Early mitral valve surgery for chronic severe mitral regurgitation optimizes left ventricular performance and left ventricular mass regression

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Objective: The optimal timing of mitral valve surgery for severe mitral regurgitation is controversial. We aimed to evaluate the changes in left ventricular performance using ventricular energetics and left ventricular mass regression after the surgery to determine the appropriate surgical timing in asymptomatic patients with severe mitral regurgitation.

Methods: Fifty consecutive asymptomatic or minimally symptomatic patients who electively underwent the surgery for severe mitral regurgitation were studied retrospectively. Contractility (end-systolic elastance), afterload (effective arterial elastance), and efficiency (ventriculoarterial coupling and ratio of stroke work to pressure–volume area), and left ventricular mass index were measured echocardiographically before and 1 month after surgery. Two-way repeated-measures analysis of variance was used to compare the parameters between patients with (n = 17) and without (n = 33) left ventricular dysfunction (ie, ejection fraction $\leq 60\%$ and/or end-systolic dimension ≥ 40 mm).

Results: Contractility did not change significantly ($P = .94$) but the afterload increased significantly ($P < .0001$) in both groups. Consequently, the efficiency deteriorated significantly (ventriculoarterial coupling, $P = .0004$; ratio of stroke work to pressure–volume area, $P < .0001$). Furthermore, the left ventricular mass index improved remarkably in both groups ($P < .0001$). Alternatively, the patients with normal left ventricular function had greater contractility ($P < .0001$), less worsened efficiency ($P < .0001$ and $P < .0001$, respectively), and a better left ventricular mass index ($P = .0002$) after surgery.

Conclusions: Early surgery for severe mitral regurgitation preserves left ventricular performance and improves left ventricular mass regression in asymptomatic patients with normal ventricular function. (J Thorac Cardiovasc Surg 2013;146:61-6)

Degenerative mitral regurgitation (MR) is the most frequent cause of organic mitral valve (MV) disease in Western countries and is often discovered accidentally in asymptomatic patients.¹

The optimal timing of MV surgery for MR remains controversial, because patients with chronic MR can be asymptomatic for a long period. In particular, the role of early surgery has been debated.^{2,3} Rosenhek and colleagues² reported good outcomes with a watchful strategy in which 132 asymptomatic patients with severe MR were followed up for 62 ± 26 months by echocardiographic and clinical

examinations. In contrast, the American College of Cardiology/American Heart Association guidelines recommend early surgery for asymptomatic patients with severe MR and a high probability of MV repair.³

Furthermore, although MV surgery for MR is followed by left ventricular (LV) adjustment to the new preload and afterload,^{4,5} little has been reported on the postoperative LV mechanics and LV reverse remodeling.

End-systolic elastance (Ees), effective arterial elastance (Ea), and ventriculoarterial coupling (Ea/Ees), and the stroke work to pressure–volume area (SW/PVA) ratio enable analysis of LV contractility, afterload, and efficiency, respectively.^{6,7} These parameters have been validated and used in previous basic and clinical studies of LV performance.⁸⁻¹⁵

An increased LV mass index (LVMI) is reportedly an independent factor for the development of symptoms in asymptomatic patients with severe aortic stenosis.¹⁶ Moreover, incomplete LVM regression after MV surgery for MR has been correlated with decreased LV function and the degree of preoperative tricuspid valve regurgitation.¹⁷

The assessment of the postoperative LV performance and LVM regression in asymptomatic patients should help

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Abbreviations and Acronyms

Ea	= effective arterial elastance
Ees	= end-systolic elastance
Ea/Ees	= ventriculoarterial coupling
EF	= ejection fraction
LV	= left ventricular
LVEDVI	= LV end-diastolic volume index
LVESVI	= LV end-systolic volume index
LVM	= LV mass
LVMI	= LV mass index
MR	= mitral regurgitation
MV	= mitral valve
SW/PVA	= stroke work/pressure–volume area (ratio)

elucidate the optimal timing of MV surgery for MR. Therefore, we evaluated the changes in LV performance and LVM regression after MV surgery on the basis of LV mechanics and LVMI, respectively, in asymptomatic patients with chronic severe MR.

METHODS**Study Population**

A total of 50 consecutive asymptomatic or minimally symptomatic patients who electively underwent MV surgery for chronic severe MR from January 1, 2007 to September 30, 2010 at Kyushu Medical Center were retrospectively studied. All patients had degenerative or myxomatous valve disease, and 4 patients had a remote history of endocarditis.

