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Original Article

Impact of Aortic Valve Replacement for Aortic Stenosis on Coexisting Mitral Stenosis

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Purpose: The course of coexisting mitral valve stenosis is not clear after aortic valve replacement (AVR) for aortic stenosis (AS). We investigated the effect of AVR for AS on coexisting mitral stenosis (MS).
Methods: Between January 2002 and December 2019, 1338 consecutive patients underwent surgical AVR at Shiga University of Medical Science. Of them, 34 patients with moderate MS (mitral valve area [MVA]: 1.5–2.0 cm^2) were included in the present study. We evaluated the postoperative clinical outcomes in these patients.
Results: Mean MVA in our cohort significantly increased 1 week after operation compared with preoperative values, and the change was maintained for 5 years after surgery. Follow-up was completed in 94.1% (32/34) patients, and mean follow-up duration was 4.0 ± 3.0 years. No patients underwent mitral surgery for remaining MS after AVR during postoperative follow-up.
Conclusion: AVR for AS resulted in increased MVA in patients with MS, and the change was maintained during follow-up.

Keywords: aortic stenosis, mitral stenosis, combined valvular disease

Introduction

Multivalvular disease has been documented in more than one-third of patients with a diagnosis of valvular heart disease.[1)] It has been reported that the prevalence of MS in patients with severe AS is around 10% and the outcome of these patients is very poor once they develop symptoms.[2)] The presence of combined AS and MS makes it difficult to evaluate the severity of each individual lesion because of hemodynamic interactions between the two lesions.

According to the 2014 American Heart Association/American College of Cardiology guidelines, concomitant mitral valve surgery is reasonable in patients with severe mitral stenosis (MS) (mitral valve area [MVA] ≤1.5 cm^2) who undergo other cardiac surgery.[3)] Generally, mitral valve replacement (MVR) is not performed for coexisting moderate MS (1.5 cm^2 <MVA) in patients undergoing aortic valve replacement (AVR) for aortic stenosis (AS).

AS induces progressive myocardial fibrosis, reduced ventricular compliance, and diastolic dysfunction.[4–9)] AVR for AS leads to reverse myocardial remodeling,[10)] but the effect of AS treatment on coexisting MS is unclear. We evaluated postoperative clinical outcomes in patients undergoing AVR for AS with moderate MS.

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Materials and Methods

The study was approved by the review board of Shiga University of Medical Science (approval No. R2020-077) and all patients had previously provided informed consent for use of their medical records for research purposes. Between January 2002 and December 2019, 1338 consecutive patients underwent surgical AVR at Shiga University of Medical Science. Of them, 34 patients with moderate MS (MVA: 1.5–2.0 cm^2) were included in the present study.

Surgical treatment

Patients were placed in the supine position, and anesthesia was maintained in the standard manner. Valve choice was based on each surgeon's preference. Bioprosthetic valves were implanted in the supra-annular position and mechanical valves were implanted in the intra-annular position. Myocardial protection was obtained for all patients with antegrade or retrograde infusion using cold blood cardioplegia solution.

Echocardiographic measurements

Patients underwent annual echocardiographic follow-up at our institution. MVA was estimated in the apical four-chamber view using spectral continuous color Doppler traces of diastolic transmitral flow. The pressure half time (PHT), the time interval between the maximum early diastolic pressure gradient, and the point where the gradient is half the maximum value were obtained. MVA was calculated as 220 divided by PHT. Aortic valve area (AVA) was calculated by reconfiguration of the continuity equation. The dimensions of the left ventricle were assessed using two-dimensionally guided M-mode tracing.

Mitral annulus calcification (MAC) was defined as the presence of dense calcium deposits at the base of the mitral leaflets between the left atrium and ventricle.[11,12] The extension of calcification to both anterior and posterior mitral leaflets was evaluated from parasternal long axis view.[13] Rheumatic MS was defined when typical features such as leaflet thickening, nodularity, commissural fusion, and chordal fusion and shortening were present.

