学位論文

Reverse Remodeling after Aortic Valve Replacement for Chronic Aortic Regurgitation
（慢性大動脈弁閉鎖不全症に対する大動脈弁置換後の reverse remodeling の検討）

生田　亜由美

Ikuta　Ayumi

熊本大学大学院医学教育部博士課程医学専攻心臓血管外科学

指導教員

福井　寿啓　教授

熊本大学大学院医学教育部博士課程医学専攻心臓血管外科学

2021 年　3 月

学　位　論　文

論文題名　：　**Reverse Remodeling after Aortic Valve Replacement for Chronic Aortic Regurgitation**
（慢性大動脈弁閉鎖不全症に対する大動脈弁置換後の reverse remodeling の検討）

著 者 名　：　生田　亜由美
Ayumi Ikuta

指導教員名　：　熊本大学大学院医学教育部博士課程医学専攻心臓血管外科学　福井寿啓　教授

審査委員名　：　災害医療教育研究センター　笠岡　俊志　教授

循環器内科学担当教授　辻田　賢一　教授

生体機能薬理学担当教授　光山　勝慶　教授

2021 年 3 月

Reverse Remodeling after Aortic Valve Replacement for Chronic Aortic Regurgitation

Ayumi Koga-Ikuta[1,2], Satsuki Fukushima, MD[1], Naonori Kawamoto[1], Tetsuya Saito[1], Yusuke Shimahara[1], Shin Yajima[1], Naoki Tadokoro[1], Takashi Kakuta[1], Toshihiro Fukui[2], Tomoyuki Fujita[1]

[1]Department of Cardiovascular Surgery, National Cerebral and Cardiovascular Center, Osaka, Japan

[2]Department of Cardiovascular Surgery, Graduate School of Medical Sciences, Kumamoto University, Kumamoto, Japan

Corresponding author: Tomoyuki Fujita

Department of Cardiovascular Surgery,

National Cerebral and Cardiovascular Center,

6-1 Kishibe-Shinmachi, Suita, Osaka 564-8565, Japan.

Phone: +81661701070; Fax: +81668727486

E-mail: tfujita@ncvc.go.jp

Meeting presentation:

This manuscript has been accepted for presentation at the 2020 EACTS 34th Annual Meeting in Barcelona, Spain 8–10 October 2020.

VISUAL ABSTRACT

- **Key question**
- How does reverse remodeling affect late outcomes, and what are the predictors of reverse remodeling after AVR for AR?
- **Key findings**
- LVEF and LVD were related to reverse remodeling, and patients without reverse remodeling showed poor late outcomes.
- **Take-home message**

Earlier surgery may help to restore normal LV size and achieve better late outcomes after AVR for AR.

Central Image legend

Distribution of preoperative LVEF and LVESDi in patients who achieved reverse remodeling (RR group: blue circles) or not (nRR group: red crosses).

ABSTRACT

Objectives: This study aimed to assess the long-term outcomes and investigate the factors related to left ventricular reverse remodeling after aortic valve replacement in patients with chronic aortic regurgitation.

Methods: A total of 246 patients who underwent aortic valve replacement for chronic aortic regurgitation at our institution were included in this retrospective study. Primary endpoints included all-cause mortality, cardiac mortality, and major adverse cerebral and cardiovascular events. Secondary endpoints included cardiac function on echocardiography 1 year after surgery. We explored the predictive factors for reverse remodeling 1 year after surgery.

Results: The 10-year survival rate was 86.0%, with no cardiac deaths in 93.8% and no major adverse cerebral and cardiovascular events in 79.9% of patients. Postoperative left ventricular function and symptoms were significantly improved 1 year after surgery, but 34 patients (13.8%) did not recover normal function and structure. A significant negative correlation was found between the incidence of cardiac death and major adverse cerebral and cardiovascular events and reverse remodeling. Multivariate logistic regression identified preoperative left ventricular ejection fraction (P = 0.001, odds ratio = 1.057) and left ventricular end-systolic dimension index (P = 0.038, odds ratio = 0.912) as significant predictive factors of reverse remodeling 1 year after surgery.

Conclusions: Preoperative left ventricular ejection fraction and left ventricular end-systolic dimension index were predictive factors for reverse remodeling after surgery, which was associated with late outcomes. Earlier surgery may thus help to restore normal left ventricular function and achieve better late outcomes after aortic valve replacement for aortic regurgitation.

Keywords: chronic aortic regurgitation, aortic valve replacement, reverse left ventricular remodeling

INTRODUCTION

Aortic valve replacement (AVR) is recommended for chronic aortic regurgitation (AR) in patients with symptoms, impaired left ventricular (LV) contraction (ejection fraction (EF) $<$ 50%), or LV enlargement (LV end-diastolic dimension (LVEDD) $>$ 70 mm, or LV indexed end-systolic dimension (LVESDi) $>$ 25 mm/m^2) [1]. In asymptomatic aortic stenosis, Rosenhek et al. reported that early surgical intervention had little benefit [2]. Conversely, Kang et al. showed that early surgical intervention is associated with a better prognosis [3]. In contrast to aortic stenosis, progression of AR is usually gradual and detecting the symptoms is often difficult. LV remodeling may progress even during the asymptomatic period, and objective evaluation is therefore essential to prevent further LV remodeling and achieve postoperative reverse LV remodeling [4–6]. Izumi et al. showed that echocardiographic parameters at 1 year after AVR were more important predictors of long-term outcomes than preoperative parameters in patients with AR [7]. Extensive remodeling due to chronic AR has been associated with worse outcomes, even after AVR. It is therefore important to determine the extent and benefit of reverse LV remodeling at 1 year after AVR in patients with AR. The current study aimed to investigate the long-term outcomes and analyze the factors related to reverse LV remodeling after AVR in patients with chronic AR.

MATERIALS AND METHODS

Study Cohort, Data Collection, and Study Endpoints

This retrospective study analyzed data for a consecutive series of patients who underwent AVR for chronic AR using a prosthetic valve at the National Cerebral and Cardiovascular Center Hospital in Japan between January 2008 and December 2018, and who were included in the institutional cardiac surgical database. The surgical indication was severe AR. Patients who underwent echocardiography 1 year after AVR were included. Patients who had received AVR previously, had active infective endocarditis, or had acute AR were excluded. Data were collected from medical charts, operation reports, and referral letters in May 2020.

