

Peer Review File

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Reviewer A

Some reports show the long-term outcomes and ascending aorta dilation rates were similar between bicuspid and tricuspid AV patients up to 15 years after AVR. Bicuspid AV was not a risk factor of mortality or aortic events during the follow-up.

BAV patients with aortic valve stenosis and concomitant mild-to-moderate ascending aortic dilation are at a considerably low risk of adverse aortic events at 15 years after an isolated AVR.

The aortic wrapping technique may be an alternative treatment for a moderately dilated ascending aorta in selected, risky patients undergoing AVR for BAS.

But your report shows follow-up of diameter of SOV and distal ascending aorta after AVR and GR of ascending aorta and the results was similar to other reports

I think moderately dilated ascending aorta with BAS is recommend individualized selection of surgical methods.

Reply: We thank the reviewer very much for the informative insights on this study. As indicated, various studies have compared the ascending aortic dilatation between patients with a BAV and a TAV. On the other hand, Yasuda H et al. demonstrated that following isolated AVR, aortic dilation in patients with a BAV tended to be faster than in patients with a TAV. Therefore, we examined the surgical result and serial change in the residual ascending aorta following BAV and ascending aorta replacement. As a consequence, postoperative SOV or DAAo was not significantly altered, showing clinical insignificance, and there was low long-term mortality or aorta-related events. Patients with high surgical risk demonstrated poor operative outcomes after AVR and GR of the ascending aorta; therefore, it would be crucial that minimal surgery, such as the wrapping technique, be considered for these patients. It was stated that the aortic wrapping approach may be a straightforward and safe option for patients receiving AVR for BAS with a mildly dilated ascending aorta. This essential topic and supporting articles have been included in the discussion and references.

Changes in the text (see Page 14, line 227-231):

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).

References (Page 20, reference 30 and 31):

Yasuda H, Nakatani S, Stugaard M, et al. Failure to prevent progressive dilation of ascending aorta by aortic valve replacement in patients with bicuspid aortic valve:

comparison with tricuspid aortic valve. Circulation 2003;108;Suppl 1:I1291-4.

Gonzalez-Santos JM, Arnaiz-Gercia ME. Wrapping of the ascending aorta revisited-is there any role left for conservative treatment of ascending aortic aneurism? J Thrac Dis 2017;9(Suppl 6):S488-97.

Reviewer B

The authors Yajima et al. are to be congratulated for their work : Does the residual aorta dilate after replacement of the bicuspid aortic valve and ascending aorta? . I think the work is well written and merits attention.

The authors are presenting very well structured paper in all patterns, such as the aim of the study, the methodology, with sufficient amount of analysis and statistics and a clear conclusion.

Although the theme of dilated aorta in patients with BAV has been frequently studied, further studies will be still needed. Therefore, I think this study should be accepted for publication.

A minor issue:

In the Kaplan-Meier analysis there are only 8 patients remaining at the 10 year. Please note this in the limitation section with additional statement that longer follow up time with bigger sample size is necessary to validate our conclusions.

Reply: We thank the reviewer very much for the informative insights. Accordingly, we have included the limitation raised here.

Change in the text (Page 15, line 251):

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.

Reviewer C

The background of the paper is clearly explained, the aim of the study is clear. Inclusion and exclusion criteria are good explained, and you have already explained the limitations. The results are very important because avoiding of the SOV and DAA replacement is associated with much less intraoperative and postoperative complications.

Reply: We thank the reviewer very much for the informative insights. Point-by-point response to the comments by Reviewer C has been provided below.

I have only a few questions and comments:

Comment 1. Why do we have only 78 % of follow up? Could you justify something more about it ?

Reply: During the follow-up, one patient occurred hospital death, another died two months after the surgery, and the remaining 18 patients were lost to follow-up. Thus, mid-term CT was obtained in 69 patients (follow-up rate 78%) after more than a year after surgery. This relatively low follow-up rate has been clarified and detailed in the Methods section.

Change in text (Page 7, line 59-64):

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).

Comment 2. It would be interesting to have a comparison and to see if there is some difference in diameter of the SOV and DAAo in patients with and without arterial hypertension.

Reply: We conducted a primary analysis stratified by patients with hypertension (n=55) and without hypertension (n=34). Due to the small sample size, the analysis lacked statistical significance. Instead, the revised text includes the effect of hypertension on the primary outcomes (see Table 7, S3 and S4). We did not observe any effect of hypertension on the development of SOV and DAAo diameters over the course of the follow-up period.