Statistical analysis and data collection

Continuous variables are presented as mean ± standard deviation or median and interquartile range. Categorical variables are presented as percentages. Comparisons of patients' clinical outcomes between the two groups were performed using unpaired t-tests for normally-distributed variables or the Mann–Whitney U test for skewed variables. Univariable and multivariable logistic regression analyses were performed to identify the independent predictors of postoperative MS. Variables reaching $p < 0.050$ in the univariable analysis or that were considered clinically important were entered into the multivariable model. The Kaplan–Meier method was used to describe survival rates. All statistical testing was two-sided. Results were considered statistically significant at $p < 0.050$, and all statistical analyses were performed using the Statistical Package for Social Sciences, version 25.0 (IBM Corp., Armonk, NY, USA) and SAS, version 9.4 (SAS Institute Inc., Cary, NC, USA).

Table 1 Preoperative patient characteristics

Number of patients	34
Age (year)	77.9 ± 8.3
Sex (male)	7 (20.6%)
Body mass index (kg/m^2)	21.9 ± 4.0
Hypertension	22 (64.7%)
Diabetes mellitus	8 (23.5%)
Dyslipidemia	9 (26.5%)
Smoking history	7 (20.6%)
Previous cerebral vascular disease	5 (14.7%)
Previous percutaneous coronary intervention	5 (14.7%)
Peripheral artery disease	4 (11.8%)
Serum creatinine (mg/dL)	1.23 (0.89 - 2.92)
Dialysis	9 (26.5%)
HbA1c (%)	5.6 ± 0.9
Bicuspid aortic valve	1 (2.9%)
Rheumatic	3 (8.8%)
Mitral annulus calcification	30 (88.2%)
Extension of calcification to leaflets	3 (8.8%)
Mitral regurgitation	
Mild	13 (38.2%)
Trivial	20 (58.8%)
None	1 (2.9%)

Results

Preoperative characteristics are listed in **Table 1**. The mean age of our study population was 77.9 ± 8.3 years, and seven patients were male (20.6%). In all, 30 patients (88.2%) had MAC and three patients (8.8%) had extension of calcification to both anterior and posterior mitral leaflets. In all, 13 patients had mild regurgitation preoperatively and the other 21 patients had less than mild. Operative and postoperative data are shown in **Table 2**. Seven patients (20.6%) underwent concomitant coronary artery bypass grafting and two patients (5.9%) underwent concomitant thoracic aortic surgery. No patients underwent

Table 2 Operative and postoperative data

Operative data	
Operation time (m)	215 ± 45
Cardiopulmonary bypass time (m)	102 ± 30
Surgical details	
Concomitant coronary artery bypass grafting	7 (20.6%)
Concomitant tricuspid valve surgery	0 (0%)
Concomitant thoracic aortic surgery	2 (5.9%)
Postoperative data	
Myocardial infarction	0 (0%)
Stroke	3 (8.8%)
Intensive care unit stay > 48 hour	3 (8.8%)
Ventilation > 48 hour	2 (5.9%)
30-day mortality	1 (2.9%)

concomitant tricuspid valve surgery or mechanical AVR in our cohort. Additionally, no patients underwent de-calcification procedure of mitral valve anterior leaflet. One patient died of sepsis 15 days after surgery.

Table 3 shows the hemodynamic changes before and after AVR. The preoperative mean value of MVA was 1.80 ± 0.15 cm^2 (1.51–2.00 cm^2) and the preoperative mean AVA was 0.79 ± 0.19 cm^2. MVA ($p < 0.001$), left ventricular end diastolic diameter ($p = 0.033$), AVA ($p < 0.001$), indexed AVA ($p < 0.001$), aortic valve peak velocity ($p < 0.001$), aortic valve peak pressure gradient ($p < 0.001$), and aortic valve mean pressure gradient ($p < 0.001$) were significantly changed 1 week postoperatively compared with values before AVR, and the changes were maintained for 5 years after the operation. **Figure 1** shows the changes in MVA over time. In all patients, MVA increased 1 week postoperatively compared with preoperatively ($p < 0.001$). Left ventricular end systolic diameter significantly decreased 3 months postoperatively ($p = 0.001$), and the changes were maintained for 4 years after surgery. Left ventricular mass significantly regressed 3 months postoperatively ($p = 0.001$), and the changes were maintained for 5 years after the operation.