The primary endpoints of the study were all-cause mortality, cardiac mortality, and major adverse cerebral and cardiovascular events (MACCE) (defined as cardiac mortality, myocardial infarction, coronary revascularization, stroke, and hospitalization because of heart failure). The secondary endpoints included cardiac function on echocardiography at 1 year after the operation.

Surgical Indication, Procedure

The surgical indication in this study cohort was discussed by the institutional heart team, consisting of cardiologists, cardiac surgeons, and co-medical staff, essentially according to the guidelines. All patients underwent preoperative examination using transthoracic and/or transesophageal echocardiography and fluoroscopy and/or computed tomography-based coronary angiography. AVR was usually performed via a median full sternotomy. The prosthetic valve was implanted under induced cardiac arrest by intermittent tepid blood cardioplegia infusion in all cases. The type of prosthesis (biological or mechanical) was determined according to the guidelines and by discussion with the patients, and the size of the prosthesis was determined by the surgeon during surgery.

Echocardiography

All patients were examined by transthoracic and/or transesophageal echocardiography within 1 month before surgery and by transthoracic echocardiography within 14 days after surgery. In addition, patients underwent annual transthoracic echocardiography postoperative follow-up examinations at the outpatient clinic of the National Cerebral and Cardiovascular Center Hospital. Echocardiography was assessed by an expert engineer and expert doctor according to established guidelines. Data were retrieved from the official echocardiographic report.

LVEF was calculated using the modified Simpson's method. LVEDD and LVESD were obtained in M-mode from a two-dimensional image. Regurgitation grade was classified by American Society of Echocardiography guidelines [8].

LV mass was estimated by LVD and wall thickness at end diastole and LV mass index (LVMI) was calculated from LV mass and body surface area (BSA) using the following formula: LV mass (g) = $0.8\{1.04[([LVEDD + IVSd + PWd]^3 - LVEDD^3)]\} + 0.6$, LVMI(g/m^2) = LV mass/BSA

Statistical Analysis

Data were presented as mean (standard deviation) for continuous normally distributed variables, median (interquartile range) for continuous non-normally distributed variables, and number and percentage for categorical variables. Normality was tested by the Shapiro–Wilk test. Categorical variables were compared using Fisher's exact test and continuous variables were compared with Student's unpaired *t*-test or the Mann–Whitney U-test as appropriate. Survival and freedom from MACCE after AVR were estimated using the Kaplan–Meier method. Multivariate logistic models were used to analyze the variables associated with postoperative reverse remodeling. Important variables were selected using a stepwise regression method among variables with a univariate P value of <.2. Consequently, four variables (mitral valve surgery, mitral regurgitation (MR) grade, LVESDi, LVEF) were entered into the multivariate logistic regression model to identify predictors. Receiver operating characteristic curve (ROC) analyses were performed to identify the cut-off values predicting reverse LV remodeling for cardiac function and the criteria for selecting the optimal cut-off point were determined using Youden's index. A P-value < 0.05 was considered statistically significant for all tests. Statistical analysis was performed using JMP® 13 (SAS Institute, Cary, NC, USA).

Ethical Statement

All patients provided written informed consent for surgery and for use of their data for diagnostic and research purposes prior to surgery. The study was approved by the ethics committee of our hospital (18th July 2018, Institutional Review Board Number: M-30-026).

RESULTS

Baseline Characteristics, Operative Procedures, and Late Outcomes

The study cohort consisted of 246 patients. The baseline characteristics and operative procedures of the cohort are shown in Table 1. New York Heart Association (NYHA) class II or greater heart failure occurred in 182 patients (74.0%). A total of 109 patients (44.3%) showed impaired LV function (LVEF < 50%). LV enlargement (LVEDD > 70 mm, LVESD > 50 mm, or LVESDi > 25 mm/m²) was present in 176 patients (71.5%). Concomitant procedures including root/ascending aorta replacement, intervention for other valves, coronary artery bypass grafting, or Maze procedure were performed in 120 patients (48.8%). AVR was performed via median full sternotomy, while a minimally invasive cardiac surgery (MICS) approach was selected in 37 patients (15.0%). A biological prosthesis was selected for older patients (Table S1), and most prosthetic valves were biological prostheses (N = 195, 79.3%).

Ten deaths (4.1%) occurred during the follow-up period of 5.1 ± 3.0 years, including four (1.6%) cardiac deaths. The causes of late death were acute myocardial infarction (N = 2), cardiac failure, stroke, sepsis, interstitial pneumonia, and cancer (N = 1 each). The 10-year survival rate was 86.0% and the 10-year freedom from cardiac death rate was 93.8% (Figure 1A). MACCE occurred in 30 patients (12.1%). The main MACCE was stroke (N = 12, 4.8%). The 10-year freedom from MACCE rate was 79.9% and the 10-year freedom from reoperation rate was 94.6 % (Figure 1B).

After 1 year (1.3 ± 0.6 years) of followup, postoperative LVEF increased significantly from 49.7 ± 19.6% to 56.2 ± 8.9% (P < 0.0001), LVESDi decreased significantly from 28.4 ± 10.8 mm/m^2 to 19.6 ± 4.1 mm/m² (P < 0.0001), and LVMI decreased significantly from 247.5 ± 106.2 g/m² to 141.1 ± 38.3 g/m² (P < 0.0001) (Figure 2).

Patients with and without Reverse LV Remodeling at 1 year after AVR

Most patients showed functional and structural recovery post-AVR, although some failed to recover normal LV function and structure. Based on echocardiographic findings at 1 year after

AVR, we defined normal LVEF and LVESDi (postoperative LVEF ≥ 55% and LVESDi ≤ 22 mm/m²) [9] as reverse LV remodeling. We divided the patients into two groups: patients with reverse LV remodeling at 1 year after AVR (*N* = 212, RR group), and patients without reverse LV remodeling at 1 year after AVR (*N* = 34, nRR group).

