Persistence of Reduced Left Ventricular Function after Aortic Valve Surgery for Aortic Valve Regurgitation: Bicuspid versus Tricuspid

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Abstract

Objective Long-term prognosis of patients with aortic regurgitation (AR) and reduced left ventricular ejection fraction (LVEF) who undergo aortic valve surgery (AVS) is unknown. Due to the congenital origin, bicuspid aortic valve (BAV) morphotype might be associated with a more severe cardiomyopathy. We aimed to evaluate the LVEF recovery after aortic valve replacement (AVR) surgery in patients with AR and reduced preoperative LVEF.

Methods This retrospective analysis included 1,170 consecutive patients with moderate to severe AR who underwent AVS at our institution between January 2005 and April 2016. Preoperative echocardiography revealed 154 (13%) patients with predominant AR and baseline LVEF $< 50\%$. A total of 60 (39%) patients had a BAV (BAV group), while the remaining 94 (61%) patients had a tricuspid morphotype (tricuspid aortic valve [TAV] group). Follow-up protocol included clinical interview using a structured questionnaire and echocardiographic follow-up.

Results A total of 154 patients (mean age 63.5 $\pm$ 12.4 years, 71% male) underwent AVS for AR in the context of reduced LVEF (mean LVEF 42 $\pm$ 8%). Fifteen (10%) patients had a severely reduced preoperative LVEF $\leq 30\%$. Mean STS (Society of Thoracic Surgeons) score was 1.36 $\pm$ 1.09%. Mean follow-up was comparable between both the study groups (BAV: 50 $\pm$ 40 months vs. TAV: 40 $\pm$ 38 months, $p = 0.140$). A total of 25 (17%) patients died during follow-up. Follow-up echocardiography demonstrated similar rate of postoperatively reduced LVEF in both groups (i.e., 39% BAV patients vs. 43% TAV patients; $p = 0.638$). Cox's regression analysis showed no significant impact of BAV morphotype (i.e., as compared with TAV) on the postoperative LVEF recovery (odds ratio [OR]: 1.065; $p = 0.859$). Severe left ventricular (LV) dysfunction at baseline (i.e., LVEF $\leq 30\%$) was a strong predictor for persistence of reduced LVEF during follow-up (OR: 3.174; 95% confidence interval: 1.517–6.640; $p = 0.002$). Survival was significantly reduced in patients with persisting LV dysfunction versus those in whom LVEF recovered (log rank: $p < 0.001$).

Keywords
- cardiac
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- heart failure
- heart valve
- surgery

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Conclusion Our study demonstrates that reduced LVEF persists postoperatively in 40 to 45% patients who present with relevant AR and reduced LVEF at baseline. Postoperative LVEF recovery is independent of aortic valve morphotype (i.e., BAV vs. TAV). Severe LV dysfunction (LVEF $\leq$ 30%) at baseline is a strong predictor for persistence of reduced LVEF in patients with AR and results in significantly reduced long-term survival.

Introduction

Aortic regurgitation (AR) can occur due to pathology of aortic valve cusps as well as enlargement of the aortic root and/or the ascending aorta. Degenerative tricuspid (tricuspid aortic valve [TAV]) and congenitally bicuspid (bicuspid aortic valve [BAV]) ARs are the most common reasons for AR in the Western population.[1] According to the recent guidelines of the European Society of Cardiology (ESC) and European Association of Cardiothoracic Surgery, aortic valve surgery (AVS) is indicated in symptomatic patients or asymptomatic patients with a severe AR left ventricular ejection fraction (LVEF) $<$ 50% and/or enlargement of left ventricular end-diastolic and -systolic diameters (LVEDD and LVESD) of $>$ 70 and $>$ 50 mm.[2] In few patients, LVESD needs to be related to body surface area ($>$ 25 mm/m^2).[2] The American Heart Association and American College of Cardiology guidelines are similar, yet choosing a cutoff value of 65 mm for LVEDD.[3]

However, at the time of presentation of symptoms in AR patients, left ventricle (LV) is often severely dilated and heart failure progresses despite successful AVS.[4–6] Progressive enlargement of left ventricular (LV) diameter is associated with a poor outcome after AVS in AR patients.[7,8] In the setting of BAV morphology, Disha et al[4] showed that AR patients with a preoperatively reduced LVEF have a significantly worse long-term outcome after aortic valve replacement (AVR) as compared with aortic valve stenosis. However, at this point, there is no data available regarding the long-term differences in outcome after AVS in patients with bicuspid versus tricuspid AR in the presence of reduced systolic LVEF. Therefore, we aimed to analyze LVEF recovery after AVR in patients with AR and reduced LVEF at baseline and to compare the LVEF recovery between BAV and TAV morphotypes.

