Effect of Left Ventricular Reverse Remodeling on Long-term Outcomes After Aortic Valve Replacement

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There have been few studies with a large number of patients on the effect of left ventricular (LV) reverse remodeling and long-term outcomes after aortic valve replacement (AVR). This study aimed to investigate long-term outcomes and the prognostic impact of follow-up echocardiographic parameters after AVR. We evaluated 456 consecutive patients from a retrospective multicenter registry in Japan (J-PROVE-Retro) who underwent AVR for aortic valve diseases (predominantly aortic stenosis [AS]; 326 patients and aortic regurgitation [AR]; 130 patients). Preoperative and follow-up echocardiography at 1 year after AVR was evaluated. The primary outcome measure was a composite of cardiac death or hospitalization due to heart failure. The median follow-up period was 9.2 years in AS group and 9.7 years in AR group. The freedom rate from the primary outcome was 92% at 5 years and 79% at 10 years in AS, and 97% at 5 years, and 93% at 10 years in AR. LV end-diastolic and end-systolic diameters, and the LV mass index decreased and LV ejection fraction increased after AVR in both AS and AR, and LV mass index was normalized in more than half of the patients. In the Cox proportional hazard model, echocardiographic parameters at 1 year after AVR were more strongly related to long-term outcomes than preoperative echocardiographic parameters. In conclusion, echocardiographic parameters at 1 year after AVR are more important as predictors of long-term outcomes than preoperative parameters in both AS and AR. More attention should be paid on early postoperative remodeling for long-term follow-up of patients after AVR. © 2019 Elsevier Inc. All rights reserved. (Am J Cardiol 2019;124:105−112)

Aortic valve replacement (AVR) is an effective treatment for patients with aortic stenosis (AS) and aortic regurgitation (AR), which may achieve postoperative left ventricular (LV) reverse remodeling. AVR is recommended before progression of myocardial damage, but latent myocardial damage might have already progressed at the time of diagnosis because of a long asymptomatic period.[1−3]

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Previous studies have investigated preoperative predictors of long-term prognosis after AVR.[4−8] However, the degree of LV reverse remodeling after AVR depends on individuals, and precisely predicting postoperative LV reverse remodeling by preoperative parameters is difficult. The degree of LV reverse remodeling after AVR rather than preoperative parameters may be related to long-term prognosis after AVR. There have been studies on postoperative reverse remodeling,[9−15] but studies regarding the effect of postoperative LV reverse remodeling on long-term outcomes are limited.[10,11,14] Additionally, the follow-up period was less than 5 years in most previous studies and there have been few longer follow-up data.[14,16] Therefore, this study aimed to investigate postoperative reverse remodeling, long-term outcomes, and the prognostic impact of follow-up echocardiographic parameters after AVR in patients with chronic aortic valve diseases.

Methods

The Japan Prosthetic Valve Registry (J-PROVE-retro) is a retrospective multicenter registry that enrolled consecutive patients who underwent mitral and/or aortic prosthetic valve replacement between January 2000 and December 2006. This registry is a project of the Japanese Society of Echocardiography and 8 centers in Japan participated where an expert in echocardiography was present. The institutional review boards in all of the participating centers approved the protocol. Informed consent from each patient was waived in this retrospective study, because we used

clinical data that were obtained in routine clinical practice. Among 743 patients enrolled in the registry, the study population consisted of 456 patients who underwent AVR for chronic aortic valve diseases. Patients with concomitant mitral valve replacement and acute AR due to aortic dissection or infective endocarditis were excluded. Perioperative death was defined as death within 30 days after AVR or in-hospital death, and early mortality was defined as death within 1 year after AVR. The incidence of perioperative and early mortality were evaluated in 456 patients. Furthermore, LV reverse remodeling comparing preoperative and early follow-up echocardiograms (at 1 year [±3 months] after AVR), long-term prognosis and predictors of long-term prognosis were evaluated in patients who survived at 1 year after AVR (Figure 1). Long-term prognosis and LV reverse remodeling after AVR were evaluated by dividing patients into those who had predominantly AS and those who had predominantly AR.

The baseline clinical information and procedural characteristics at AVR were obtained from hospital charts or database review. Follow-up data were mainly collected thorough review of hospital charts, relatives, and/or referring physicians using mail with questions regarding survival and subsequent hospitalization. We investigated the preoperative clinical characteristics, including age at AVR, gender, underlying disease, smoking habit, cardiac rhythm, and medications. Preoperative laboratory data were investigated, including hemoglobin levels, and blood levels of urea nitrogen, creatinine, total cholesterol, and B-type natriuretic peptide. Medications at the time of follow-up echocardiography were also investigated. Procedural characteristics at AVR included the usage rate of bioprosthetic and mechanical valve, valve size, and the rate of concomitant procedure at AVR, such as coronary artery bypass grafting, or replacement of the ascending aorta.

Comprehensive transthoracic echocardiography was performed before AVR and at 1 year (±3 months) after AVR, using high-quality, commercially available ultrasound systems. LV end-diastolic and end-systolic diameters (LVDd and LVDs), the LV ejection fraction (EF), left atrial dimension (LAD), diastolic interventricular septal wall thickness (IVSTd), and diastolic left ventricular posterior wall thickness (LVPWTd) were measured. The LVEF was calculated using the modified Simpson's method. The LV mass index (LVMI) was calculated using the formula for estimating LV mass from LV linear dimensions as described in the guidelines of the American Society of Echocardiography,[17] as follows: LV mass = 0.8 $(1.04[LVDd+LVPWTd+IVSTd]^3 -[LVDd]^3)+0.6$, and was indexed to the body surface area. According to the American Society of Echocardiography recommendations,[17] a high LVMI was defined as an LVMI >115 g/m^2 for males and >95 g/m^2 for females. In preoperative echocardiography, the aortic valve area was calculated using a continuity equation in patients with AS and the degree of AR was evaluated qualitatively. Peak velocity of tricuspid regurgitation was also measured. In postoperative follow-up echocardiography, trans-aortic valve velocity was measured.