The inclusion criteria were (1) preoperative New York Heart Association class I or II; and (2) MR due to degenerative or myxomatous MV disease, even in the case of a remote history of endocarditis. The patients who underwent tricuspid annuloplasty, the maze procedure, or closure of atrial septal defects were not excluded. The exclusion criteria were (1) preoperative New York Heart Association class III or IV; (2) associated mitral stenosis; (3) associated aortic or tricuspid valve replacement or coronary artery bypass grafting; (4) ischemic MR, cardiomyopathy, rheumatic valve disease, or acute endocarditis; (5) LV ejection fraction (EF) ≤ 0.30 ; and (6) previous valve surgery.

Surgical Procedures

The MV surgery was performed under cardiopulmonary bypass, with aortic and bicaval cannulation and moderate hypothermia. Myocardial protection was achieved using antegrade and retrograde cardioplegia. MV repair ($n = 36$) was performed singly or in combination with the following techniques: artificial chordal reconstruction in 17, quadrangular or triangular resection in 18, commissuroplasty in 11, and an edge-to-edge technique in 13. Ring annuloplasty was performed in all the MV repair cases. The posterior leaflet and chords were preserved in the MV replacement cases ($n = 14$). Finally, 6 and 8 patients received mechanical valves and biologic prostheses, respectively.

Echocardiographic Data

The MR severity was assessed by transesophageal or transthoracic echocardiography before and approximately 1 month after the surgery. It was graded according to the published guidelines using an integrated approach that included valvular morphologic characteristics, regurgitant jet

size in the left atrium, proximal regurgitant jet width, and pulmonary venous flow pattern.¹⁸

LV mechanics. The blood pressure (BP) was measured using the Korotkoff technique and the manchetle method. The mean arterial BP was calculated as follows:

$$\text{Mean arterial BP} = (\text{systolic BP} - \text{diastolic BP})/3 + \text{diastolic BP}$$

The LV volume was calculated using the Teichholz M-mode method based on the transthoracic echocardiographic data.¹⁹ The LV end-diastolic volume index (LVEDVI) and LV end-systolic volume index (LVESVI) were calculated. Next, the EF (%) was calculated as follows:

$$\text{EF} = (1 - \text{LVESV}/\text{LVEDV}) \times 100$$

The Ees, Ea, and Ea/Ees were calculated using an approximation method on the basis of the arterial BP and volumetric data obtained by transthoracic echocardiography.⁸⁻¹⁴ The approximation of Ees and Ea was as follows:

$$\text{Ees} = \text{mean arterial BP}/\text{LVESV}$$

$$\text{Ea} = \text{systolic BP}/(\text{LVEDV} - \text{LVESV})$$

The LV volume was normalized by the body surface area. Ea/Ees⁷ and SW/PVA were calculated as indexes of LV efficiency. The SW/PVA (%) was calculated as follows²⁰:

$$\text{SW/PVA} = 1/(1 + 0.5 \text{ Ea}/\text{Ees}) \times 100$$

LVM index. The LVM (g) was calculated as follows²¹:

$$\text{LVM} = 0.80 (1.04 [\text{LVEDD} + \text{posterior wall thickness in diastole} + \text{septal wall thickness in diastole}]^3 - \text{LVEDD}^3) + 0.6$$

where LVEDD is the LV end-diastolic dimension. The obtained result was indexed for body surface area in grams per square meter.

Statistical Analysis

For analysis, the patients were grouped as follows: group A, patients with LV dysfunction (LVEF $\leq 60\%$ and/or LV end-systolic dimension [LVESD] ≥ 40 mm); and group B, patients without LV dysfunction (LVEF $> 60\%$ and LVESD < 40 mm).

The data are presented as the mean $\pm$ standard deviation. Categorical variables were compared using the unpaired *t* test and chi-square test. Two-way repeated measures analysis of variance was used to compare the LV parameters before and after surgery. It was used to clarify whether the repeated (measurement points) and nonrepeated (groups) factors were significantly different among the levels and whether the interactions between these factors were significant. The analysis was also used to determine whether the variables were significantly different between the measurement points or between the patients groups. The Student-Newman-Keuls test was used as a post hoc test. A *P* value less than .05 was considered to be statistically significant.