The baseline and surgical characteristics of the two groups are shown in Table 1. BSA was significantly smaller and the prevalence of annuloaortic ectasia was lower in the nRR compared with the RR group. In terms of preoperative echocardiographic findings, LVESD and LVESDi were significantly higher and LVEF was significantly lower in the nRR compared with the RR group. There was no difference in AR grade, LVEDD, or LVMI between the two groups. Operation time, cardiopulmonary bypass time, and aortic cross clamp time were also similar in both groups. There were more root replacements and fewer mitral valve replacements and tricuspid valve plasties in the nRR compared with the RR group. However, the total proportion of concomitant procedures did not differ between the groups. MICS was used significantly more frequently in the RR group, but there was no significant difference in prosthesis type or valve size between the two groups.

The relationship between reverse LV remodeling and long-term outcomes was analyzed using the Cox proportional hazards model (Table 3). For the risk of cardiac mortality, age (*P* = 0.038, hazard ratio [HR] = 1.121) and reverse LV remodeling (*P* = 0.035, HR = 0.109) were significant with a univariate analysis. For the risk of MACCE, age (*P* = 0.014, HR = 1.035) and reverse LV remodeling (*P* = 0.002, HR = 0.293) were significant with a univariate analysis. Age (*P* = 0.027, HR = 1.032) and reverse LV remodeling (*P* = 0.008, HR = 0.322) were independent factors with a multivariate analysis.

Predictive Factors for Reverse LV Remodeling Post-AVR

We explored the predictive factors for reverse LV remodeling post-AVR for chronic AR by multivariate logistic regression analysis (Table 4). Preoperative LVEF (*P* = 0.007, odds ratio [OR] = 1.059) and LVESDi (*P* = 0.039, OR = 0.914) were identified as independent predictive factors for reverse LV remodeling. ROC analysis showed cut-off values were of 49% (AUC

0.78) for LVEF (Figure 3A) and 33.2 mm/m² (AUC 0.74) for LVESDi (Figure 3B). Patients with LVEF < 49% had significantly worse outcomes in terms of freedom from cardiac death than patients with LVEF ≥ 49% (Figure 4A), and patients with LVESDi > 33.2 mm/m² had significantly worse outcomes than patients with LVESDi ≤ 33.2 mm/m² (Figure 4B).

DISCUSSION

The present study demonstrated that AVR had favorable early and long-term outcomes in patients with AR, and reverse LV remodeling was observed 1 year post-AVR in most patients with AR. Favorable long-term outcomes included 10-year freedom from cardiac mortality and freedom from reoperation rates of 93.8% and 94.6%, respectively, similar to a previous study reporting mid- to long-term outcomes of AVR for severe chronic AR [10–14]. AVR is a definitive treatment for patients with AR, with the potential to achieve postoperative reverse LV remodeling and satisfactory long-term results.

Regarding reverse remodeling 1 year post-AVR, LVESDi and LVMI decreased significantly and LVEF increased significantly at 1 year after AVR compared with preoperative levels. Notably, late outcomes were significantly better in patients with, compared with those without reverse LV remodeling at 1 year after AVR, and preoperative LVEF and LVESDi were significant predictors of reverse LV remodeling 1 year post-AVR. Previous studies showed that LVEDD, LVESD, and LVMI decreased and LVEF increased after AVR [15–21]. Substantial improvements in clinical and hemodynamic statuses have been observed after successful valve replacement in most patients with severe AR [22, 23].

However, some patients fail to achieve reverse LV remodeling even after successful AVR, resulting in a poorer prognosis. Henry et al. showed that patients with LVESD ≥ 55 mm and % fractional shortening < 25% had a poor prognosis and more frequent postoperative complications [24]. Another study similarly showed that patients with a preoperative LVEF < 60% had lower survival rates up to 10 years than patients with a higher preoperative LVEF, while patients with no improvement in LV function by 1 year after surgery had a three-fold greater risk of subsequent overall death [25]. We defined an LVEF > 55% and LVESDi > 22 mm/m^2 at 1 year after AVR as reverse LV remodeling, and investigated the relationship between reverse LV remodeling and long-term outcomes. Reverse LV remodeling was an independent variable for the risk of cardiac mortality and MACCE. It is therefore important to recognize if patients have achieved reverse LV remodeling at 1 year after AVR, to predict the late outcome of each patient.

It is also clinically important to identify the factors associated with reverse LV remodeling after AVR. The current results showed that preoperative LVEF and LVESDi were significant predictors of reverse LV remodeling at 1 year after AVR, with optimal cut-off values for predicting reverse LV remodeling of 49% and 33.2 mm/m^2, respectively. When patients were divided into two groups, patients with a preoperative LVEF ≥ 49% had better late outcomes, with significantly less cardiac mortality, compared with patients with a lower LVEF. Other reports also showed that persistent LV dysfunction after AVR was a predictor of prolonged LV dysfunction before surgery [26–28]. The current recommendations [1] for treating asymptomatic patients with chronic severe AR stipulate prompt surgical repair in patients with a LVEF < 50% or LVESDi > 25 mm/m^2. Nevertheless, combined with the results of other studies, we propose that it is important to perform AVR in patients with chronic severe AR before their LVEF has declined to 50%, and an early indication for AVR can be justified by good surgical outcomes.

This study had several limitations associated with its retrospective nature. First, postoperative medication might influence LV reverse remodeling. However, we had a lot of missing data on medication. Therefore, we could not provide information about medical therapy in this study. Second, the number of patients in the nRR group was small because of the favorable outcomes of AVR for chronic AR. Third, the follow-up period was limited, and longer follow-up may have revealed prosthesis valve dysfunction that might have influenced late outcomes and cardiac function. Furthermore, patients with significant MR were included in this cohort, which potentially influenced LV reverse remodeling. However, mitral valve surgery was not identified as an independent predictive factor for reverse LV remodeling with a multivariate analysis. Therefore, in this study, we think mitral valve surgery for patients with significant MR has little effect on LV reverse remodeling.

CONCLUSIONS

AVR is a safe and effective treatment for patients with AR in terms of survival and improvements in LV function and structure, and symptoms. Reverse LV remodeling occurs in most patients, but patients without LV recovery are more likely to have a poor long-term prognosis. Earlier surgery may help to restore normal LV size and achieve better late outcomes after AVR in patients with chronic AR.