The primary outcome measure was a composite of cardiac death or hospitalization due to heart failure. The secondary outcome measure was all-cause death. Cardiac death was defined as sudden death unexplained by extracardiac causes, death related to congestive heart failure, lethal arrhythmia, reoperations, and prosthesis related treatment.

Statistical analysis was performed with JMP, V.9.0.2 (SAS Institute, Cary, North Carolina) and STATA, V.15 (StataCorp LP, College Station, Texas). Categorical variables are presented as numbers and percentages, and were compared using the chi-square test or Fisher's exact test. Continuous variables are presented as mean ± standard deviation [SD] or median (interquartile range [IQR]). Based on their distributions, continuous variables were compared using the Student's t test or the Wilcoxon rank sum test between 2 groups. The study patients were dichotomized into 2 groups by a median value of echocardiographic parameters which were independent predictors for primary outcome. The cumulative incidence of clinical outcomes after AVR was evaluated using the Kaplan-Meier method, and comparison between 2 groups dichotomized by echocardiographic parameters was performed using the log-rank test. Univariable Cox proportional hazards regression models were used to calculate HRs for primary outcome and 95% confidence intervals. Multivariable Cox regression analysis was performed using age, gender, and echocardiographic parameters that significantly predicted primary outcome in the univariable analysis (model 1). Regarding the echocardiographic parameters with collinearity, such as LVDd and LVDs, one of them was included for multivariable analysis. Stepwise selection with a p value of 0.1 for backward elimination was used to select the best predictive model (model 2). To compare prognostic importance of preoperative and postoperative echocardiographic parameters, both parameters were incorporated separately into model 3 and model 4 using C-index. All statistical tests were 2-sided and p values <0.05 were regarded as statistically significant.
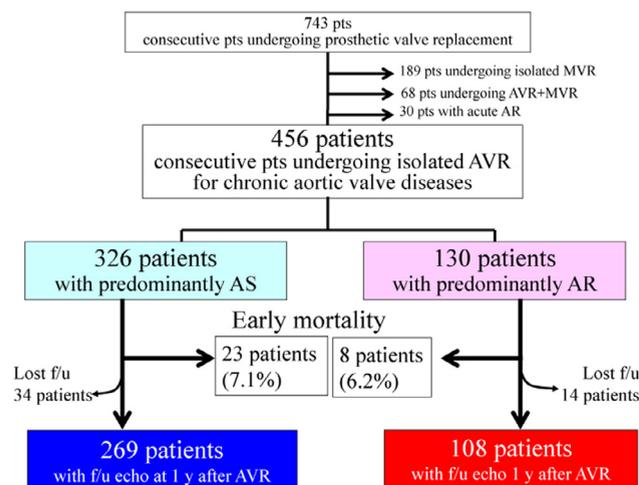
Results

Of the 456 patients who underwent AVR, 326 patients with predominantly AS (AS group), and 130 patients with

Figure 1. Flow chart of the study patients.
AS = aortic stenosis; AR = aortic regurgitation; AVR = aortic valve replacement; y = year.

predominantly AR (AR group). The mean age at AVR was 70 ± 9 years in the AS group and 61 ± 13years in the AR group.

The clinical background and preoperative echocardiographic parameters of both groups is shown in Table 1. Patients in the AS group were older (p < 0.0001), there were more female patients (p < 0.0001), more patients receiving 21 mm or smaller valve (p < 0.0001), and they had a higher prevalence of diabetes (p = 0.013), dyslipidemia (p = 0.008), and coronary artery disease (p = 0.020) than those in the AR group. There were more patients taking angiotensin-converting enzyme inhibitor, angiotensin receptor blocker, and diuretics in AR group than AS group. As is expected, LVDd, LVDs and the LVMI were larger

Table 1
Baseline clinical and echocardiographic characteristics

Variables	AS group (n = 326)	AR group (n = 130)	p Value
Age at AVR (years)	70 ± 9	60 ± 13	<0.0001
Woman	172 (53%)	32 (25%)	<0.0001
Body surface area (cm^2)	1.52 ± 0.17	1.64 ± 0.20	<0.0001
NYHA class 3 or 4	61 (19%)	30 (23%)	0.36
Hypertension	141 (43%)	64 (49%)	0.83
Dyslipidemia	69 (21%)	16 (12%)	0.008
Diabetes mellitus	56 (17%)	12 (9%)	0.013
Coronary artery disease	35 (11%)	6 (5%)	0.020
Atrial fibrillation	35 (11%)	18 (14%)	0.13
Hemodialysis	25 (8%)	7 (5%)	0.32
Hemoglobin (g/dL)	12.4 ± 1.8	12.2 ± 2.1	0.22
Total cholesterol (mg/dL)	189 ± 34	182 ± 39	0.061
Blood urea nitrogen (mg/dL)	21.6 ± 12.8	22.2 ± 12.6	0.68
Creatinine (mg/dL)	1.5 ± 2.2	1.4 ± 1.8	0.81
BNP (pg/ml)	382 ± 407	578 ± 1598	0.31
Echocardiographic parameters			
LVDd (mm)	46.6 ± 7.7	61.8 ± 7.4	<0.0001
LVDs (mm)	30.3 ± 8.9	43.1 ± 7.2	<0.0001
LVEF (%)	62.7 ± 14.2	56.8 ± 12.8	<0.0001
LVMI (g/m^2)	149 ± 44	183 ± 45	<0.0001
LAD (mm)	40.6 ± 8.6	40.8 ± 7.4	0.80
TR peak velocity (m/sec)	2.67 ± 0.46 (n=147)	2.57 ± 0.43 (n=68)	0.16
AVA at diagnosis (cm^2)	0.65 ± 0.18		
AV-Vel at diagnosis (m/sec)	4.79 ± 0.71		
Procedural characteristics at AVR			
Bioprosthesis	240 (74%)	80 (62%)	0.016
Valve size 21mm or smaller	202 (62%)	17 (13%)	<0.0001
Coronary artery bypass grafting	53 (16%)	11 (9%)	0.036
Ascending aorta replacement	26 (8%)	24 (19%)	0.0023
Perioperative death	12 (3.7%)	5 (3.8%)	0.28
Early deaths	23 (7.1%)	8 (6.2%)	0.84
Medication			
ACEi/ARB	99 (30%)	77 (59%)	<0.0001
Beta blocker	55 (17%)	23 (18%)	0.99
Diuretics	105 (32%)	64 (49%)	0.009