Follow-up was completed in 94.1% (32/34) of the patients, and the mean follow-up duration was 4.0 ± 3.0 years (maximum: 11.6 years). One patient died of stroke, one patient died of caducity, and one patient died of unknown causes. The 5-year estimated rate of survival free from overall death was 91.4% (**Fig. 2**). In one patient in our cohort, MVA decreased to less than 1.5 cm^2 during the postoperative follow-up. Multivariable logistic regression analysis revealed that there was no independent predictor of postoperative MS (MVA <1.5 cm^2). No patient underwent mitral surgery for remaining MS after AVR during postoperative follow-up.

Discussion

As the prevalence of rheumatic fever decreases globally, the incidence of rheumatic MS is decreasing. In contrast, there is an increase in the incidence of MAC with degenerative MS because of an increasing aging patient population with multiple comorbidities such as chronic kidney disease and diabetes mellitus.[14] In the presence of MAC, it is difficult to evaluate diastolic function using Doppler tissue imaging such as E-wave, E/e' ratio, and deceleration time. Although left atrial diameter is also considered as an indicator of diastolic function, it is not feasible for evaluation of diastolic function when MS remains after AVR for AS. Therefore, the improvement of diastolic function after AVR for AS in patients with MS is difficult to measure.

One of the major findings of the current study is that an increase in MVA after AVR was observed 1 week after surgery. To the best of our knowledge, this is the first study assessing the speed of change of MVA after AVR for AS. Previous studies have regarded MS as a potential risk factor for increased cardiac morbidity and mortality,[15,16] so the rapid increase in MVA in patients undergoing AVR is meaningful. Diastolic PHT is dependent not only on the degree of mitral obstruction but also the compliance of the left ventricle and left atrium.[1] Ikonomidis et al. have reported improvement of diastolic function 2 weeks after surgery in patients undergoing AVR for AS.[17] Sari et al. have reported the recovery of left atrial and left ventricular diastolic function 24 hours after transcatheter aortic valve implantation.[18] In our study, acute improvement of left atrial and left ventricular diastolic function after AVR may have resulted in the improvement of MVA 1 week after surgery. Additionally, MVA increased 1 week postoperatively compared with preoperative values in all patients. Brown et al. have reported that patient–prosthesis mismatch after AVR is associated with persisting diastolic dysfunction.[19] No patients had 1-week postoperative indexed AVA ≤0.85 cm^2/m^2 in our cohort, which may have resulted in the increased MVA observed in all patients.

Another finding of our study is that the increase in MVA after AVR was maintained for 5 years after surgery. Improvement in diastolic function after AVR has mainly been attributed to the subsequent regression of left ventricular hypertrophy.[20] In the present study, left ventricular mass slowly regressed over 5 years postoperatively (**Table 3**). Therefore, the improved diastolic function after AVR was maintained by the persistent

