | 1 (1%) | 0.557 |
| Reoperation for bleeding | 1 (7%) | 4 (5%) | 0.794 |
| Atrial fibrillation | 4 (29%) | 11 (15%) | 0.237 |
| Aortic dissection | 1 (7%) | 0 | 0.053 |
| Ventilation time (hour) | 9±5 | 12±13 | 0.270 |
| ICU stay (day) | 3±2 | 3±2 | 0.651 |
| Hospital stay (day) | 18±10 | 15±6 | 0.200 |
| Follow-up (years) | 4.7±2.6 | 6.5±2.9 | 0.026 |
| Late mortality | 0 | 1 (1%) | 0.557 |
| MACCEs | 1 (7%) | 13 (17%) | 0.297 |
| Reoperation | | | 0.334 |
| Pseudo-aneurysm at sinus of Valsalva | 0 | 1 (1%) | |
| Structural valve deterioration | 0 | 3 (4%) | |
| Prosthetic valve endocarditis | 0 | 1 (1%) | |
| Diameter at late follow-up (mm) | | | |
| Sinus of Valsalva | 37.3±5.6 | 36.6±5.1 | 0.752 |
| Distal ascending aorta | 42.2±1.5 | 36.9±2.9 | <0.0001 |
| Expansion rate (mm/year) | | | |
| Sinus of Valsalva | –0.11±0.51 | 0.03±0.50 | 0.917 |
| Distal ascending aorta | –0.11±0.24 | 0.15±0.42 | 0.013 |

DAAo, distal ascending aorta, ICU, intensive care unit, MACCEs, major adverse cardiac and cerebrovascular events.


https://dx.doi.org/10.21037/jtd-22-1118

**Table S3** Generalized linear estimate for dilatation of the SOV and DAAo

| | Coefficient | SE | P-value |
|---|---|---|---|
| Generalized linear estimate for SOV | | | |
| Years | 0.039 | 0.137 | 0.778 |
| Age | –0.245 | 0.438 | 0.577 |
| Female Sex | –6.477 | 0.868 | <0.001 |
| COPD | –0.244 | 1.481 | 0.869 |
| Hypertension | –0.109 | 1.160 | 0.925 |
| BAV phenotype | 0.414 | 0.756 | 0.585 |
| CMN grade | –0.791 | 0.639 | 0.218 |
| SOV < 40 mm *vs.* ≥ 40 mm | 9.073 | 0.749 | <0.001 |
| Aortic valve etiology | –3.102 | 0.842 | <0.001 |
| Prosthetic valve type | 0.666 | 1.098 | 0.545 |
| Aortic graft size | 0.755 | 0.195 | <0.001 |
| Generalized linear estimate for DAAo | | | |
| Years | 0.096 | 0.089 | 0.283 |
| Age | 0.361 | 0.262 | 0.170 |
| Female Sex | –0.990 | 0.682 | 0.149 |
| COPD | 1.185 | 0.927 | 0.203 |
| Hypertension | 0.308 | 0.802 | 0.702 |
| BAV phenotype | 0.089 | 0.466 | 0.849 |
| CMN grade | 0.723 | 0.394 | 0.068 |
| DAAo <40 mm *vs.* ≥40 mm | 5.941 | 0.560 | <0.001 |
| Aortic valve etiology | 0.211 | 0.598 | 0.725 |
| Prosthetic valve type | 0.739 | 0.746 | 0.324 |
| Aortic graft size | 0.245 | 0.138 | 0.078 |

BAV, bicuspid aortic valve, CMN, cystic medial necrosis, COPD, chronic obstructive pulmonary disorder, DAAo, distal ascending aorta, SE, standard error, SOV, sinus of Valsalva.