ACEi = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; AR = aortic regurgitation; AS = aortic stenosis; AVR = aortic valve replacement; NYHA = New York Heart Association; BNP = B-type natriuretic peptide; LVDd = left ventricular end-diastolic diameter; LVDs = left ventricular end-systolic diameter; LVEF = left ventricular ejection fraction; LVMI = left ventricular mass index; LAD = left atrial dimension; TR = tricuspid regurgitation; AVA = aortic valve area; AV-Vel = aortic jet velocity.

and the LVEF was lower in the AR group than the AS group (all p < 0.0001).

Early death occurred in 23 (7.1%), including 12 (3.7%) perioperative deaths of 326 patients in the AS group. In the AR group, early death occurred in 8 (6.2%), including 5 (3.8%) perioperative deaths of 130 patients. The causes of perioperative death are congestive heart failure in 5, sepsis in 3, infective endocarditis in 1, myocardial infarction in 1, ventricular fibrillation in 1 and mediastinitis in 1 patient in AS group, while heart failure in 1, infective endocarditis in 1, sepsis in 1, mediastinitis in 1, and hepatic failure in 1 patient in AR group. Comparison of baseline clinical and echocardiographic characteristics between patients with and without early death is shown in Table 2. In the AS group, blood urea nitrogen levels were higher, hemoglobin levels were lower, preoperative transaortic valve velocity was lower and more patients received hemodialysis and had concomitant coronary artery disease in those who died within 1 year after AVR. There were no differences in preoperative echocardiographic parameters, except for transaortic valve velocity, between patients with and without early death. In the AR group, hemoglobin levels were lower, and more patients had hemodialysis in those who died within 1 year after AVR.

Among the 326 patients in the AS group, 23 patients died within 1 year after AVR and 34 were not followed up with echocardiography at 1 year (± 3 months) after AVR. Among the 130 patients in the AR group, 8 patients died within 1 year after AVR and 14 were not followed up with echocardiography at 1 year (±3 months) after AVR. Consequently, chronological changes in echocardiographic parameters, long-term prognosis and predictors of long-term prognosis were evaluated in 269 patients in the AS group and in 108 patients in the AR group (Figure 1).

LVDd, LVDs, LAD, and the LVMI decreased and the LVEF increased after AVR in both the AS and AR groups (Figure 2). Preoperative LVEF was less than 50% in 50 (19%) patients in the AS group, and LVEF improved to more than 50% after AVR in 42 (84%) of the 50 patients. Preoperative LVEF was less than 50% in 31 (28%) patients in the AR group, and LVEF improved to more than 50% after AVR in 23 (74%) of the 31 patients. The LVMI was normalized in 126 (55%) patients in the AS group and in 56 (52%) patients in the AR group. In the AS group, patients without postoperative normalization of LVMI showed larger LV and LA size (LVDd: 49.1 ± 7.9 vs 45.0 ± 7.4 mm, p < 0.0001, LAD: 42.1 ± 7.7 vs 39.0 ± 8.4 mm, p = 0.002), lower LVEF (59.5 ± 15.3 vs 65.3 ± 12.6%, p = 0.0009), and greater LVMI (165 ± 47 vs 135 ± 36 g/m^2, p < 0.0001) preoperatively. In the AR group, patients without postoperative normalization of LVMI showed larger LAD (43.1 ± 7.6 vs 39.1 ± 7.5 mm, p = 0.008) and greater LVMI (190 ± 44 vs 171 ± 92 g/m^2, p = 0.02) preoperatively. The decrease in LVDd, LVDs, and LVMI after AVR was more prominent in AR than AS (LVDd reduction: 15.4 ± 8.3 vs 3.7 ± 6.9 mm, p < 0.0001, LVDs reduction: 13.5 ± 8.1 vs 4.1 ± 7.9 mm, p < 0.0001, LVMI reduction: 69.6 ± 45.0 vs 42.8 ± 37.5 g/m^2, p < 0.0001).

The median follow-up period was 9.2 years (IQR: 7.0-10.9 years) in the AS group and 9.7 years (IQR: 7.9-12.3 years) in the AR group. The freedom rate from the primary

Table 2
Baseline clinical and echocardiographic characteristics between patients with and without early death