Table 3 Hemodynamics before and after aortic valve replacement

	preop	1-week postop	P value	3-month postop	P value	1-year postop	P value	2-year postop	P value	3-year postop	P value	4-year postop	P value	5-year postop	P value
Number of followers	34	32		28		22		16		15		14		12	
Mitral valve area (cm^2)	1.80 ± 0.15	2.41 ± 0.40	<0.001	2.42 ± 0.46	<0.001	2.32 ± 0.41	<0.001	2.26 ± 0.58	0.007	2.27 ± 0.57	0.006	2.19 ± 0.62	0.033	2.32 ± 0.48	0.006
Left ventricular ejection fraction (%)	61.1 ± 8.5	59.5 ± 7.9	0.443	62.5 ± 5.6	0.448	63.0 ± 4.6	0.265	64.0 ± 3.4	0.079	61.5 ± 2.1	0.423	62.3 ± 4.4	0.406	62.2. ± 3.7	0.710
Left ventricular end diastolic diameter (mm)	48.6 ± 7.3	45.0 ± 6.2	0.033	42.4 ± 4.7	<0.001	42.3 ± 3.1	<0.001	42.2 ± 3.8	<0.001	44.4 ± 5.2	0.014	41.9 ± 3.8	0.004	42.5 ± 3.8	0.027
Left ventricular end systolic diameter (mm)	32.5 ± 7.0	31.2 ± 5.2	0.412	27.8 ± 3.2	0.002	27.9 ± 2.8	0.001	27.7 ± 3.2	0.001	29.3 ± 3.7	0.043	26.7 ± 2.9	<0.001	28.3 ± 2.9	0.109
Left ventricular mass (g)	253 ± 87	225 ± 72	0.155	187 ± 52	0.001	175 ± 47	0.001	162 ± 41	<0.001	169 ± 37	<0.001	163 ± 34	0.001	161 ± 47	0.001
Left atrial diameter (mm)	45.3 ± 7.6	42.9 ± 6.9	0.184	42.7 ± 6.9	0.162	41.3 ± 6.0	0.038	42.8 ± 4.7	0.204	45.4 ± 6.1	0.702	43.1 ± 6.4	0.368	41.8 ± 6.0	0.235
E/e' (lateral)	19.3 ± 10.4	22.5 ± 12.0	0.308	20.0 ± 9.9	0.804	19.9 ± 10.6	0.837	19.2 ± 7.3	0.983	25.2 ± 12.9	0.126	24.3 ± 8.3	0.226	28.7 ± 9.9	0.040
E/e' (septal)	25.7 ± 14.3	28.0 ± 11.9	0.529	29.2 ± 14.5	0.399	28.0 ± 14.5	0.572	29.6 ± 9.2	0.321	30.7 ± 10.4	0.264	29.0 ± 9.6	0.573	34.0 ± 9.3	0.158
Aortic valve															
Aortic valve area (cm^2)	0.79 ± 0.19	1.72 ± 0.31	<0.001	1.72 ± 0.26	<0.001	1.80 ± 0.25	<0.001	1.71 ± 0.26	<0.001	1.71 ± 0.27	<0.001	1.71 ± 0.31	<0.001	1.67 ± 0.23	<0.001
Indexed aortic valve area (cm^2/m^2)	0.56 ± 0.13	1.23 ± 0.23	<0.001	1.23 ± 0.23	<0.001	1.30 ± 0.21	<0.001	1.21 ± 0.19	<0.001	1.21 ± 0.20	<0.001	1.20 ± 0.23	<0.001	1.18 ± 0.17	<0.001
Peak velocity (m/s)	4.8 ± 0.8	2.5 ± 0.6	<0.001	2.4 ± 0.4	<0.001	2.2 ± 0.4	<0.001	2.3 ± 0.5	<0.001	2.1 ± 0.4	<0.001	2.3 ± 0.7	<0.001	2.6 ± 0.9	<0.001
Peak pressure gradient (mmHg)	92.8 ± 30.6	26.1 ± 13.2	<0.001	23.4 ± 8.5	<0.001	21.6 ± 7.3	<0.001	22.4 ± 9.6	<0.001	18.9 ± 7.4	<0.001	22.1 ± 13.1	<0.001	28.9 ± 19.6	<0.001
Mean pressure gradient (mmHg)	51.4 ± 18.5	12.1 ± 6.1	<0.001	10.9 ± 4.0	<0.001	10.2 ± 3.3	<0.001	10.7 ± 5.6	<0.001	9.1 ± 3.0	<0.001	11.2 ± 7.2	<0.001	14.1 ± 10.1	<0.001