Materials and Methods

Study Protocol

We retrospectively reviewed our institutional database of 1,170 consecutive patients with severe chronic AR who underwent elective AVS at our institution between January 2005 and April 2016. Inclusion criteria were the presence of severe chronic isolated AR (i.e., mean transvalvular gradient $\leq$ 20 mm Hg) and a reduced baseline LVEF $\leq$ 50%. The LVEF was calculated using the Simpson's formula (i.e., volumetric method) by measuring the end-diastolic and end-systolic volumes in the apical four- and two-chamber views.[9] The valve morphology was assessed intraoperatively by the surgeon. Exclusion criteria were the presence of aortic valve stenosis (i.e., mean transvalvular gradient $\geq$ 20 mm Hg), LVEF $>$ 50%, acute AR due to type A aortic dissection or infective endocarditis, and concomitant relevant coronary artery disease treated via simultaneous percutaneous coronary intervention or coronary artery bypass grafting.

Primary end point was the recovery of LVEF $\geq$ 50% as identified by the most recent follow-up echocardiography. Secondary end points were overall survival and freedom from adverse cardiac events defined as cardiac-related death (i.e., valve-related complications, congestive heart failure, and sudden cardiac death) or subsequent reinterventions due to progressive congestive heart failure (cardiac resynchronization therapy [CRT], implantable cardioverter–defibrillator therapy, LV assist device implantation, or heart transplantation).

Study Population

Preoperative echocardiography revealed 154 (13%) patients with isolated severe AR and baseline LVEF $\leq$ 50% who served as our study cohort. A total of 60 (39%) patients had a BAV (BAV group), while the remaining 94 (61%) patients had a tricuspid morphotype (TAV group).

AVS was performed via a partial upper ministernotomy (or conventional sternotomy) using a standard cardiopulmonary bypass with mild systemic hypothermia in all patients. Surgical and anesthetic protocols were standardized and underwent only minor changes over time. Patients who received an aortic valve-sparing procedure or biological AVR received lifelong treatment with acetylsalicylic acid. Patients with a mechanical valve replacement were treated with lifelong Marcumar with an international normalized ratio of 2 to 3. The treatment of heart failure was performed according to the ESC guidelines for the treatment of chronic heart failure.[10]

Follow-up

All hospital survivors were followed up using a standardized follow-up protocol. Follow-up protocol consisted of a structured questionnaire via telephone interview with the patients, their family members, and/or patients' family physician. In addition, we obtained the most recent echocardiography reports from the patients' cardiologist or family physician. Adverse cardiac advents were identified from the follow-up questionnaires and hospital charts (cardiac death, aortic valve redo surgery, implantation of CRT device and/or defibrillator and/or assist device, and heart transplantation). For all patients who died during the follow-up, the cause of death was obtained from the patients' hospital charts (i.e., requested from an external hospital or family physician).

Echocardiographic Follow-up Population

Echocardiographic follow-up was available for 128 (83%) patients (52 BAV patients; 76 TAV patients). A total of 15 patients were lost during the echocardiographic follow-up as they changed their address and could not be identified by civil registry office. Further, 11 patients died during follow-up and no echocardiographic data were obtained. Mean echocardiographic follow-up was comparable in both the study groups (i.e., 48 ± 41 months in the BAV group vs. 42 ± 37 months in the TAV group, $p = 0.321$).

Statistical Analysis

Standard definitions were used for patient variables and outcomes. Categorical variables are expressed as frequencies and percentages and analyzed using chi-square test or Fisher's exact test, as appropriate. Continuous variables are presented as mean ± standard deviation and were compared using Student's *t*-test or the Mann–Whitney's test, as appropriate. Survival analysis and freedom from adverse cardiac events during follow-up was analyzed using Kaplan–Meier's method and univariate comparisons between the groups were performed using log-rank test. All reported *p*-values are two sided and *p*-values of 0.05 or less were considered statistically significant. Multivariate Cox's regression analysis was used to examine the predictors of LVEF nonrecovery during follow-up. All statistical analyses were accomplished with the IBM SPSS 23 software (IBM Corp., New York, United States).