Variables	AS group(n = 326)			AR group(n = 130)		
	Early death (+) (n = 23)	Early death (−) (n = 303)	p Value	Early death (+) (n = 8)	Early death (−) (n = 122)	p Value
Age at AVR (years)	72 ± 6	70 ± 9	0.18	69 ± 8	60 ± 13	0.054
Woman	10 (44%)	162 (54%)	0.39	1 (13%)	31 (25%)	0.68
Body surface area (cm^2)	1.47 ± 0.15	1.53 ± 0.17	0.14	1.58 ± 0.18	1.65 ± 0.20	0.36
NYHA class 3 or 4	3 (13%)	58 (19%)	0.58	2 (25%)	18 (15%)	1.00
Hypertension	9 (39%)	132 (44%)	1.00	5 (63%)	51 (42%)	0.25
Dyslipidemia	3 (13%)	66 (22%)	0.57	1 (13%)	15 (12%)	1.00
Diabetes mellitus	1 (4%)	11 (4%)	0.21	0 (0%)	12 (10%)	1.00
Coronary artery disease	7 (30%)	28 (9%)	0.002	1 (13%)	5 (4%)	0.31
Atrial fibrillation	4 (17%)	31(10%)	0.30	0 (0%)	18 (15%)	0.59
Hemodialysis	6 (26%)	19 (6%)	0.002	2 (25%)	5 (4%)	0.054
Hemoglobin (g/dL)	11.2 ± 2.0	12.5 ± 1.8	0.0058	10.4 ± 2.6	12.3 ± 2.0	0.012
Total cholesterol (mg/dL)	183 ± 36	190 ± 34	0.44	158 ± 37	184 ± 39	0.075
Blood urea nitrogen (mg/dL)	28.7 ± 20.2	21.2 ± 12.1	0.019	28.7 ± 16.5	21.8 ± 12.3	0.13
Creatinine (mg/dL)	3.0 ± 3.4	1.4 ± 2.0	0.0028	2.1 ± 2.4	1.4 ± 1.7	0.28
Echocardiographic parameters						
LVDd (mm)	45.2 ± 6.2	46.7 ± 7.9	0.38	56.8 ± 5.7	62.1 ± 7.4	0.048
LVDs (mm)	30.0 ± 6.8	30.3 ± 9.0	0.85	38.8 ± 6.0	43.4 ± 7.2	0.076
LVEF (%)	59.2 ± 14.4	63.0 ± 14.2	0.23	59.6 ± 17.2	56.7 ± 12.5	0.56
LVMI (g/m^2)	149 ± 44	149 ± 44	0.98	180 ± 52	183 ± 45	0.85
LAD (mm)	40.1 ± 9.7	40.6 ± 8.5	0.79	36.8 ± 5.4	41.1 ± 7.5	0.11
TR peak velocity (m/sec)	2.86 ± 0.63 (n = 10)	2.65 ± 0.45 (n = 137)	0.17	2.86 ± 0.28 (n = 5)	2.55 ± 0.44 (n = 63)	0.12
AVA at diagnosis (cm^2)	0.62 ± 0.14	0.66 ± 0.18	0.37			
AV-Vel at diagnosis (m/sec)	4.41 ± 0.76	4.81 ± 0.70	0.017			
Procedural characteristics at AVR						
Bioprosthesis	20 (87%)	220 (73%)	0.077	7 (88%)	73 (60%)	0.16
Valve size 21mm or smaller	15 (65%)	187 (62%)	0.65	1 (13%)	16 (13%)	1.00
Coronary artery bypass grafting	7 (30%)	46 (15%)	0.083	0 (0%)	11 (9%)	1.00
Ascending aorta replacement	3 (13%)	23 (8%)	0.42	2 (25%)	22 (18%)	0.65

Abbreviations are same as Table 1.

outcome (cardiac death or hospitalization due to heart failure) was 92% at 5 years and 79% at 10 years after AVR in the AS group, and 97% at 5 years and 93% at 10 years in the AR group (Figure 3). The survival rates from all-cause death in the AS and AR groups were 93% and 95% at 5 years, and 75% and 88% at 10 years, respectively (Figure 3).

Table 3 shows the results of univariable analysis with the Cox proportional hazard model for predictors of the primary outcome event. In the AS group, the number of patients with the primary outcome event was 52. Preoperative symptomatic conditions (NYHA class 3 or 4), diabetes mellitus, taking angiotensin-converting enzyme inhibitor/angiotensin receptor blocker, and hemoglobin, blood urea nitrogen, creatinine and B-type natriuretic peptide levels were related to the primary outcome event. With regard to echocardiographic parameters, preoperative LVDs, LVEF, LAD, LVMI, peak velocity of tricuspid regurgitation, and postoperative LVDd, LVDs, LVEF, LAD, and LVMI were related to the primary outcome event. In multivariable analysis with the Cox proportional hazard model regarding echocardiographic parameters, postoperative LAD and LVMI, but no preoperative parameters were related to the primary outcome event in stepwise method. Postoperative echocardiographic parameters were more strongly related

to the primary outcome event compared with preoperative echocardiographic parameters (difference in C index: 0.065 (0.05 to 0.17), p = 0.033) (Table 4). The median value of postoperative LAD and LVMI was 40 mm and 102 g/m^2, respectively. The freedom rate from the primary outcome was a higher in patients with a postoperative LAD < 40 mm than in those with an LAD ≥ 40 mm (89.8% vs 69.7% at 10 years, p = 0.0001) and in patients with a postoperative LVMI < 102 g/m^2 than in those with an LVMI ≥ 102 g/m^2 (83.9% vs 74.3% at 10 years, p = 0.013) (Figure 4).

In the AR group, the number of patients with the primary outcome event was 10. Preoperative symptomatic conditions (NYHA class 3 or 4) and blood urea nitrogen levels were related to the primary outcome event. With regard to preoperative echocardiographic parameters, there were no significant predictors of the primary outcome event. However, postoperative echocardiographic parameters such as LVDd, LVDs, LVEF, LAD, and LVMI were related to the primary outcome event.