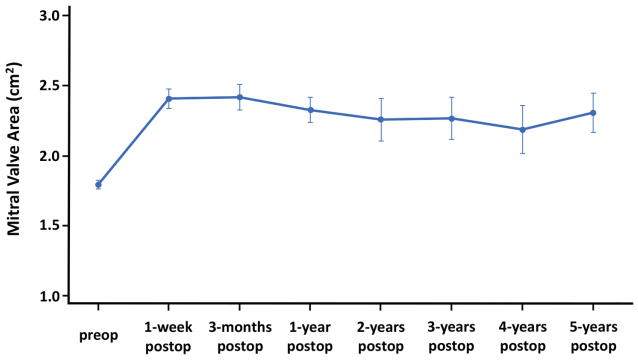

Fig. 1 Changes in MVA over time. Data are expressed as mean ± standard error of the mean. MVA: mitral valve area

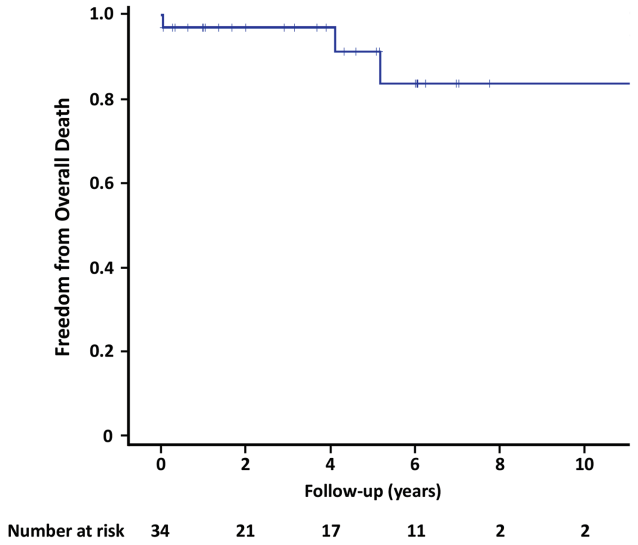

Fig. 2 Freedom from overall death

regression of left ventricular mass, which may have resulted in a sustained increase of MVA.

For MS with a high frequency of MAC, performing MVR carries the risks of causing complications such as atrioventricular disruption, left ventricular rupture, and neurological complications due to calcium embolization. Moreover, performing AVR for AS in addition to MVR further increases the risk of surgery. However, performing mitral valve surgery for MS as a reoperation after AVR surgery is a high-risk procedure. In the present study, increased MVA was maintained for 5 years after surgery, and no patients underwent reoperation for remaining MS. This result may be useful for understanding the pathophysiology of combined valvular disease of AS and MS.

Multivariable logistic regression analysis showed that there was no independent predictor of postoperative MS (MVA <1.5 cm^2). However, MVA only decreased to less than 1.5 cm^2 in one patient during our follow-up. This result may be due to the small number of samples. A much larger study is needed to accurately evaluate the postoperative course of remaining MS after AVR for AS.

Study Limitations

There are several limitations in this study. First, this is a retrospective study in a single center. Second, the small number of patients might have resulted in insufficient statistical power. Third, the main evaluation method for the severity of MS is the evaluation of MVA using PHT and planimetry orifice area was used as a supplement in our institution. Of all echocardiographic reports in our all cohort, only 84 (48.6%) reports revealed planimetry orifice area, so we could not show the MVA using planimetry orifice area. Other measurements such as planimetry orifice area and transmitral gradient should be measured preoperatively and postoperatively. Finally, the follow-up period was short at 4.0 ± 3.0 years after operation, which could explain why no patients underwent reoperation for remaining MS.

Conclusions

AVR for AS resulted in increased MVA in patients with MS, and the change remained for during follow-up. This result may be meaningful for understanding the pathophysiology of combined valvular disease of AS and MS.

Disclosure Statement

The authors declare that there is no conflict of interest.

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