ACKNOWLEDGEMENT

We thank Susan Furness, PhD, and Emily Woodhouse, PhD, from Edanz Group (https://en-author-services.edanz.com/ac) for editing a draft of this manuscript.

FUNDING STATEMENT

This study was partially supported by the Japan Cardiovascular Research Foundation (Suita, Osaka).

CONFLICTS OF INTEREST STATEMENT

None declared.

AUTHOR CONTRIBUTIONS STATEMENT

All authors have contributed to the content of the article by designing the study; performing data collection, analysis, and interpretation; drafting and revising the manuscript; and providing approval of the final version of the manuscript. All authors agreed with submission of the manuscript in its final form.

FIGURE LEGENDS

Figure 1. Late outcomes after AVR for chronic AR

(A) Survival rate (blue line) and freedom from cardiac death rate (red line) after AVR. The 5- and 10-year survival rates were 97.6% and 86.0% and the 5- and 10-year freedom from cardiac death rates were 99.3% and 93.8%, respectively. (B) Freedom from MACCE rate (yellow line) and freedom from reoperation rate (green line) after AVR. The 5- and 10-year freedom from MACCE rates were 89.2% and 79.9%, respectively, and the 5- and 10-year freedom from reoperation rates were 97.6% and 94.6%, respectively. AR: aortic regurgitation; AVR: aortic valve replacement; MACCE: major adverse cerebral and cardiovascular events.

Figure 2. Cardiac function on echocardiography before and 1 year after AVR

(A) LVESDi, (B) LVEF, and (C) LVMI. Postoperative LVEF increased significantly and LVESDi and LVMI decreased significantly after AVR. LVESDi: left ventricular end-systolic dimension index; LVEF: left ventricular ejection fraction; LVMI: left ventricular mass index; AVR: aortic valve replacement.

Figure 3. ROC analyses of predictors for reverse LV remodeling

(A) ROC curve of preoperative LVEF as a predictor for reverse LV remodeling. (B) ROC curve of preoperative LVESDi as a predictor for reverse LV remodeling. ROC: receiver operating characteristic; LV: left ventricular; LVEF: left ventricular ejection fraction; LVESDi: left ventricular end-systolic dimension index

Figure 4. Relationship between freedom from cardiac death and predictors for reverse LV remodeling

(A) Freedom from cardiac death rates in patients with LVEF ≥ 49% (red line) and LVEF < 49% (blue line). The 5- and 10-year freedom from cardiac death rates in patients with LVEF ≥ 49% were both 100.0% and the 5- and 10-year freedom from cardiac death rates in patients with

LVEF $< 49\%$ were 98.3% and 86.0%, respectively. (B) Freedom from cardiac death rates in patients with LVESDi ≤ 33.2 mm/m^2 (red line) and > 33.2 mm/m^2 (blue line). The 5- and 10-year freedom from cardiac death rates in patients with LVESDi ≤ 33.2 mm/m^2 were both 100.0%, and the 5- and 10-year freedom from cardiac death rates in patients with LVESDi > 33.2 mm/m^2 were 96.7% and 68.7%, respectively. LV: left ventricular; LVESDi: left ventricular end-systolic dimension index; LVEF: left ventricular ejection fraction.

Table 1. Baseline characteristics and operative procedures

Characteristic	**All** (***N*** **= 246)**	**RR** (***N*** **= 212)**	**nRR** (***N*** **= 34)**	***P*** **value**
Age, years	61.6 ± 25.0	60.9 ± 24.5	66.1 ± 22.1	0.069
Male, n (%)	182 (74.0)	160 (75.5)	22 (64.7)	0.240
BSA, m^2	1.68 ± 0.59	1.69 ± 0.59	1.59 ± 0.52	0.017
NYHA class				
II, n (%)	155 (63.0)	135 (63.7)	20 (58.8)	0.114
III, n (%)	20 (8.1)	15 (7.1)	5 (15.0)	0.300
IV, n (%)	5 (2.0)	5 (2.4)	0	0.326
Hypertension, n (%)	152 (61.8)	131 (61.8)	21 (61.8)	0.941
Dyslipidemia, n (%)	81 (32.9)	68 (32.1)	13 (38.2)	0.595
Diabetes, n (%)	21 (8.5)	18 (8.5)	3 (8.8)	0.994
Chronic kidney dysfunction, n (%)	28 (11.4)	23 (10.8)	5 (14.7)	0.280
COPD, n (%)	12 (4.9)	11 (5.2)	1 (2.9)	0.515
Current smoker, n (%)	12 (4.9)	10 (4.7)	2 (5.9)	0.818
Etiology				

Annuloaortic ectasia, n (%)	34 (13.8)	33 (15.6)	1 (2.9)	0.018
Bicuspid aortic valve, n (%)	27 (11.0)	25 (11.8)	2 (5.9)	0.247
Degenerative valve, n (%)	125 (50.8)	104 (49.1)	21 (61.8)	0.122
Valve prolapse, n (%)	37 (15.0)	32 (15.1)	5 (14.7)	0.892
Rheumatic valve, n (%)	19 (7.7)	15 (7.1)	4 (11.8)	0.400
Others, n (%)	10 (4.1)	8 (3.8)	2 (5.9)	0.611
Echocardiography				
AR grade (0–4)	3.6 ± 1.3	3.6 ± 1.3	3.5 ± 1.1	0.097
MR grade (0–4)	1.2 ± 1.0	1.2 ± 0.9	1.8 ± 0.7	0.002
LVEDD, mm	65.6 ± 23.1	65.4 ± 22.6	67.3 ± 22.4	0.213
LVESD, mm	47.3 ± 17.8	46.4 ± 17.0	52.8 ± 22.4	0.005
LVESDi, mm/m²	28.4 ± 10.8	27.7 ± 10.2	33.3 ± 11.1	<0.0001
LVEF, %	49.7 ± 19.6	51.3 ± 19.4	39.6 ± 13.5	<0.0001
LVMI, g/m²	247.5 ± 106.2	245.3 ± 106.4	261.4 ± 90.2	0.229
TRPG, mmHg	25.8 ± 8.9	25.0 ± 13.5	29.5 ± 8.8	0.902
LVEF ≥ 55%, n (%)	93 (37.8)	90 (42.5)	3 (8.8)	<0.0001
LVESDi ≤ 22 mm/m², n （%）	25 (10.2)	25 (11.8)	0	<0.0001