Discussion

The main findings of this study are that LV reverse remodeling at 1 year after AVR was observed in patients with AS and AR, and postoperative echocardiographic
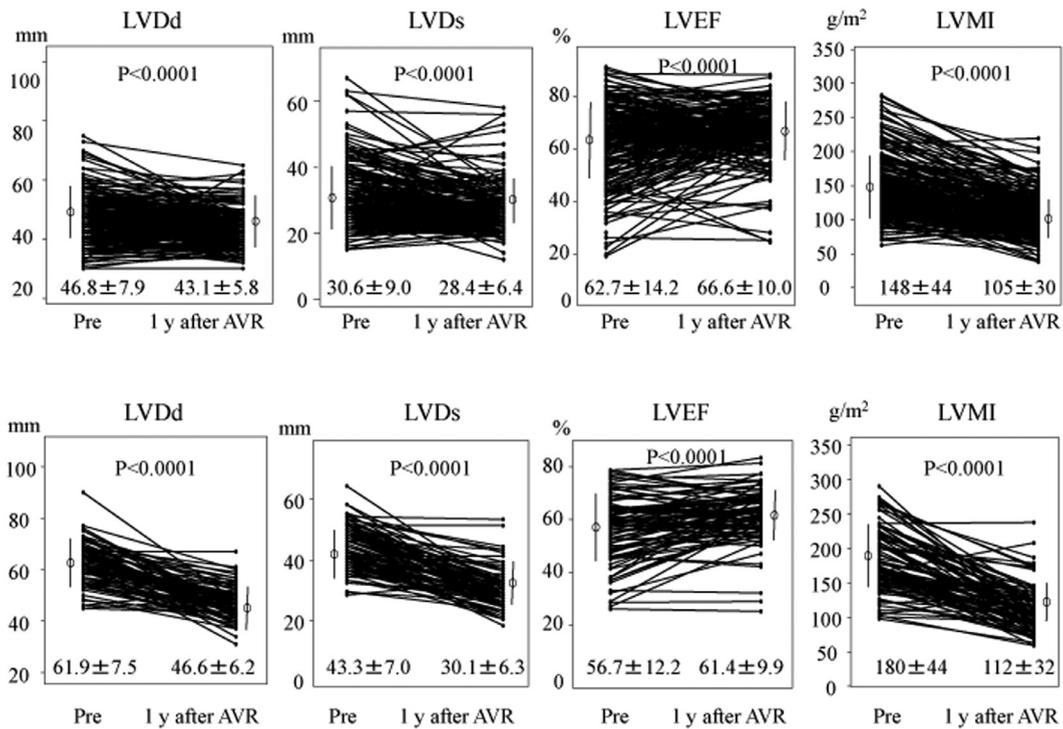
Figure 2. Postoperative changes in echocardiographic parameters.
Upper panels show the AS group and lower panels show the AR group. LVDd = left ventricular end-diastolic diameter; LVDs = left ventricular end-systolic diameter; LVEF = left ventricular ejection fraction; LVMI = left ventricular mass index; AS = aortic stenosis; AR = aortic regurgitation; pre=preoperative; AVR = aortic valve replacement; y = year.
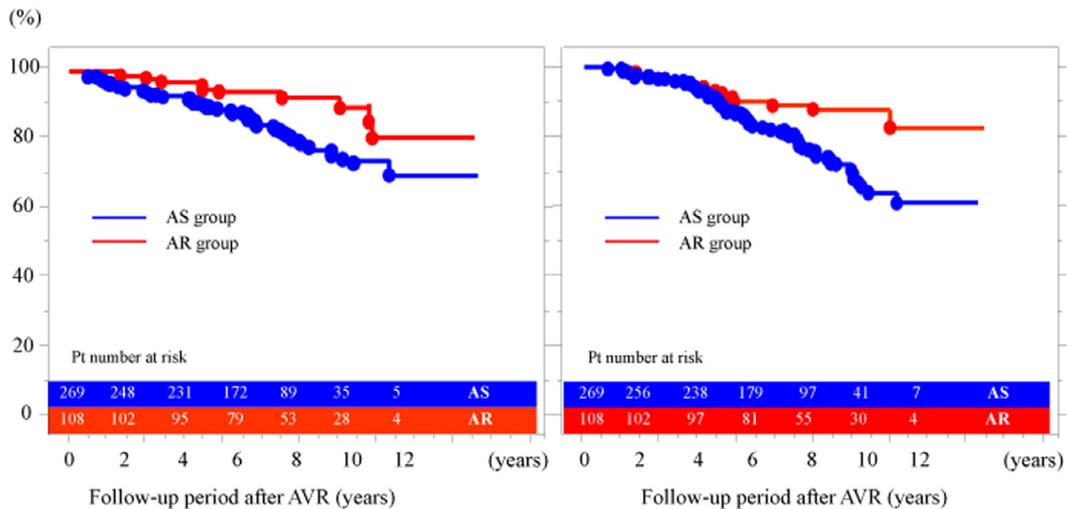

Figure 3. Kaplan−Meier curves for the freedom rate from the primary outcome (left) and all-cause death (right) in AS and AR groups.

parameters at 1 year after AVR were better predictors of long-term outcomes than preoperative echocardiographic parameters.

AVR is an effective treatment for patients with AS and AR, which may achieve a postoperative reverse remodeling of LV. In the present study with a relatively large number of patients, LVDd, LVDs, and the LVMI decreased and the LVEF increased after AVR as shown in previous studies.[9−15] The decrease in LV size and LVMI was more prominent in patients with AR than those with AS. It may be because AR causes both chronic pressure and volume overload of the LV. Therefore, preoperative LVM is greater in AR than in AS. Importantly, the degree of postoperative changes in LV size and LVEF varies depending on individuals. Latent myocardial damage preoperatively may relate to the degree of LV remodeling.

With regard to early postoperative mortality in AS group, preoperative echocardiographic parameters were not predictors except for low transaortic valve peak velocity, while the presence of anemia and renal dysfunction were

Table 3

Univariable analysis for composite of cardiac death or hospitalization due to heart failure