Results

Baseline Data

Pre- and perioperative data of the baseline population are outlined in ►**Table 1**. The BAV group was significantly younger as compared with the TAV patients (54.9 ± 11.4 vs. 68.9 ± 9.5 years; $p < 0.001$) and had a significant lower perioperative risk score (EuroSCORE II: 2.67 ± 1.89 vs. 4.5 ± 4.7; $p = 0.005$). Biological valve replacement was performed in 92 patients (TAV) compared with 45 patients in the BAV group ($p < 0.001$). In both groups, the Hancock II/Hancock II Ultra (41%) and Carpentier-Edwards Perimount (26%) valves were used most frequently with a mean diameter of 25.5 ± 2.1 mm.

Furthermore, mechanical valve prostheses were used more frequently in the BAV group as compared with the TAV group (10 vs. 2; $p = 0.001$). In all 12 patients, the CarboMedics bileaflet mechanical heart valve (Sorin Group, Milano, Italy) was used. An additional five BAV patients received valve-sparing root surgery. The remaining pre- and intraoperative variables were comparable in both the groups (►**Table 1**). LVEF at baseline was 42.9 ± 8.2% in the BAV group as compared with 41.9 ± 8.7% in the TAV group ($p = 0.478$). A severely reduced preoperative LVEF ≤ 30% was present in 13% BAV patients compared with 18% TAV patients ($p = 0.419$). In-hospital outcome was similar in both the study groups. There was a trend toward a more frequent use of intra-aortic balloon pump (BAV: 7%; TAV: 1%; $p = 0.076$) and postoperative implantable cardioverter–defibrillator (ICD) implantation in the BAV group (BAV: 5%; TAV: 0%; $p = 0.055$). The intensive care unit and in-hospital stay were similar in both groups (►**Table 2**).

Table 1 Pre- and intraoperative data

Variables	Baseline study population		*p*-Value
	BAV ($n = 60$)	TAV ($n = 94$)	
Mean age (y)	54.9 ± 11.4	68.9 ± 9.5	**< 0.001**
Male sex	51 (85%)	59 (63%)	**0.003**
BMI (kg/m^2)	27.5 ± 5.6	26.2 ± 4.6	0.185
BSA (m^2)	1.91 ± 0.61	1.741 ± 0.60	0.141
Baseline LVEF (%)	42.9 ± 8.2	41.9 ± 8.7	0.478
Baseline LVEF ≤ 30 (%)	8 (13%)	17 (18%)	0.419
NYHA class ≥ 2	45 (75%)	65 (69%)	0.967
Hyperlipidemia	5 (8%)	15 (16%)	0.166
Smoking	14 (23%)	17 (18%)	0.690
Arterial hypertension	36 (60%)	57 (60%)	0.908
EuroSCORE II	2.67 ± 1.88	4.5 ± 4.7	**0.005**
STS score	0.86 ± 0.55	1.66 ± 1.23	**< 0.001**
CPB time (min)	150.9 ± 58.8	153.6 ± 76.7	0.861
Aortic cross-clamp time (min)	97.4 ± 42.3	96.3 ± 49.7	0.913
Mechanical valve prosthesis	10 (20%)	2 (3%)	**0.001**
Mean prosthesis size (mm)	26 ± 2.1 (21–32)	25 ± 2.0 (21–29)	0.266
Isolated aortic valve procedure	13 (22%)	15 (16%)	0.397
Concomitant procedures			
Mitral valve repair/ replacement	30 (50%)	50 (53%)	0.397
Replacement of ascending aorta	26 (43%)	34 (36%)	0.402
Ablation	5 (8%)	15 (16%)	0.222
LAA occlusion	1 (2%)	6 (6%)	0.248
Tricuspid valve repair	0	3 (3%)	0.282
Closure of ASD/PFO	2 (3%)	1 (1%)	0.561

Abbreviations: ASD, atrial septal defect; BAV, bicuspid aortic valve; BMI, body mass index; BSA, body surface area; CPB, cardiopulmonary bypass; LAA, left atrial appendage; LVEF, Left ventricular ejection fraction; NYHA, New York Heart Association; PFO, persistent foramen ovale; TAV, tricuspid aortic valve.
Note: Data presented as numbers (%) or as mean ± standard deviation (range). Values in bold are significant values.