RESULTS**Patient Characteristics**

Perioperative and in-hospital deaths did not occur. The patients in group A had a larger left atrium ($P = .006$), LVEDD ($P < .0001$), and LVESD ($P < .0001$) and lower LVEF ($P < .0001$) than the patients in group B (Table 1). Moreover, they had a greater rate of atrial fibrillation or

TABLE 1. Baseline characteristics

Parameter	Total (n = 50)	Group A (n = 17)	Group B (n = 33)	P value (A vs B)
Age (y)	63.9 ± 12.6	62.8 ± 9.5	64.5 ± 14.1	.64
Male	35 (70)	12 (71)	23 (70)	.95
BSA (m ²)	1.6 ± 0.2	1.7 ± 0.2	1.6 ± 0.2	.14
Smoking	22 (44)	8 (47)	14 (42)	.76
Diabetes	8 (16)	3 (18)	5 (15)	.82
Hypertension	27 (54)	11 (65)	16 (48)	.28
Total cholesterol (mg/dL)	179 ± 38	185 ± 42	176 ± 37	.44
Serum creatinine (mg/dL)	0.9 ± 0.2	0.9 ± 0.3	0.9 ± 0.2	.87
ACEI or ARB	33 (66)	14 (82)	19 (58)	.08
β-blocker	18 (36)	8 (47)	10 (30)	.24
Diuretic	40 (80)	16 (94)	24 (73)	.07
Warfarin	24 (48)	11 (65)	13 (39)	.09
Antiplatelet agent	11 (22)	5 (29)	6 (18)	.37
Af or AF	17 (34)	9 (53)	8 (24)	.04
Systolic PAP (mm Hg)	40.1 ± 14.0	46.8 ± 17.2	36.1 ± 10.2	.01
LA size (mm)	50.5 ± 12.7	57.2 ± 12.0	47.1 ± 11.8	.006
LVEDD (mm)	57.9 ± 7.6	64.6 ± 1.5	54.5 ± 1.0	<.0001
LVESD (mm)	34.7 ± 1.0	43.3 ± 3.0	30.3 ± 3.5	<.0001
LVEF (%)	64.5 ± 10.5	54.7 ± 10.7	69.5 ± 5.9	<.0001
TR				.06
Absent	11 (22)	1 (6)	10 (30)	
Trivial to mild	29 (58)	10 (59)	19 (58)	
Moderate	7 (14)	5 (29)	2 (6)	
Severe	3 (6)	1 (6)	2 (6)	

Data presented as the mean ± standard deviation or number (percentages). Group A, patients with LV dysfunction; group B, patients without LV dysfunction. BSA, Body surface area; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; Af, atrial fibrillation; AF, atrial flutter; PAP, pulmonary artery pressure; LA, left atrium; LVEDD, left ventricular end-diastolic dimension; LVESD, left ventricular end-systolic dimension; LVEF, left ventricular ejection fraction; TR, tricuspid regurgitation.

flutter ($P = .04$) and greater systolic pulmonary artery BP ($P = .01$). Tricuspid annuloplasty was performed more frequently in group A than in group B ($P = .03$). However, the cardiopulmonary bypass and aortic cross-clamping times were not significantly different (Table 2). Echocardiograms at 1 month after MV repair revealed no MR in 15 patients and trivial regurgitation in 21 patients. No patient who underwent MV replacement had paravalvular leaks. The mean gradient across the MV was 2.9 ± 1.1 and 3.6 ± 0.8 mm Hg at 1 month after MV repair and MV replacement, respectively.

LV Volume and Parameters

As shown in Figure 1, the LVEDVI decreased significantly in both groups after surgery (group A, from 170.1 ± 36.0 to 123.7 ± 29.8 mL · m⁻²; group B, from 126.6 ± 26.3 to 95.1 ± 14.8 mL · m⁻²; $P < .0001$). However, group A had a significantly greater LVEDVI than group B preoperatively and postoperatively ($P < .0001$). The

TABLE 2. Surgical data

Parameter	Total (n = 50)	Group A (n = 17)	Group B (n = 33)	P value (A vs B)
Region of MV prolapse				.65
Anterior	14 (28)	4 (24)	10 (30)	
Posterior	25 (50)	8 (47)	17 (52)	
Bileaflet	11 (22)	5 (29)	6 (18)	
MV repair	36 (72)	12 (71)	24 (73)	.87
TAP	22 (44)	11 (65)	11 (33)	.03
Maze procedure	14 (28)	7 (41)	7 (21)	.14
CPB time (min)	179 ± 45	195 ± 49	171 ± 41	.08
Aortic cross-clamp time (min)	123 ± 39	135 ± 48	116 ± 33	.11

Data presented as mean ± SD or number (percentages). Group A, patients with LV dysfunction; group B, patients without LV dysfunction. MV, Mitral valve; TAP, tricuspid annuloplasty; CPB, cardiopulmonary bypass.

interaction of LVEDVI between the groups was not significant ($P = .17$).