Variables	AS group (n = 269) Hazard ratio (95% CI)	p Value	AR group (n = 109) Hazard ratio (95% CI)	p Value
Age at AVR (per 1 year)	1.03 (0.99−1.06)	0.12	1.05 (0.98−1.11)	0.15
Woman	1.07 (0.62−1.85)	0.81	1.07 (0.28−4.15)	0.92
Body surface area	0.39 (0.07−2.01)	0.26	2.31 (0.10−54.4)	0.61
NYHA 3 or 4	2.06 (1.12−3.80)	0.02	4.32 (1.16−16.1)	0.03
Hypertension	1.93 (1.03−3.60)	0.04	0.44 (0.11−1.70)	0.23
Dyslipidemia	1.24 (0.65−2.36)	0.51	0.99 (0.21−4.66)	0.99
Diabetes mellitus	2.26 (1.23−4.15)	0.008	3.21 (0.90−11.4)	0.07
Coronary artery disease	1.38 (0.71−2.69)	0.35	1.26 (0.16−9.97)	0.83
Hemodialysis	1.08 (0.52−2.25)	0.84	1.62 (0.34−7.63)	0.54
Hemoglobin (per g/dL)	0.64 (0.53−0.77)	<0.0001	0.89 (0.66−1.21)	0.46
Total cholesterol (per mg/dL)	0.99 (0.98−1.00)	0.05	1.00 (0.98−1.01)	0.77
Blood urea nitrogen (per mg/dL)	1.06 (1.04−1.08)	<0.0001	1.05 (1.02−1.08)	0.001
Creatinine (per mg/dL)	1.24 (1.12−1.37)	<0.0001	1.19 (0.99−1.45)	0.07
Log BNP (per log unit)	6.82 (1.33−34.9)	0.02	3.22 (0.99−10.5)	0.05
Preoperative echocardiographic parameters				
LVDd (per mm)	1.03 (1.00−1.06)	0.09	1.01 (0.93−1.11)	0.76
LVDs (per mm)	1.04 (1.01−1.07)	0.006	1.06 (0.97−1.17)	0.22
LVEF (per %)	0.98 (0.96−0.99)	0.01	0.95 (0.90−1.00)	0.05
LVMI (per g/m^2)	1.01 (1.00−1.01)	0.02	1.00 (0.98−1.01)	0.50
LAD (per mm)	1.05 (1.02−1.08)	0.003	1.06 (0.97−1.15)	0.19
TR peak velocity (per m/sec)	4.32 (2.13−8.77) (n = 116)	<0.0001	0.54 (0.09−3.17) (n = 55)	0.50
AVA at diagnosis (per cm^2)	0.15 (0.03−0.77)	0.02		
AV-Vel at diagnosis (per m/sec)	0.70 (0.47−1.05)	0.08		
Postoperative echocardiographic parameters				
LVDd (per mm)	1.06 (1.01−1.11)	0.01	1.12 (1.02−1.23)	0.02
LVDs (per mm)	1.07 (1.04−1.12	<0.0001	1.14 (1.05−1.24)	0.002
LVEF (per %)	0.94 (0.92−0.97)	<0.0001	0.93 (0.88−0.98)	0.004
LVMI (per g/m^2)	1.02 (1.01−1.02)	<0.0001	1.02 (1.00−1.03)	0.04
LAD (per mm)	1.07 (1.04−1.11)	<0.0001	1.09 (1.01−1.16)	0.02
TR peak velocity (per m/sec)	5.88 (2.32−14.90) (n = 114)	0.0002	1.55 (0.64−3.74) (n = 52)	0.33
AV-Vel (per m/sec)	0.77 (0.47−1.26) (n = 238)	0.77	1.50 (0.46−4.91) (n = 90)	0.50
Valve size 21 mm or smaller	1.33 (0.75−2.34)	0.33	2.45 (0.51−11.69)	0.26
Medication at follow−up echocardiography				
ACEi/ARB	1.98 (1.03−3.80)	0.04	1.20 (0.34−4.28)	0.78
Beta blocker	0.82 (0.42−1.61)	0.57	0.89 (0.23−3.47)	0.87
Diuretics	1.76 (0.93−3.36)	0.08	2.56 (0.72−9.15)	0.15

CI = confidence interval and the other abbreviations are same as Table 1.

predictors. In contrast, preoperative and postoperative echocardiographic parameters were predictors of long-term outcomes. Our results indicated that early mortality was attributed to co-morbidity and the general status of the patients rather than cardiac function itself. After surviving

Table 4

Comparison between preoperative and postoperative models

Characteristics	C-index (95% CI)	p Value
Preoperative-based model	0.67 (0.59-0.74)	<0.001
Postoperative-based model	0.73 (0.66-0.81)	<0.001
	Difference in C-index	p Value
Comparison between pre-based and post-based models	0.065 (0.05-0.17)	0.033

CI = confidence interval.

early after AVR, pre-existing myocardial damage may strongly relate to long-term outcomes.

We also found that postoperative echocardiographic parameters were better predictors of long-term outcome than preoperative parameters (difference in C-index: 0.065 [0.05 to 0.17], p = 0.033) in patients with AS. Previous studies have examined preoperative predictors of long-term outcomes after AVR in patients with AS, and criteria for the indication of AVR were determined in guidelines based on these data.[18,19] However, it is difficult to estimate the myocardial damage by only preoperative echocardiographic parameters. Previous studies demonstrated that myocardial fibrosis evaluated by cardiac magnetic resonance imaging or cardiac biopsy can predict inappropriate reverse remodeling.[1−3] However, performing cardiac magnetic resonance imaging or cardiac biopsy in all patients is difficult in the clinical setting. LV function and reverse
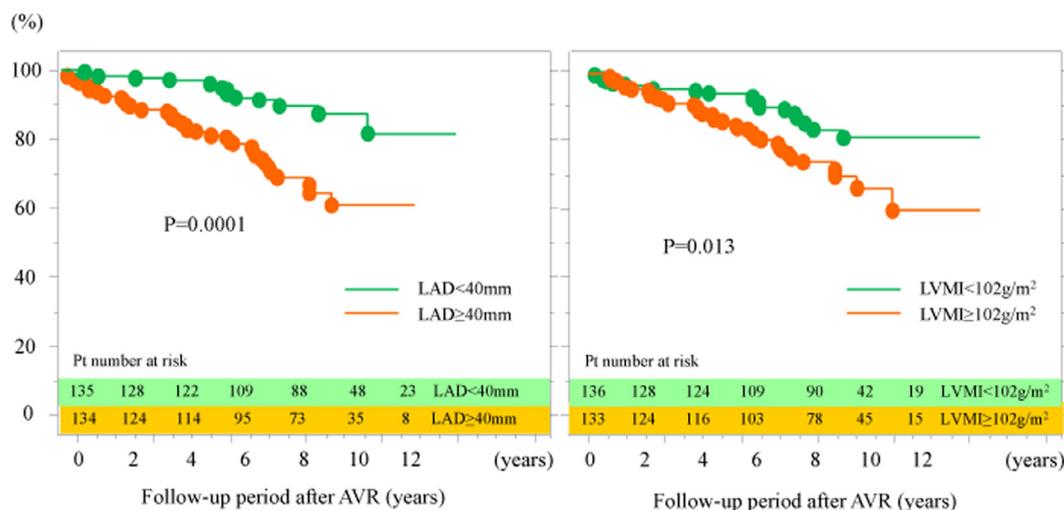
Figure 4. Kaplan−Meier curves for the freedom rate from the primary outcome in the AS group, which was dichotomized into two groups according to the median value of postoperative LAD (left) and LVMI (right).
LAD = left atrial dimension; LVMI = left ventricular mass index.