Survival

A total of 25 of 154 (17%) patients died during follow-up. A 30-day mortality was similar in both groups (BAV group: three patients vs. TAV group: one patient; $p = 0.229$). Overall, 7 (12%) patients died in the BAV group (cardiac reasons: 2; noncardiac reason: 3; unknown: 2) and 18 (20%) patients died in the TAV group (cardiac reasons: 2; noncardiac reason: 7; unknown: 8). Survival rate at 10 years was 87.5% in the BAV group compared with 58.1% in the TAV group; *p* (log

Table 2 In-hospital outcome

Variables	Baseline study population		*p*-Value
	BAV ($n = 60$)	TAV ($n = 94$)	
Intraaortic balloon pump	4 (7%)	1 (1%)	0.076
Redo surgery for bleeding	1 (2%)	3 (3%)	1.000
Implantation of ICD	3 (5%)	0	0.055
ICU stay (d)	2.8 ± 1.6 (1–8)	3.4 ± 2.2 (1–13)	0.072
In-hospital stay (d)	9.4 ± 3.9 (5–29)	9.99 ± 4.5 (5–39)	0.438
In-hospital mortality	3 (5%)	1 (1%)	0.299

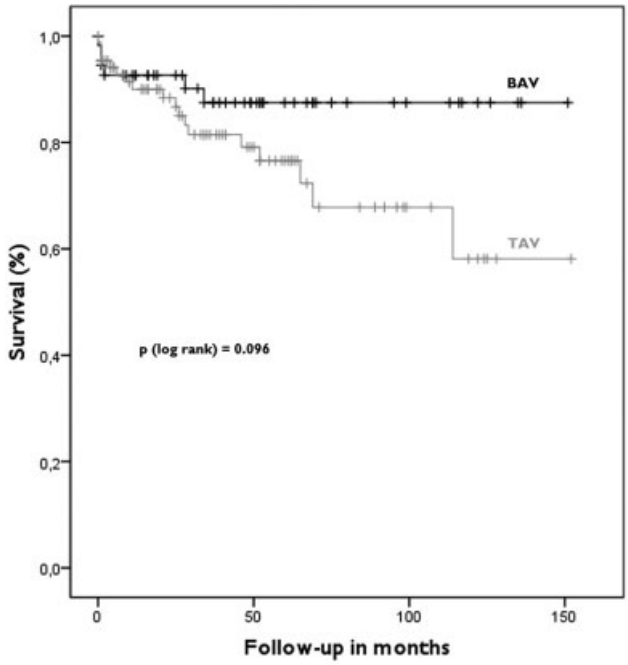
Abbreviations: BAV, bicuspid aortic valve; ICD, implantable cardioverter defibrillator; ICU, intensive care unit; TAV, tricuspid aortic valve.
Note: Data presented as numbers (%) or as mean ± standard deviation (range).

Table 3 Echocardiographic data at follow-up

Variables	Echocardiographic follow-up population		*p*-Value
	BAV ($n = 52$)	TAV ($n = 76$)	
Mean follow-up time (mo)	50 ± 40	40 ± 38	0.140
Maximal aortic valve gradient (mm Hg)	25.5 ± 7.5	25.6 ± 12.6	0.984
Mean aortic valve gradient (mm Hg)	14.4 ± 4.5	15.1 ± 8.3	0.703
Mean LVEF at follow-up (%)	49.9 ± 14.0	49.1 ± 11.8	0.720
Improvement of LVEF ≥ 10%	25 (49%)	33 (44%)	0.579
Persistence of reduced LVEF	20 (39%)	33 (43%)	0.638

Abbreviations: BAV, bicuspid aortic valve; LVEF, left ventricular ejection fraction; TAV, tricuspid aortic valve.
Note: Data presented as numbers (%) or as mean ± standard deviation (range).

rank) = 0.096 (►**Fig. 1**). Overall, there was no significant difference between patients undergoing concomitant mitral valve surgery (MVR) (66.2%) compared with those patients without significant mitral valve disease (74.6%) at 10 years of follow-up ($p = 0.299$). In the BAV (concomitant MVR: 85%; no MVR: 89%; $p = 0.687$) as well as in the TAV subgroup, similar results were seen at follow-up (concomitant MVR: 55%; no MVR: 62%; $p = 0.687$).