Although the LVESVI in group A decreased (from 75.1 ± 14.0 to 65.4 ± 27.3 mL · m⁻²), it increased slightly in group B (from 38.4 ± 10.1 to 40.7 ± 9.5 mL · m⁻²). Group A had a significantly greater LVESVI than group B preoperatively and postoperatively ($P < .0001$). The interaction of LVESVI between the groups was not significant ($P = .06$).

Consequently, the LVEF deteriorated remarkably in both groups (group A, from $54.7\% \pm 10.7\%$ to $47.9\% \pm 14.4\%$; group B, from $69.5\% \pm 5.9\%$ to $57.1\% \pm 8.3\%$; $P < .0001$). Moreover, group B had a significantly greater LVEF than group A pre- and postoperatively ($P < .0001$). The interaction of LVEF between the groups was not significant ($P = .16$).

LV Performance and LVM Regression Parameters

As shown in Figure 2, the Ees did not change significantly ($P = .94$) in either group A (from 1.2 ± 0.2 to 1.4 ± 0.6 mm Hg · m² · mL⁻¹) or group B (from 2.4 ± 0.8 to 2.1 ± 0.5 mm Hg · m² · mL⁻¹). However, the difference in Ees between the groups was significant ($P < .0001$). The interaction of Ees between the groups was not significant ($P = .08$). The Ea increased dramatically and similarly in both groups after surgery (group A, from 1.4 ± 0.6 to 2.1 ± 0.7 mm Hg · m² · mL⁻¹; group B, from 1.4 ± 0.4 to 2.2 ± 0.5 mm Hg · m² · mL⁻¹; $P < .0001$). The interaction of Ea between the groups was not significant ($P = .63$).

Consequently, Ea/Ees and SW/PVA deteriorated significantly after surgery (group A, from 1.3 ± 0.8 to 1.8 ± 1.2 and $63.6\% \pm 11.1\%$ to $56.5\% \pm 13.5\%$; group B, from 0.6 ± 0.2 to 1.1 ± 0.3 and $76.6\% \pm 4.8\%$ to $65.7\% \pm 6.8\%$; $P = .0004$ and $P < .0001$, respectively). Group B had significantly superior Ea/Ees and SW/PVA before and after surgery compared with group A ($P < .0001$ and $P < .0001$, respectively). The interactions of Ea/Ees and SW/PVA between the groups were not significant ($P = .83$ and $P = .29$, respectively).

FIGURE 1. Changes in left ventricular (LV) volume and ejection fraction (EF) in the patients with (black circles, group A) and without (white circles, group B) LV dysfunction. LVEDVI, Left ventricular end-diastolic volume index; LVESVI, left ventricular end-systolic volume index. ***Before versus after surgery and ###group A versus B denote significant differences ($P < .001$).

Finally, the LVMI decreased remarkably in both groups after surgery (group A, from 179.4 ± 38.6 to 136.5 ± 37.5 $\text{g} \cdot \text{m}^{-2}$; group B, from 153.0 ± 40.5 to 105.6 ± 24.9 $\text{g} \cdot \text{m}^{-2}$; $P < .0001$; Figure 3). The difference in the LVMI between the groups was significant ($P = .0002$), but the interaction was not ($P = .76$).

DISCUSSION

The major findings from the present study were as follows: (1) LV contractility (Ees) remained unchanged, but the LV afterload (Ea) increased evenly; (2) LV efficiency (Ea/Ees and SW/PVA) deteriorated; (3) LVM reduced remarkably; and (4) early surgery preserved LV performance (greater contractility and less worsened efficiency) and improved LVM regression.

The effects of MR and subsequent MV surgery are not well understood because of the dramatic hemodynamic changes after surgery. A better understanding of the LV responses to changes in preload and afterload would help to clarify the mechanism of MR and its effect on the left ventricle. In the present study, we focused on the LV performance and LVM regression in the early postoperative phase. Suri and colleagues⁴ suggested that the early decrease in the LVEF after MV surgery is explainable by the compensatory alterations in LV volume and dimension rather than by postoperative LV dysfunction due to impaired myocardial contractility. Moreover, Ashikhmina and colleagues⁵

indicated that these changes are immediately noticeable after MV surgery for degenerative MR. Furthermore, they concluded that early LV remodeling after the surgery might be a compensatory mechanism to ensure a constant forward stroke volume.^{4,5} Our postoperative findings were similar to those of Suri and colleagues⁴; the patients had decreased LVEF and LVEDD but unchanged LVESD postoperatively, and the changes in LV dimension and LVEF in preserved LV function were superior to those with impaired LV function. Therefore, we believe that these findings were volumetric adjustments to maintain the forward stroke volume according to the preoperative LV function.