remodeling evaluated by follow-up echocardiography at approximately 1 year after AVR are useful for predicting long-term outcomes.

LAD was the strongest predictor of long-term outcomes in patients with AS. AS induces LV hypertrophy and LV diastolic dysfunction resulting in overload to the left atrium.[2,3,20−22] Actually, postoperative LVMI was also an independent predictor of long-term outcomes. Because the present study was retrospective, available echocardiographic parameters of LV diastolic function are limited. However, LAD may be a surrogate marker of LV diastolic dysfunction. The guidelines for managements of aortic valve diseases do not focus on LAD and LVMI, but physicians should pay attention to LA function and LV hypertrophy as parameters of LV diastolic dysfunction in patients with AS.

Patient-prosthetic mismatch has been reported to relate to postoperative remodeling and long-term outcomes after AVR. However, the use of a less than 21 mm valve and postoperative peak transaortic valve velocity were not related to long-term outcomes in the present study. It has been reported that aortic valve replacement with a small sized valve provided good late outcomes in the Japanese population.[23]

In patients with AR, postoperative echocardiographic parameters were predictors of long-term outcomes, but preoperative echocardiographic parameters were not. Postoperative parameters may reflect myocardial damage, while preoperative parameters may reflect both myocardial damage and the loading condition to the LV. There have been several studies on longitudinal data after AVR for chronic AR. Amano et al demonstrated that LV function improved after AVR in almost all patients with severe chronic AR, but late recurrence of LV dysfunction often occurred and preoperative and follow-up echocardiographic parameters were predictors of recurrence of LV dysfunction.[15] Prevalence of LV reverse remodeling is different in studies,[13,15] which might be due to differences in the timing of follow-up echocardiography and the length

of the follow-up period. LV function of patients who have a low preoperative EF markedly improves during the first year after AVR. Therefore, we evaluated LV function at 1 year after AVR. They also studied long-term outcomes, and showed that postoperative LV function at 1 year after AVR was useful as a predictor of long-term outcomes.[14] Echocardiographic parameters at 1 year after AVR may reflect latent myocardial damage better than preoperative parameters.

The present study has several limitations mainly caused by its retrospective nature. First, not all of the patients could be followed up systematically resulting in bias with respect to the evaluation of the event free rate. The number of patients with the primary end point was 10 in the AR group, thus multivariate analysis could not be performed. Echocardiographic parameters were not measured in a core laboratory. In addition, our study included 53 patients with atrial fibrillation, which may have some influences on accuracy of echocardiographic measurements. Postoperative echocardiographic data of the LV outflow tract flow velocity was not stored in many of the study patients, thus effective orifice area of the prosthetic valve could not be evaluated. Patient-prosthetic mismatch could not be assessed, but the use of a less than 21 mm valve and postoperative peak transaortic valve velocity were not related to long-term outcomes in the present study. Finally, we have no data of LV strain with speckle tracking imaging. If latent preoperative myocardial damage affects postoperative remodeling and the long-term outcomes, preoperative evaluation of LV strain may be useful.

Despite these limitations, the present study included a relatively large number of patients with approximately 10-year follow-up period, and demonstrated the importance of follow-up echocardiography for predicting long-term prognosis. Echocardiographic parameters at 1 year after AVR are more important as predictors of long-term outcomes than preoperative parameters in both AS and AR. More attention should be paid on early postoperative reverse remodeling for long-term follow-up of patients after AVR.