Months	0	12	60	120
BAV	57	45	17	4
TAV	88	67	24	4

Fig. 1 Overall survival (Kaplan–Meier)—bicuspid aortic valve (BAV) versus tricuspid aortic valve (TAV).

LVEF Recovery during Follow-up

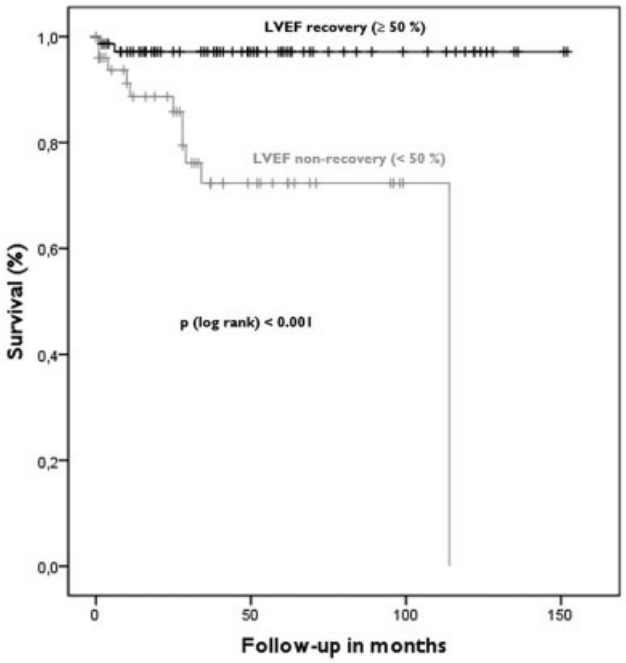
Follow-up echocardiographic parameters are outlined in ►**Table 3**. Mean LVEF at the time of last follow-up did not differ significantly between the groups (i.e., BAV: 49.9 ± 14.0%; TAV: 49.1 ± 11.8%; $p = 0.720$). Nearly one half of the BAV as well as the TAV patients showed an LVEF improvement ≥ 10%. LVEF recovery to the normal values (i.e., LVEF ≥ 60%) was seen in 33% BAV patients versus 22% TAV patients ($p = 0.171$). Progressive LVEF decline and/or persistence of the reduced LVEF ≤ 50% during the follow-up was seen in 39% BAV patients versus 43% TAV patients ($p = 0.638$). Further, postoperative LVEF decline and/or persistence of reduced LVEF ≤ 50% was significantly associated with higher long-term mortality after AVS (97.1 vs. 76.1%; p [log rank] < 0.001) (►**Fig. 2**). Depending on the valve morphology, there were significant long-term survival differences between patients with persistence of reduced LVEF ≤ 50% compared with LVEF recovery > 50% (►**Fig. 3**). In the nonrecovery cohort, the long-term survival was significantly lower in the TAV subgroup compared with the BAV subgroup (65.3 vs. 84.4%; $p < 0.001$).

Adverse Cardiac Events

A total of six patients had adverse cardiac events during the follow-up in the BAV group as compared with seven patients in the TAV group ($p = 0.772$).

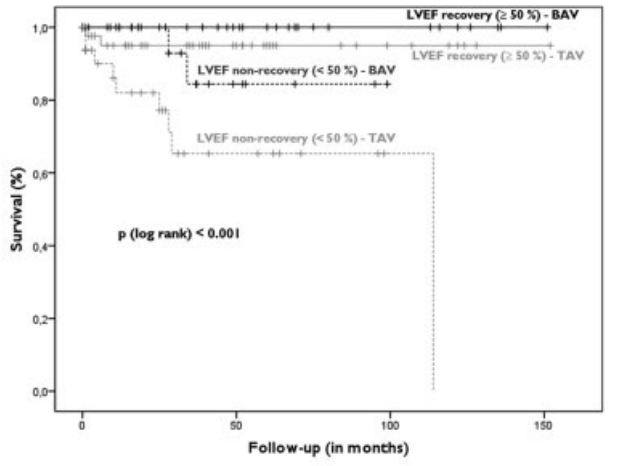
Two BAV patients underwent a redo AVS because of prosthetic valve endocarditis, two patients further required a CRT-ICD implantation and remaining two patients were listed for heart transplantation.