Comment 3. Could you write something more about the patients with preoperative diameter of the SOV and DAAo with more than 40 mm (how many patients, follow up, complications, diameter of the SOV and DAAo)

Reply: As suggested, we stratified the baseline SOV and DAAo with < 40 mm or ≥ 40 mm, respectively. Consequently, 20 patients (22%) 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 operative 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 (Supplementary Table 1). Fourteen patients (16%) had DAAo > 40 mm at baseline. Preoperative, intraoperative, and postoperative results were similar, except for 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 \leq 40 mm had a greater expansion rate (Supplementary Table 2). This result was consistent with the outcome of the trajectory analysis (Figure 3b). Nevertheless, the potential underlying mechanisms remain unknown. These significant results have been included to the Results section (see Page 11, line 159-168).

Reviewer D

General comments:

- > Overall, the manuscript is well composed and written.
- > This manuscript describes characteristics and outcomes of a moderately sized cohort of BAV patients undergoing AVR and GR.
- > The study investigates potential associations with post-operative dilatation in this cohort.
- > Some results are unsurprising, such as association of aortic diameter before operation with aortic diameter after operation.
- > Conclusions are supported by results.

Reply: We thank the reviewer very much for the informative insights. We have provided point-by-point response to the comments of Reviewer D.

Specific comments:

- > It might be of interest to know dilation rate prior to operation if available and any associations of that with rate after operation.

We were unable to display the dilatation rate prior to surgery due to a lack of information regarding the preoperative time-course diameters of SOV and DAAo. Therefore, we have proposed an intriguing insight into the limitation as a prospective issue.

Change in text (Page 15, line 261-265):

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: a) time at follow-up measurements was random for both investigators and patients, and b) validation study for model probability in trajectory analyses revealed that it was universally high (Supplementary Table S2).

- > There is unfamiliar notation on line 160 "... risk factors at baseline*time follow-up ..."; does this mean "(risk factors at baseline) \times (time at follow-up)"?

We apologize for the confusion, but your understanding is correct.

We have modified the relevant sentence to "(risk factors at baseline) \times (time

follow-up)" as indicated.

Change in text (Page 9, Line 100-101):

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.

> Conclusion statement "... the GR of the ascending aorta ... seem reasonable based on mid-term outcomes ..." is qualitative and hedging; suggest providing firmer perspective.

We have modified our conclusion and Abstract as below.

Change in text (Page 15-16, line 273-279):

In selected patients with a bicuspid aortic valve 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 lesser 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 aortic valve replacement and graft replacement of the ascending aorta may be sufficient surgical options.

Questions:

> Did all patients have a single follow-up measurement available, or can analysis be strengthened by including multiple follow-ups (e.g., to improve estimate of growth rates for each patient)?

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, a) time at follow-up measurements was random for both investigators and patients, and b) validation study for model probability in trajectory analyses revealed that it was universally high (see Supplementary Table S2). We concluded, therefore, that this limitation would not have a substantial impact on the overall principal results and conclusion. This important discussion has been included in the limitation of the Discussion section (see Page 15, line 261-268).

> There appear to be a moderate number of patients that experienced higher levels of growth in the dAAo (see figure 2b); can this group be treated as a separate cohort and differences between them and lower dilation-rate patients be identified?

As noted, the dilatation rate of some patients was higher than usual. Using cut-off values with an average dilatation of 0.08 mm/year for SOV and 0.11 mm/year for DAAo, higher expansion cohorts were detected in 26 (38%) and 29 (42%) patients,

respectively. 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. In contrast, patients with a larger DAAo expansion had a higher CMN grade, prevalence of MACCEs, and reoperation rates, and a smaller DAAo diameter at baseline. As indicated by the generalized linear estimate for dilatation of the SOV and DAAo, baseline diameters were substantially linked with diameters at late follow-up, but the time-scaled multilevel analysis could not discover any time-dependent dilatation (Table 7). In both SOV and DAAo, the CMN grade did not influence the diameter at late follow-up or the time-dependent dilatation. These significant results were included in the Results section together with new Tables 5 (SOV) and 6 (DAAo), and the pertinent discussion was indicated (Page 11, line 157-163).

> What is the meaning of the coefficient for BAV in table 5? Do all patients in the cohort not have BAV?