Operative procedure				
Operation time, min	300.6 ± 148.2	299.6 ± 147.7	307.0 ± 105.3	0.238
Cardiopulmonary bypass time, min	147.6 ± 77.0	146.5 ± 75.0	154.5 ± 54.1	0.32
Aortic cross clamp time, min	101.6 ± 52.2	101.4 ± 51.1	102.6 ± 35.8	0.842
Concomitant procedure, n(%)	120 (48.8)	101 (47.6)	19 (55.9)	0.482
Root replacement, n(%)	34 (13.8)	33 (15.6)	1 (2.9)	0.018
Ascending aorta replacement, n(%)	15 (6.1)	14 (6.6)	1 (2.9)	0.344
Mitral valve replacement, n(%)	11 (4.5)	5 (2.4)	6 (17.6)	0.001
Mitral valve plasty, n(%)	34 (13.8)	27 (12.7)	7 (20.6)	0.274
Tricuspid valve plasty, n(%)	21 (8.5)	12 (5.7)	9 (26.5)	0.001
Coronary artery bypass grafting, n(%)	30 (12.2)	27 (12.7)	3 (8.8)	0.461
Maze procedure, n(%)	33 (13.4)	25 (11.8)	8 (23.5)	0.097
MICS approach, n(%)	37 (15.0)	36 (17.0)	1 (2.9)	0.011
Partial sternotomy, n(%)	23 (5.3)	23 (10.8)	0	0.091
Right minithoracotomy, n(%)	14 (5.7)	13 (6.1)	1 (2.9)	0.043
Prosthesis				
Biological prosthesis, n(%)	195 (79.3)	168 (79.2)	27 (79.4)	0.908

Mechanical prosthesis, n(%)	48 (19.5)	41 (19.3)	7 (20.6)	0.938
Homograft, n(%)	3 (1.2)	3 (1.4)	0	0.336
Valve size, mm	23.7 ± 8.2	23.8 ± 8.2	23.4 ± 7.7	0.628

Values are number of patients (percentage) or mean ± standard deviation.

BSA: body surface area; NYHA: New York Heart Association; COPD: chronic obstructive pulmonary disease; AR: aortic regurgitation; MR: mitral regurgitation; LVEDD: left ventricular end-diastolic dimension; LVESD: left ventricular end-systolic dimension; LVESDi: left ventricular end-systolic dimension index; LVEF: left ventricular ejection fraction; LVMI: left ventricular mass index; TRPG: tricuspid regurgitation pressure gradient; MICS: minimally invasive cardiac surgery

Table 2. One year outcome after AVR

1-year outcome	**All (*N* = 246)**	**RR group (*N* = 212)**	**nRR group (*N* = 34)**	***P* value**
LVEDD, mm	48.2 ± 6.1	47.1 ± 20.7	55.4 ± 18.3	<0.0001
LVESD, mm	32.8 ± 6.9	31.2 ± 14.0	42.9 ± 14.4	<0.0001
LVESDi, mm/m²	19.6 ± 4.1	19.4 ± 4.3	26.7 ± 8.9	<0.0001
LVEF, %	56.2 ± 8.9	58.4 ± 25.9	42.7 ± 14.3	<0.0001
LVMI, g/m²	141.1 ± 38.3	140.9 ± 38.8	185.8 ± 63.2	<0.0001
LVEF ≥ 55%, n (%)	160 (65.0)	160 (75.5)	0	<0.0001
LVESDi ≤ 22 mm/m², n (%)	194 (78.9)	194 (91.5)	0	<0.0001
NYHA class				
I, n(%)	233 (94.7)	202 (95.3)	31 (91.2)	0.587
II, n(%)	13 (5.3)	10 (4.7)	3 (8.8)	0.587

Values are number of patients (percentage) or mean ± standard deviation.

AR: aortic regurgitation; LVEDD: left ventricular end-diastolic dimension; LVESD: left ventricular end-systolic dimension; LVESDi: left ventricular end-systolic dimension index; LVEF: left ventricular ejection fraction; LVMI: left ventricular mass index; NYHA: New York Heart Association

Table 3. Risk of cardiac mortality and MACCEs

Variable for cardiac mortality	Univariate analysis			Multivariate analysis		
	P value	HR	95% CI	*P* value	HR	95% CI
Age, years	0.038	1.121	1.005–1.316	0.047	1.130	1.001–1.323
Valve size, mm	0.218	1.308	0.859–2.133			
Reverse remodeling	0.035	0.109	0.012–0.976	0.058	0.124	0.014–1.093

Variable for MACCEs	Univariate analysis			Multivariate analysis		
	P value	HR	95% CI	*P* value	HR	95% CI
Age, years	0.014	1.035	1.007–1.069	0.027	1.032	1.003–1.067
Male sex	0.592	1.272	0.552–3.444			
Hypertension	0.116	1.894	0.859–4.597			
Dyslipidemia	0.892	0.947	0.408–2.037			
Diabetes	0.596	1.404	0.334–4.008			
Mechanical prosthesis	0.478	0.714	0.240–1.729			
Valve size, mm	0.872	1.013	0.864–1.193			
Reverse remodeling	0.002	0.293	0.139–0.658	0.008	0.322	0.152–0.724

HR: hazard ratio; CI: confidence interval

Table 4. Predictive factors for reverse LV remodeling

Variable	Univariate analysis			Multivariate analysis		
	***P* value**	**OR**	**95% CI**	***P* value**	**OR**	**95% CI**
Age, years	0.069	0.977	0.952–1.003			
Mitral valve surgery	0.004	3.305	1.512–7.225	0.129	2.353	0.775–6.927
AR grade (0–4)	0.097	1.843	0.897–3.784			
MR grade (0–4)	0.002	0.578	0.410–0.816	0.650	0.642	0.093–4.450
LVEDD, mm	0.213	0.974	0.934–1.015			
LVESDi, mm/m²	<0.0001	0.841	0.784–0.901	0.039	0.914	0.836–0.996
LVEF, %	<0.0001	1.091	1.054–1.129	0.007	1.059	1.016–1.105
LVMI, g/m²	0.229	0.992	0.998–1.002			

OR: odds ratio; CI: confidence interval; AR: aortic regurgitation; MR: mitral regurgitation; LVEDD: left ventricular end-diastolic dimension; LVESDi: left ventricular end-systolic dimension index; LVEF: left ventricular ejection fraction; LVMI: left ventricular mass index

REFERENCES

[1] Baumgartner H, Falk V, Bax JJ, Bonis M De, Hamm C, Holm PJ, et al. 2017 ESC/EACTS Guidelines for the management of valvular heart disease. Eur Heart J France 2017;38:2739–86.