**Table S4** Baseline characteristics according to trajectory groups for the SOV and DAAo

| | Class 1 | Class 2 | Class 3 | Class 4 |
|---|---|---|---|---|
| SOV | | | | |
| Number.at risk | 16 | 36 | 24 | 13 |
| Age, years | 67.7 | 61.3 | 60.8 | 59.2 |
| Female sex, % | 12.5 | 47.2 | 87.5 | 84.6 |
| COPD, % | 12.5 | 13.9 | 20.8 | 15.4 |
| Hypertension | 53.8 | 65.2 | 81.8 | 64.7 |
| BAV phenotype, % | | | | |
| Type 0 | 43.8 | 36.1 | 37.5 | 23.1 |
| Type 1 (R-L) | 25.0 | 50.0 | 33.3 | 69.2 |
| Type 1 (R-N) | 31.3 | 13.9 | 29.2 | 7.7 |
| CMN grade, % | | | | |
| Grade 0 | 6.3 | 11.8 | 4.8 | 16.7 |
| Grade 1 | 18.8 | 50.0 | 33.3 | 58.3 |
| Grade 2 | 56.3 | 23.5 | 42.9 | 8.3 |
| Grade 3 | 18.8 | 14.7 | 19.1 | 16.7 |
| SOV >40 mm, % | 0.0 | 0.0 | 33.3 | 100.0 |
| Aortic valve etiology, % | | | | |
| AS | 54.5 | 65.0 | 68.4 | 87.5 |
| AR | 18.2 | 10.0 | N.A. | N.A. |
| ASR | 18.2 | 17.5 | 31.6 | N.A. |
| Prosthetic valve type, % | 90.9 | 77.5 | 89.5 | 87.5 |
| Graft size, % | 27.2 | 27.0 | 27.3 | 26.3 |

**Table S4** (*continued*)


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**Table S4** (*continued*)

| | Class 1 | Class 2 | Class 3 | Class 4 |
|---|---|---|---|---|
| DAAo | | | | |
| Number.at risk | 13 | 24 | 35 | 17 |
| Age, years | 56.2 | 64.6 | 61.7 | 63.3 |
| Female sex, % | 38.5 | 50.0 | 65.7 | 64.7 |
| COPD, % | 0.0 | 16.7 | 20.0 | 17.6 |
| Hypertension | 47.1 | 60.0 | 68.8 | 75.0 |
| BAV phenotype, % | | | | |
| Type 0 | 38.5 | 33.3 | 37.1 | 35.3 |
| Type 1 (R-L) | 46.2 | 45.8 | 42.9 | 41.2 |
| Type 1 (R-N) | 15.4 | 20.8 | 20.0 | 23.5 |
| CMN grade, % | | | | |
| Grade 0 | 33.3 | 4.4 | 9.1 | 0.0 |
| Grade 1 | 33.3 | 43.5 | 39.4 | 46.7 |
| Grade 2 | 25.0 | 39.1 | 33.3 | 26.7 |
| Grade 3 | 8.3 | 13.0 | 18.2 | 26.7 |
| DAAo >40 mm, % | 0.0 | 0.0 | 14.3 | 100.0 |
| Aortic valve etiology, % | | | | |
| AS | 58.6 | 85.7 | 52.9 | 68.1 |
| AR | 20.7 | N.A. | 11.8 | 4.3 |
| ASR | 13.8 | 14.3 | 17.6 | 23.4 |
| Prosthetic valve type, % | 93.1 | 71.4 | 88.2 | 80.9 |
| Graft size, % | 27.4 | 26.0 | 27.5 | 26.9 |

AR, aortic valve regurgitation, AS, aortic valve stenosis, ASR; aortic valve stenosis and regurgitation, BAV, bicuspid aortic valve, CMN, cystic medial necrosis, COPD, chronic obstructive pulmonary disorder, DAAo, distal ascending aorta, N.A., not available, SOV, sinus of Valsalva.

**Table S5** Model probabilities for trajectory analysis

| | Model probability | SD |
|---|---|---|
| SOV | | |
| Class 1 | 0.95 | 0.09 |
| Class 2 | 0.94 | 0.08 |
| Class 3 | 0.93 | 0.08 |
| Class 4 | 0.95 | 0.12 |
| DAAo | | |
| Class 1 | 0.95 | 0.11 |
| Class 2 | 0.92 | 0.10 |
| Class 3 | 0.91 | 0.11 |
| Class 4 | 0.97 | 0.05 |

DAAo, distal ascending aorta, SD, standard deviation, SOV, sinus of Valsalva.