1. Azevedo CF, Nigri M, Higuchi ML, Pomerantzeff PM, Spina GS, Sampaio RO, Tarasoutchi F, Grinberg M, Rochitte CE. Prognostic significance of myocardial fibrosis quantification by histopathology and magnetic resonance imaging in patients with severe aortic valve disease. *J Am Coll Cardiol* 2010;56:278–287.
2. Villari B, Sossalla S, Ciampi Q, Petruzziello B, Turina J, Schneider J, Turina M, Hess OM. Persistent diastolic dysfunction late after valve replacement in severe aortic regurgitation. *Circulation* 2009;120:2386–2392.
3. Yarbrough WM, Mukhergee R, Ikonomidis JS, Zile MR, Spinale FG. Myocardial remodeling with aortic stenosis and after aortic valve replacement: mechanisms and future prognostic implications. *J Thorac Cardiovasc Surg* 2012;143:656–664.
4. Klodas E, Enriquez-Sarano M, Tajik AJ, Mullany CJ, Bailey KR, Seward JB. Optimizing timing of surgical correction in patients with severe aortic regurgitation: role of symptoms. *J Am Coll Cardiol* 1997;30:746–752.
5. Tornos P, Sambola A, Permanyer-Miralda G, Evangelista A, Gomez Z, Soler-Soler J. Long-term outcome of surgically treated aortic regurgitation: influence of guideline adherence toward early surgery. *J Am Coll Cardiol* 2006;47:1012–1017.
6. Brown ML, Schaff HV, Suri RM, Zhuo L, Sundt TM, Dearani JA, Daly RC, Orszulak TR. Indexed left ventricular dimensions best predict survival after aortic valve replacement in patients with aortic valve regurgitation. *Ann Thorac Surg* 2009;87:1170–1176.
7. Chaliki HP, Mohty D, Avierinos JF, Scott CG, Schaff HV, Tajik AJ, Sarano ME. Outcome after aortic valve replacement in patients with severe aortic regurgitation and markedly reduced left ventricular function. *Circulation* 2002;106:2687–2693.
8. Carabello BA, Paulus WJ. Aortic stenosis. *Lancet* 2009;373:956–966.
9. Haverich A, Wahlers TC, Borger MA, Shrestha M, Kocher AA, Walther T, Roth M, Msifeld M, Mohr FW, Kempfert J, Dohmen PM, Schmitz C, Rahmanian P, Wiedemann D, Duhay FG, Laufer G. Three-year hemodynamic performance, left ventricular mass regression, and prosthetic-patient mismatch after rapid deployment aortic valve replacement in 287 patients. *J Thorac Cardiovasc Surg* 2014;148:2854–2861.
10. Petrov G, Dworatzek E, Schulze TM, Dandel M, Kararigas G, Mahmoodzadeh S, Knosalla C, Hetzer R, Zagrosek VR. Maladaptive remodeling is associated with impaired survival in women but not in men after aortic valve replacement. *JACC Cardiovasc Imag* 2014;7:1073–1080.
11. Helder MRK, Ugur M, Bavaria JE, Kshettry VR, Groh MA, Petracek MR, Jones KW, Suri RM, Schaff HV. The effect of postoperative medical treatment on left ventricular mass regression after aortic valve replacement. *J Thorac Cardiovasc Surg* 2015;149:781–786.
12. Sharma UC, Barenbrug P, Pokharel S, Dassen WRM, Pinto YM, Maessen JG. Systematic review of the outcome of aortic valve replacement in patients with aortic stenosis. *Ann Thorac Surg* 2004;78:90–95.
13. Bonow RO, Dodd JT, Maron BJ, O'Gara PT, White GG, McIntosh CL, Clark RE, Epstein SE. Long-term serial changes in left ventricular function and reversal of ventricular dilatation after valve replacement for chronic aortic regurgitation. *Circulation* 1988;78:1108–1120.
14. Amano M, Izumi C, Imamura S, Onishi N, Sakamoto J, tamaki Y, Enomoto S, Miyake M, Tamura T, Kondo H, Kaitani K, Yamanaka K, nakagawa Y. Pre- and Postoperative predictors of long-term prognosis after aortic valve replacement for severe chronic aortic regurgitation. *Cir J* 2016;80:2460–2467.
15. Amano M, Izumi C, Imamura S, Onishi N, Tamaki Y, Enomoto S, Miyake M, Tamura T, Kondo H, Kaitani K, Yamanaka K, Nakagawa Y. Late recurrence of left ventricular dysfunction after aortic valve replacement for severe chronic aortic regurgitation. *Int J Cardiol* 2016;224:240–244.
16. Corti R, Binggeli C, Turina M, Jenni R, Luscher TF, Turina. Predictors of long-term survival after valve replacement for chronic aortic regurgitation. Is M-mode echocardiography sufficient? *Eur Heart J* 2001;22:866–873.
17. Lang RM, Badano LP, Mor-Avi V, Afilalo J, Armstrong A, Ernande L, Flachskampf FA, Foster E, Goldstein SA, Kuznetsova T, Lancellotti P, Muraru D, Picard MH, Rietzschel ER, Rudski L, Spencer KT, Tsang W, Voigt JU. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *J Am Soc Echocardiogr* 2015;28:1–39.
18. Nishimura RA, Otto CM, Bonow RO, Carabello BA, Erwin JP 3rd, Guyton RA, O'Gara PT, Ruiz CE, Skubas NJ, Sorajja P, Sundt TM 3rd, Thomas JD, American College of Cardiology/American Heart Association Task Force on Practice Guidelines. 2014 AHA/ACC guideline for the management of patients with valvular heart disease: executive summary: a report of the American College of Cardiology/ American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol* 2014;63:2438–2488.
19. Joint Task Force on the Management of Valvular Heart Disease of the European Society of Cardiology (ESC); European Association for Cardio-Thoracic Surgery (EACTS), Vahanian A, Alfieri O, Andreotti F, Antunes MJ, Barón-Esquivias G, Baumgartner H, Borger MA, Carrel TP, De Bonis M, Evangelista A, Falk V, Iung B, Lancellotti P, Pierard L, Price S, Schäfers HJ, Schuler G, Stepinska J, Swedberg K, Takkenberg J, Von Oppell UO, Windecker S, Zamorano JL, Zembala M. Guidelines on the management of valvular heart disease (version 2012). *Eur Heart J* 2012;33:2451–2496.
20. Hess OM, Ritter M, Schneider J, Grimm J, Turina M, Krayenbuehl HP. Diastolic stiffness and myocardial structure in aortic valve disease before and after valve replacement. *Circulation* 1984;69:855–865.
21. Murakami T, Hess OM, Gage JE, Grimm J, Krayenbuehl HP. Diastolic filling dynamics in patients with aortic stenosis. *Circulation* 1986;73:1162–1174.
22. Carebello BA. Aortic stenosis: from pressure overload to heart failure. *Heart Failure Clin* 2006;2:435–442.
23. Kobayashi Y, Fukushima Y, Hayase T, Kojima K, Endo G. Clinical outcome of aortic valve replacement with 16-mm ATS-advanced performance valve for small aortic annulus. *Ann Thorac Surg* 2010;89:1195–1199.