Two TAV patients died of sepsis due to prosthetic valve endocarditis. Redo surgery in the TAV group was necessary in three patients: one patient after David procedure due to recurrence of relevant AR, one redo surgery because of prosthetic valve endocarditis, and one valve-in-valve transcatheter aortic valve replacement due to degeneration of aortic valve bioprosthesis. One TAV patient was listed for



Months	0	12	60	120
LVEF recovery	74	61	26	8
LVEF non-recovery	53	34	9	0

Fig. 2 Overall survival (Kalplan–Meier)—comparison of patients with a LVEF ≥50% at follow-up versus patients with a LVEF < 50% at follow-up. LVEF, left ventricular ejection fraction.



Months	0	12	60	120
LVEF recovery (≥ 50 %) - BAV	31	27	13	4
LVEF non-recovery (< 50 %) - BAV	18	13	3	0
LVEF recovery (> 50 %) - TAV	43	33	12	4
LVEF non-recovery (< 50 %) - TAV	33	19	7	0

Fig. 3 Overall survival (Kaplan–Meier)—comparison of patients with a LVEF > 50% at follow-up versus patients with a LVEF ≤50% at follow-up considering AV morphology. AV, aortic valve; LVEF, left ventricular ejection fraction.

Table 4 Predictors of persistence and/or reduction of LVEF post-AVR (as determined by Cox's regression analysis)

Variables	Hazard ratio	*p*-Value	95% CI
BAV morphology	1.065	0.859	0.532–2.132
Baseline LVEF ≤ 40%	0.959	0.899	0.499–1.843
Baseline LVEF ≤ 30%	3.174	**0.002**	1.517–6.640
gender	0.990	0.977	0.520–1.888
Age > 65 y	1.759	0.087	0.921–3.362

Abbreviations: BAV, bicuspid aortic valve; CI, confidence interval; LVEF, left ventricular ejection fraction.
Note: Data presented as numbers (%) or as mean ± standard deviation (range).

heart transplantation, and further, one patient underwent an ICD implantation during the follow-up.

Predictors for LVEF Nonrecovery

We performed a multivariate Cox's regression analysis to identify potential predictors of persistence and/or reduction of LVEF after AVR surgery (►**Table 4**, ►**Fig. 4**). Valve morphology (i.e., BAV vs. TAV) had no significant impact on the persistence of reduced LVEF during the follow-up. The only predictor for persistent LVEF decline postoperatively was a baseline LVEF ≤ 30% (hazard ratio: 3.174; $p = 0.002$).

Discussion

Severe AR results in a higher long-term mortality as compared with the general population.[11] Chronic LV volume overload causes eccentric LV hypertrophy[11] and is associated with a progressive LV enlargement and thereby increases risk of sudden cardiac death.[12] Ten years after diagnosis of severe AR, heart failure is present in at least half of the patients and AVS is often necessary.[11] Reduced LVEF is a perioperative risk factor in AR patients undergoing AVR surgery.[13,14] However, differences in the long-term outcome based on the aortic valve morphology (i.e., BAV vs. TAV) are not well studied.

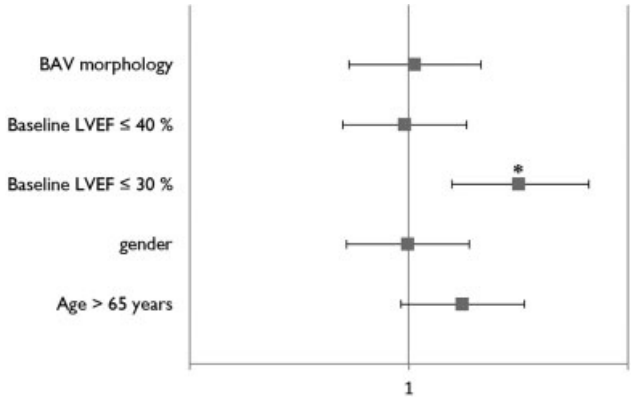


Fig. 4 Predictors of persistently reduced LVEF post-AVR (as determined by Cox's regression analysis; $^*p < 0.05$). AVR, aortic valve replacement; LVEF, left ventricular ejection fraction.