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**Table S6** Comparison of GR of the ascending aorta with clamped and with DHCA in pre-, intra-, and post-operative variables

| Comparison of GR of the ascending aorta with clamped and with DHCA | With clamped (N=68) | With DHCA (N=21) | P-value |
|---|---|---|---|
| Preoperative characteristics | | | |
| Age (years) | 63±10 | 59±14 | 0.219 |
| Female sex | 34 (50%) | 4 (19%) | 0.013 |
| Body surface area ($m^2$) | 1.62±0.20 | 1.70±0.17 | 0.064 |
| Hypertension | 45 (66%) | 10 (48%) | 0.198 |
| Chronic obstructive pulmonary disorder | 9 (13%) | 5 (24%) | 0.305 |
| Aortic valve etiology | | | 0.396 |
| Stenosis | 47 (69%) | 14 (67%) | |
| Regurgitation | 15 (22%) | 3 (14%) | |
| Mixed | 6 (9%) | 4 (19%) | |
| Phenotype of bicuspid aortic valve | | | 0.190 |
| Type 0 | 27 (40%) | 5 (24%) | |
| Type 1 (R-L fusion) | 30 (44%) | 9 (43%) | |
| Type 1 (R-N fusion) | 11 (16%) | 7 (33%) | |
| Diameter (mm) | | | |
| Sinus of Valsalva | 35.3±5.0 | 38.3±5.0 | 0.016 |
| Middle ascending aorta | 46.5±4.4 | 49.9±4.6 | 0.002 |
| Distal ascending aorta | 36.6±3.3 | 39.0±3.7 | 0.003 |
| EuroSCORE II | 4.16±2.14 | 3.92±3.58 | 0.045 |
| Intraoperative results | | | |
| Operation time (min) | 298±72 | 379±72 | < 0.001 |
| Cardiopulmonary bypass time (min) | 136±31 | 196±26 | < 0.001 |
| Aortic cross-clamp time (min) | 102±24 | 131±18 | < 0.001 |
| Cerebral perfusion time (min) | – | 29±7 | NA |
| Circulatory arrest time (min) | – | 31±7 | NA |
| Cystic medial necrosis grade | | | 0.285 |
| 0 | 6 (10%) | 2 (10%) | |
| 1 | 26 (41%) | 8 (40%) | |
| 2 | 23 (36%) | 4 (20%) | |
| 3 | 8 (13%) | 6 (30%) | |
| Postoperative outcomes | | | |
| In-hospital mortality | 1 (1%) | 0 | 0.578 |
| Reoperation for bleeding | 1 (1%) | 3 (14%) | 0.039 |
| Atrial fibrillation | 12 (18%) | 3 (14%) | 0.756 |
| Aortic dissection | 1 (1%) | 0 | 0.980 |

**Table S6** (*continued*)


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**Table S6** (*continued*)

| Comparison of GR of the ascending aorta with clamped and with DHCA | With clamped (N=68) | With DHCA (N=21) | P-value |
|---|---|---|---|
| Ventilation time (hour) | 10±8 | 14±19 | 0.283 |
| ICU stay (day) | 3±2 | 3±1 | 0.402 |
| Hospital stay (day) | 13±4 | 21±10 | < 0.001 |
| Follow-up (years) | 5.8±2.9 | 7.5±2.7 | 0.014 |
| Late mortality | 1 (1%) | 0 | 1.000 |
| MACCEs | 8 (12%) | 1 (5%) | 0.108 |
| Reoperation | | | 0.334 |
| Pseudo-aneurysm at sinus of Valsalva | 1 (1%) | 0 | |
| Structural valve deterioration | 3 (4%) | 0 | |
| Prosthetic valve endocarditis | 1 (1%) | 0 | |
| Diameter at late follow-up (mm) | | | |
| Sinus of Valsalva | 35.6±4.7 | 38.5±4.7 | 0.024 |
| Distal ascending aorta | 37.2±3.3 | 38.7±3.3 | 0.055 |
| Expansion rate (mm/year) | | | |
| Sinus of Valsalva | 0.03±0.53 | 0.03±0.20 | 0.587 |
| Distal ascending aorta | 0.10±0.39 | −0.08±0.33 | 0.062 |

GR, graft replacement, DHCA, deep hypothermic circulatory arrest, ICU, intensive care unit, MACCEs, major adverse cardiac and cerebrovascular events.


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