[2] Rosenhek R, Binder T, Porenta G, Lang I, Christ G, Schemper M, et al. Predictors of Outcome in Severe, Asymptomatic Aortic Stenosis. New England Journal of Medicine. 2000.

[3] Kang D-H, Park S-J, Lee S-A, Lee S, Kim D-H, Kim H-K, et al. Early Surgery or Conservative Care for Asymptomatic Aortic Stenosis. N Engl J Med 2020;382:111–9.

[4] Azevedo CF, Nigri M, Higuchi ML, Pomerantzeff PM, Spina GS, Sampaio RO, et al. Prognostic significance of myocardial fibrosis quantification by histopathology and magnetic resonance imaging in patients with severe aortic valve disease. J Am Coll Cardiol 2010;56:278–87.

[5] Villari B, Sossalla S, Ciampi Q, Petruzziello B, Turina J, Schneider J, et al. Persistent diastolic dysfunction late after valve replacement in severe aortic regurgitation. Circulation 2009;120:2386–92.

[6] Yarbrough WM, Mukherjee 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;143:656–64.

[7] Izumi C, Kitai T, Kume T, Onishi T, Yuda S, Hirata K, et al. Effect of Left Ventricular Reverse Remodeling on Long-term Outcomes After Aortic Valve Replacement. Am J Cardiol 2019;124:105–12.

[8] Zoghbi WA, Adams D, Bonow RO, Enriquez-Sarano M, Foster E, Grayburn PA, et al. Recommendations for noninvasive evaluation of native valvular regurgitation: a report from the American Society of Echocardiography developed in collaboration with the Society for Cardiovascular Magnetic Resonance. J Am Soc Echocardiogr 2017;30:303–71.

[9] Lang RM, Badano LP, Victor MA, Afilalo J, Armstrong A, Ernande L, et al. 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.e14.

[10] Sambola A, Tornos P, Ferreira-Gonzalez I, Evangelista A. Prognostic value of preoperative indexed end-systolic left ventricle diameter in the outcome after surgery in patients with chronic aortic regurgitation. Am Heart J 2008;155:1114–20.

[11] Brown ML, Schaff H V, Suri RM, Zhuo L, Sundt TM, Dearani JA, et al. Indexed Left Ventricular Dimensions Best Predict Survival After Aortic Valve Replacement in Patients

With Aortic Valve Regurgitation. Ann Thorac Surg 2009;87:1170–6.

[12] Cho SH, Byun CS, Kim KW, Chang BC, Yoo KJ, Lee S. Preoperative indexed left ventricular dimensions to predict early recovery of left ventricular function after aortic valve replacement for chronic aortic regurgitation. Circ J 2010;74:2340–5.

[13] Chaliki HP, Mohty D, Avierinos JF, Scott CG, Schaff H V., Tajik AJ, et al. Outcomes after aortic valve replacement in patients with severe aortic regurgitation and markedly reduced left ventricular function. Circulation 2002;106:2687–93.

[14] Enriquez-Sarano M, Tajik AJ. Aortic regurgitation. N Engl J Med 2004;351:1539–46.

[15] Haverich A, Wahlers TC, Borger MA, Shrestha M, Kocher AA, Walther T, et al. 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;148:2854–61.

[16] Petrov G, Dworatzek E, Schulze TM, Dandel M, Kararigas G, Mahmoodzadeh S, et al. Maladaptive remodeling is associated with impaired survival in women but not in men after aortic valve replacement. JACC Cardiovasc Imaging 2014;7:1073–80.

[17] Helder MRK, Ugur M, Bavaria JE, Kshettry VR, Groh MA, Petracek MR, et al. The effect of postoperative medical treatment on left ventricular mass regression after aortic valve

replacement. J Thorac Cardiovasc Surg 2015;149:781–6.

[18] 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;78:90–5.

[19] Bonow RO, Dodd JT, Maron BJ, O'Gara PT, White GG, McIntosh CL, et al. Long-term serial changes in left ventricular fuction and reversal of ventricular dilatation after valve replacement for chronic aortic regurgitation. Circulation 1988;78:1108–20.

[20] Amano M, Izumi C, Imamura S, Onishi N, Sakamoto J, Tamaki Y, et al. Pre- and postoperative predictors of long-term prognosis after aortic valve replacement for severe chronic aortic regurgitation. Circ J 2016;80:2460–7.

[21] Amano M, Izumi C, Imamura S, Onishi N, Tamaki Y, Enomoto S, et al. Late recurrence of left ventricular dysfunction after aortic valve replacement for severe chronic aortic regurgitation. Int J Cardiol 2016;224:240–4.

[22] Khan SS, Siegel RJ, DeRobertis MA, Blanche CE, Kass RM, Cheng W, et al. Regression of hypertrophy after Carpentier-Edwards pericardial aortic valve replacement. Ann Thorac Surg 2000;69:531–5.

[23] Lamb HJ, Beyerbacht HP, Roos A De, Laarse A Van Der, Vliegen HW, Leujes F, et al.

Left ventricular remodeling early after aortic valve replacement: Differential effects on diastolic function in aortic valve stenosis and aortic regurgitation. J Am Coll Cardiol Elsevier Masson SAS 2002;40:2182–8.