Therefore, in the current study, we focused on the LVEF recovery after AVS in patients with severe AR and impaired LVEF and compared the outcome in bicuspid versus tricuspid morphology.

Outcomes in AR Patients with Impaired Systolic LV Function—BAV versus TAV

BAV is the most common congenital cardiac malformation and has a prevalence of 1 to 2% in the general population.[15] Although aortic stenosis is the most often clinical manifestation of BAV disease, AR is often present in younger BAV patients and remains asymptomatic for many decades.[15] In case of severe BAV-associated AR, Disha et al[4] reported a significantly higher rate of adverse cardiac events as compared with the BAV stenosis patients. The authors hypothesized that in the presence of long-standing BAV regurgitation, a fixed myocardial damage may occur, resulting into a persistent systolic LV dysfunction despite surgical correction of valvular lesion. Demir[16] proposed that in BAV, even without significant valvular disease, an impaired systolic and diastolic ventricular functions exist. In contrast, our study could not reveal any significant difference in the LVEF recovery between bicuspid and tricuspid morphologies. However, if reduced LVEF persists, a trend toward differences in survival are seen between BAV and TAV (►**Fig. 3**) (p [log-rank] $= 0.112$). Therefore, our results indicate that the recovery of impaired systolic LV function after AVS is independent of the aortic valve morphology.

Clinical Outcomes in AR Patients with Impaired LVEF

Wang et al[7] reported a worse long-term outcome in AR patients undergoing AVR surgery with a LVEF of 50 to 55% compared with patients with a LVEF $>$ 55% at 5 and 10 years postoperatively. Similar findings were published by Amano et al[17] in a cohort of 80 patients with severe AR undergoing AVS. A recent study by Zhang et al[18] aimed to determine a cutoff value of preoperative LVEF in AR patients which is associated with the postoperative LVEDD reduction. According to their study, one-third of AR patients did not experience postoperative LV re-remodeling after AVS. In summary, these data indicate that corrective AVS might be generally too late if LVEF is severely impaired in case of severe AR. However, when is it too late to operate on an AR patient with an impaired systolic LV function?

Rothenburger et al[13] outlined that surgery in patients with severe LV dysfunction (LVEF $<$ 30%) is possible with a reasonable risk and results into improvement of symptoms and LVEF (AR and AS patients). Similarly, Chaliki et al[14] pointed out that in AR patients with a LVEF $<$ 35% at baseline, postoperative LVEF improves. However, such a "rescue" surgery is associated with higher perioperative mortality rates as compared with the patients with a preserved LVEF. Our study demonstrates that severe LV dysfunction (LVEF $\leq$ 30%) at baseline is a strong predictor for persistence of reduced LVEF in patients with AR (►**Fig. 4**) and results in a reduced long-term survival (►**Fig. 2**). Therefore, based on our data, we strongly believe that AVR surgery in AR patients should be performed early before LV dysfunction occurs and the downward spiral takes its course.

Study Limitations

There are some important limitations of our study. This is a retrospective analysis with all known limitations associated with such a study design. Another important limitation is the fact that one half of AR patients underwent a concomitant mitral valve procedure. However, mitral valve pathology was predominantly a functional mitral valve regurgitation which can be interpreted as a progressive heart failure due to the chronic volume overload of the LV. Further limitation is the age difference between the BAV and TAV groups which has an obvious impact on the survival analysis. In addition, for a total of 26 patients, echocardiographic follow-up was not possible to obtain which obviously limits the scientific value of our data. Therefore, a prospective study with a structured follow-up is necessary in order to confirm our retrospective findings.

Conclusion

Our study demonstrates that reduced systolic LVEF persists postoperatively in 40 to 45% patients who present with a relevant AR and reduced LVEF at baseline. Postoperative LVEF recovery is independent of aortic valve morphotype (i.e., BAV vs. TAV). Severe LV dysfunction (LVEF $\leq$ 30%) at baseline is a strong predictor of persistently impaired LVEF in patients with AR and results in a significantly reduced long-term survival. Therefore, aortic valve repair surgery should be strongly considered early in the course of relevant AR before systolic LV dysfunction occurs.

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Conflict of Interest
There is no conflict of interest in any of the authors

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