The LV performance parameters in the present study support this viewpoint. LV contractility remained unchanged, but LV afterload significantly increased after the surgery, irrespective of the LV functional status. Consequently, LV efficiency worsened. However, the patients with normal LV function had better LV contractility and efficiency than those with LV dysfunction. The effect of the deteriorated LV efficiency remains unknown. However, these findings show that early surgery should be recommended for patients with chronic severe MR and normal LV function.

Moreover, Starling²² reported that such patients with preserved LVEF have impaired LV contractility that is reversible 1 year after MV surgery. However, Starling²² also demonstrated that some patients with impaired LV contractility do not have improved contractile function and LV

FIGURE 2. Changes in left ventricular (LV) performance in patients with (black circles, group A) and without (white circles, group B) LV dysfunction. *Ees*, End-systolic elastance; *Ea*, effective arterial elastance; *Ea/Ees*, ventriculoarterial coupling; *SW/PVA*, stroke work/pressure–volume area ratio. ***Before versus after surgery and ###group A versus B denote significant differences ($P < .001$).

efficiency. Therefore, the indexes of LV contractility (*Ees*) and LV efficiency (*Ea/Ees* or *SW/PVA*) possibly predict the recovery of normal LV function.

FIGURE 3. Changes in left ventricular mass index in patients with (black circles, group A) and without (white circles, group B) LV dysfunction. ***Before versus after surgery and ###group A versus B denote significant differences ($P < .001$).

Stulak and colleagues¹⁷ reported that MV repair for leaflet prolapse performed before a decrease in the EF and development of significant secondary tricuspid regurgitation is associated with a greater likelihood of significant LVM regression after 3 years. In the present study, we found that the LVM had already regressed in the early postoperative phase. Moreover, the extent of regression was superior in the patients with normal LV function compared with those with LV dysfunction. Schuler and colleagues²³ and Zile and colleagues²⁴ observed that patients who achieved a normal LVEDD after MV replacement had a better functional result than those with persistent LV enlargement. In our study, the advantage of LVM regression in the patients with normal LV function was the associated superiority of the LV performance. At present, LV performance and LVM regression are not covered in the guidelines of MV surgery for severe MR. Despite the insufficient follow-up in our study, we believe that LV performance and LVM regression are important factors for early MV surgery.

Study Limitations

First, all data were obtained retrospectively by chart and database review, which has inherent limitations. Second, the Simpson method is more suitable than the Teichholz

method for calculating the LV volume; however, only the LV diameter values were available in our study. Third, the approximation of Ees and Ea is not as accurate as measurements obtained using a conductance catheter system, and the volume intercept could not be measured. This approximation was validated using a canine right-heart bypass, which can draw the maximum capacity of a conductance catheter system.^{8,15} Furthermore, the validation was performed only on normal canine hearts, which differ from diseased human hearts. However, we believe that the limitations of such an approximation are consistent across groups and did not detract the validity of our conclusions. Fourth, the short follow-up period (1 month after surgery) is another limitation. The LVEF, LV dimension, and LVM after the MV surgery for chronic severe MR have been found to improve and lead to recovery of normal LV function over time.^{17,25} Studies evaluating the long-term effects of earlier surgery in terms of LV mechanics are therefore required. Finally, the New York Heart Association functional classification system has inherent limitations, which might have altered the inclusion and exclusion processes. Ideally, patients should be classified according to the results of an exercise test. Unfortunately, these data were unavailable for most of our patients.

CONCLUSIONS

LV efficiency in asymptomatic or minimally symptomatic patients with chronic severe MR deteriorates because of increased LV afterload at 1 month after MV surgery. However, treated patients with normal LV function benefit from the greater LV contractility, less worsened LV efficiency, and better LVM regression. Furthermore, LVM regression occurs immediately after surgery, and the extent of LVM regression in the case of normal LV function was superior to that in the case of LV dysfunction. These data support the view that early MV surgery for chronic severe MR optimizes LV performance and LVM regression during the early postoperative period (1 month after the surgery). However, long-term evaluations of LV performance and LVM regression are needed before any definitive conclusion can be drawn.

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