[24] Henry WL, Bonow RO, Borer JS, Ware JH, Kent KM, Redwood DR, et al. Observations on the optimum time for operative intervention for aortic regurgitation. I. Evaluation of the results of aortic valve replacement in symptomatic patients. Circulation 1980;61:471–83.

[25] Murashita T, Schaff H V, Suri RM, Daly RC, Li Z, Dearani JA, et al. Impact of Left Ventricular Systolic Function on Outcome of Correction of Chronic Severe Aortic Valve Regurgitation: Implications for Timing of Surgical Intervention. Annals of Thoracic Surgery. , 2017.

[26] Hein S, Arnon E, Kostin S, Schönburg M, Elsässer A, Polyakova V, et al. Progression from compensated hypertrophy to failure in the pressure-overloaded human: Heart structural deterioration and compensatory mechanisms. Circulation 2003;107:984–91.

[27] Carabello BA. Aortic Stenosis. In: New England Journal of Medicine N Engl J Med, 2002; pp. 677–82.

[28] Krayenbuehl HP, Hess OM, Monrad ES, Schneider J, Mall G, Turina M. Left ventricular myocardial structure in aortic valve disease before, intermediate, and late after aortic valve

replacement. Circulation 1989;79:744–55.

Abbreviations

AVR: aortic valve replacement

AR: aortic regurgitation

LVEF: left ventricular ejection fraction

LV: left ventricle

LVESDi: left ventricular end-systolic dimension index

LVEDD: left ventricular end-diastolic dimension

Central image

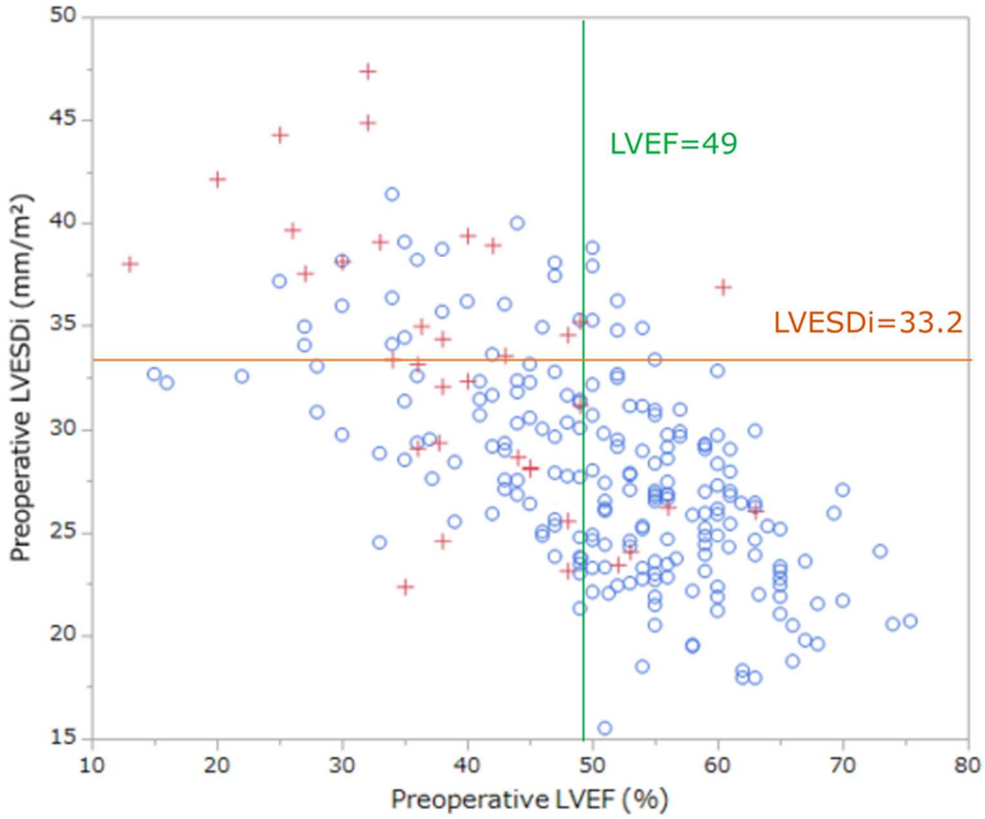


Figure 1

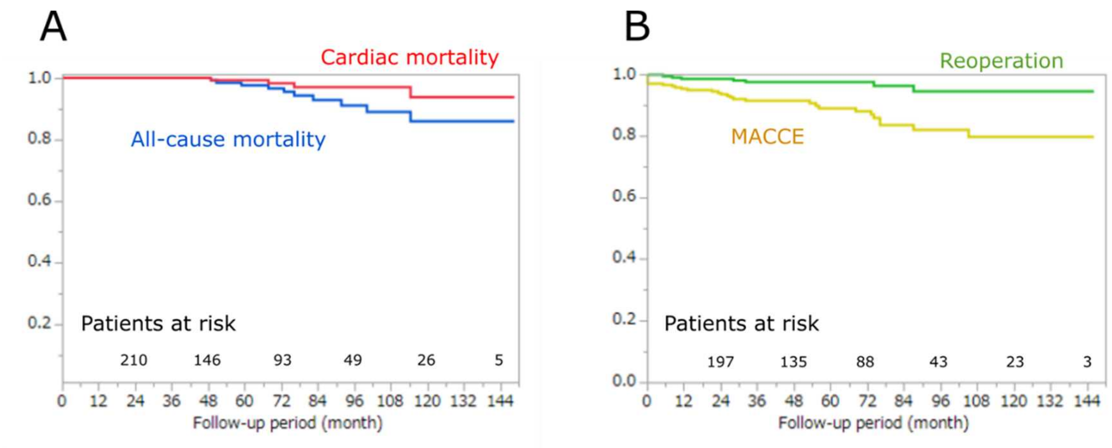


Figure 2

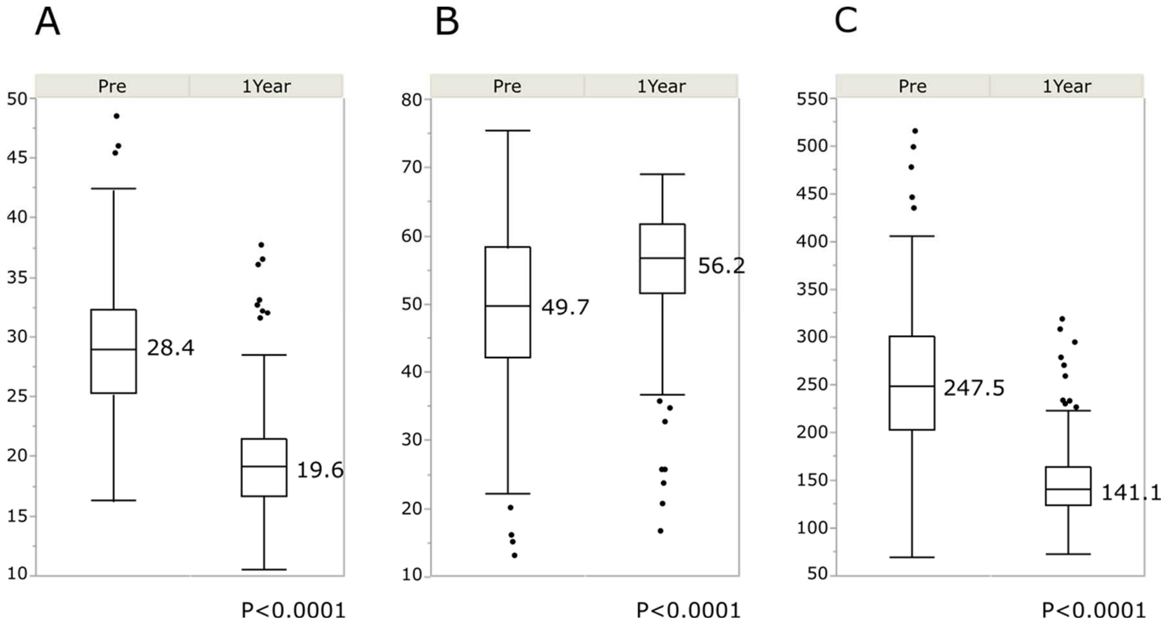


Figure 3

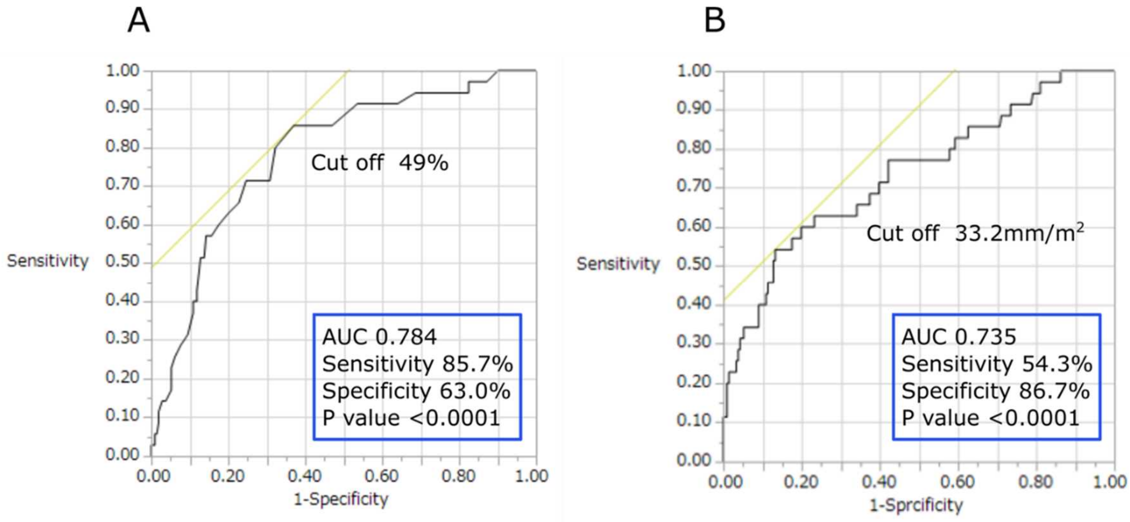
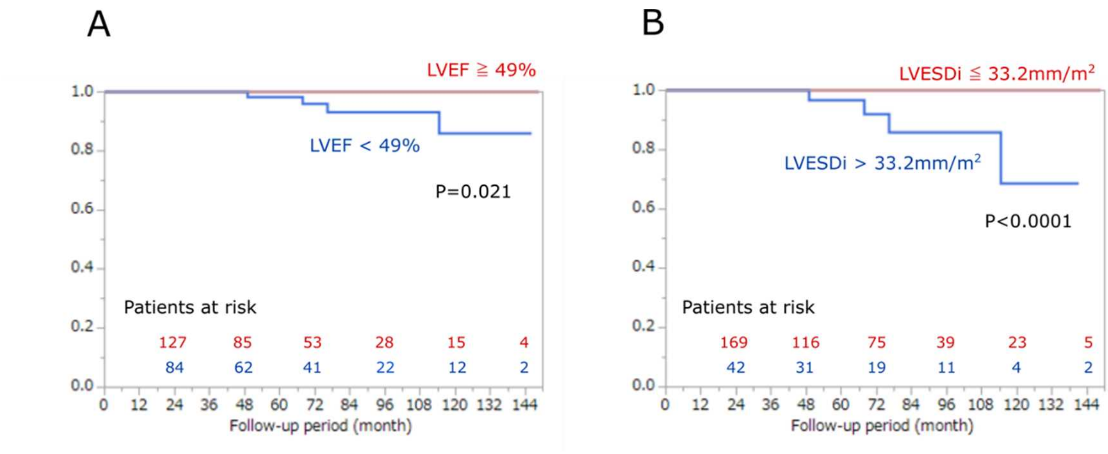


Figure 4


A
LVEF ≧ 49%
LVEF < 49%
P=0.021
Patients at risk
127 85 53 28 15 4
84 62 41 22 12 2
Follow-up period (month)
B
LVESDi ≦ 33.2mm/m2
LVESDi > 33.2mm/m2
P<0.0001
Patients at risk
169 116 75 39 23 5
42 31 19 11 4 2
Follow-up period (month)