We apologize for the confusion. The intended meaning was “the BAV phenotype” and not “the presence of BAV”. We have corrected the relevant description in Table 5.

Reviewer E

Thank you for submitting this manuscript to the JTD. This manuscript investigates a very relevant subject concerning dilatation of the residual aorta after aortic valve and ascending aortic replacement in patients with bicuspid aortic valves. This is a very relevant matter, and the study is performed well. Although retrospectively in nature, this study investigates both size of the residual aorta and outcome in this patient cohort.

The aim is clear; however, the hypotheses of the study are lacking. What did the authors expect to find based on previous relevant studies? The results are clearly written and the discussion is well-written. The illustrations, figures and tables are of good quality; however the number of tables is excessive, and should be restricted. In my opinion this is a very relevant study, that has been performed well. There are surely some limitations as this is a retrospective study with few patients over a period of 10-years. Despite of this, I believe that the scientific value and impact of the manuscript is high, and I recommend acceptance with major revision.

Reply: We thank the reviewer very much for the informative insights. We have provided point-by-point response to the comments of Reviewer E.

General comments:

Comment 1. The authors have CT-scanned all patients 1-year postoperatively, to

assess if the residual aorta have dilated after the procedure. I would like the authors to elaborate on why they have chosen such a short follow-up for the CT-scans. One would expect that any redilatation of the residual aorta would happen after one year postoperatively.

Reply: As noted in the Methods section, we obtained aortic diameters prior to surgery, one week following surgery, and at appropriate postoperative visits. Consequently, the patients underwent CT scans with a mean of 4.9 ± 2.8 years (1.0-10.6 years) after surgery. Therefore, it does not suggest that 78% of patients underwent CT one year after surgery; rather, 78% of the patients underwent CT more than one year after surgery. We have updated the appropriate sentence (Page 7, Line 62-64) to clarify this point.

Comment 2. The authors state, that the ascending aorta was 47.3 ± 4.7 mm preoperatively, which means that some of the patients were operated with ascending aortic replacement despite the diameter being less than 45 mm, which is the recommended threshold for ascending aortic replacement with concomitant aortic valve replacement. Can the authors elaborate on this matter?

Reply: 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. This description was added to the method section (see Page 6, line 28-31).

Comment 3. In the abstract, the authors conclude: “Low surgical risks and good mid-term outcomes would justify the concomitant replacement of only the ascending aorta at the time of aortic valve replacement for a bicuspid aortic valve”. The conclusion is not in line with the study performed, and furthermore, the indication for replacing the ascending aorta is dilatation of the ascending aorta, and not because there is good mid-term outcome. The conclusion is a bit misleading, and should be changed.

Reply: We have modified the relevant sentence accordingly.

Change in text (see abstract section and Page 16, line 273):

For selected patients with a surgical indication for ascending aortic dilatation, simple aortic valve replacement and graft replacement of the ascending aorta may be sufficient surgical options.

Comment 4. There is no hypothesis for the study, which should be mentioned in the introduction section.

Reply: We have included our hypothesis accordingly in the Introduction section.

Change in text (Page 5, line 17-19):

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.

Comment 5. The number of tables are high. The authors could consider moving some of the tables into the appendix.

The instruction for authors state that "figures and tables has no limit, but 10 figures are deemed sufficient". Therefore, we constructed the manuscript with no more than 10 figures and tables, and the others were included as supplementary tables.

Comment 6. In the conclusion, the authors state, that in selected bicuspid aortic valve STENOSIS patients, with ascending aorta > 45 mm, graft replacement seems reasonable. However, this should also include aortic valve insufficiency patients, as the guidelines do not distinguish between the etiology if an aortic valve replacement is needed.

Reply: We have removed the word “stenosis” in the conclusion to avoid any confusion and misleading statements as advised (see Page 15, line 269).

Specific comments:

Line 74: Change to “1-2%”.

Reply: We have modified our text as advised (see Page 5, line 3).

Change in the text: 1-2%

Line 138: The mean follow-up period is stated to be 6.1 +/- 2.7 years. Please provide the range as well.

Reply: We have provided the range as well as mean value as advised (see Page 7, line 63 and Page 8, line 76-77).

Changes in the text: The mean follow-up period was 6.1 ± 2.7 years (0.6-11.2 years).

Line 256: Change to “ascending aorta phenotype”.

Reply: We have modified our text as advised (see Page 13, line 210).

Change in the text: ascending aorta phenotype