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Original Article

Surgical Strategy for Ischemic Mitral Regurgitation Adopting Subvalvular and Ventricular Procedures

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Purpose: The progression of left ventricular (LV) remodeling and subsequent mitral valve tethering impair the results of reduction annuloplasty for ischemic mitral regurgitation (MR).
Methods: We studied 90 patients who underwent surgical repair of ischemic MR between 1999 and 2013 according to our surgical strategy adding submitral and ventricular procedures to annuloplasty as follows: annuloplasty alone (stage 1, n = 30), additional papillary muscle approximation (PMA) for progression of tethering (stage 2, n = 26), and additional left ventriculoplasty with PMA for progression of LV remodeling and tethering (stage 3, n = 34).
Results: The preoperative New York Heart Association (NYHA) functional classes (2.5 ± 0.7, 3.1 ± 0.7 and 3.3 ± 0.7 for stages 1, 2 and 3, respectively, P <0.001), LV end-diastolic diameters (56 ± 7 mm, 66 ± 5 mm and 70 ± 7 mm, P <0.001), and LV ejection fractions (45 ± 12%, 32 ± 9% and 27 ± 9%, P <0.001) significantly differed among the stages. In contrast, the MR grades did not significantly differ (2.9 ± 0.8, 3.0 ± 1.0, and 2.9 ± 1.1, respectively; P = 0.93). Both the rates of cardiac-related survival and freedom from reoperation were comparable among the 3 groups (log-rank P = 0.92 and 0.58, respectively).
Conclusion: Additional submitral and ventricular procedures can compensate for the possible impairment of the outcomes after annuloplasty alone for ischemic MR in patients with severe LV remodeling and tethering.

Keywords: Coronary artery disease, cardiomyopathy, mitral regurgitation, mitral valve repair

Introduction

Ischemic mitral regurgitation (MR) is a predictor of mortality in patients with ischemic heart failure,[1] and is predominantly caused by left ventricular (LV) remodeling and subsequent displacement of the papillary muscles, usually without structural valve lesions.[2] The displacement of the papillary muscles results in tethering of the mitral valve, which is associated with increased stiffness of the mitral valve leaflet and loss of the normal leaflet opening and closure.[3] Since Bolling and Bach first reported the efficacy of reduction annuloplasty,[4] this procedure has been the gold standard of surgical treatment for ischemic MR. However, previous studies reported that further progression of LV remodeling and mitral valve tethering could impair the results of reduction annuloplasty alone.[5] Therefore, we hypothesized that additional subvalvular and ventricular procedures could compensate for the possible impairment of the results of annuloplasty alone for

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Table 1 Clinical stages of ischemic mitral regurgitation and surgical procedures

	Stage 1	Stage 2	Stage 3
Severity of MV tethering and LV remodeling			
MV tethering	Not extensive (CD <10 mm and IPMD <30 mm)	Extensive (CD ≥10 mm or IPMD ≥30 mm)	Extensive (CD ≥10 mm or IPMD ≥30 mm)
LV remodeling	Small LV (LVDd <65 mm)	Small LV (LVDd <65 mm) or large LV (LVDd ≥65 mm) with a small scar or no scar	Large LV (LVDd ≥65 mm) with a large scar
Surgical procedures			
Valvular	Annuloplasty (downsized)	Annuloplasty (true-sized)	Annuloplasty (true-sized)
Subvalvular	None	PMA (transvalvular or transventricular)	PMA (transventricular)
Ventricular	None	None	Left ventriculoplasty

CD: coaptation distance; IPMD: interpapillary muscle distance; LV: left ventricle; LVDd: LV end-diastolic diameter; MV: mitral valve; PMA: papillary muscle approximation

patients with progression of LV remodeling. In this study, we assessed the results of mitral valve repair for ischemic MR that was performed according to our surgical strategy in which papillary muscle approximation (PMA) and left ventriculoplasty were added to annuloplasty according to the severity of mitral valve tethering and LV remodeling.[6]

Materials and Methods

Study Design

Our surgical strategy for ischemic MR uses 3 clinical stages that are graded according to the indications for additional subvalvular and ventricular procedures considering the severity of mitral valve tethering and LV remodeling as follows (**Table 1**):

- Stage 1 (annuloplasty alone): Additional submitral and ventricular procedures are not indicated because of mild mitral valve tethering and a relatively small LV.
- Stage 2 (annuloplasty plus PMA): PMA is indicated for extensive mitral valve tethering. Left ventriculoplasty is not indicated because of a small LV or a small (or no) scar lesion even in a large LV.
- Stage 3 (annuloplasty plus PMA and left ventriculoplasty): Both PMA and left ventriculoplasty are indicated for extensive mitral valve tethering and a large LV with a large scar lesion.

Of the 117 consecutive patients who underwent mitral valve repair for ischemic MR between 1999 and 2013, this strategy was applied for 104 (stage 1, n = 33; stage 2, n = 30; and stage 3, n = 41). After exclusion of those without follow-up data (n = 13), and one patient with a left ventricular assist device (n = 1), 90 patients were studied (stage 1, n = 30; stage 2, n = 26; and stage 3, n = 34). All data were collected retrospectively from medical records and our database. The study protocol was approved by the Hokkaido University Hospital institutional review board for clinical research.

Assessment of cardiac parameters

Echocardiography was performed within 1 week before surgery and repeated before discharge at 0.8 ± 0.6 months (range, 0.2 to 4.2 months) after surgery. After discharge, follow-up echocardiography was performed regularly on an outpatient basis. The latest echocardiographic study was performed at a mean follow-up time of 2.6 ± 2.5 years. The following cardiac parameters were acquired: LV end-diastolic diameter (LVDd), LV ejection fraction (LVEF), MR grade, coaptation distance of the mitral valve, and interpapillary muscle distance. The LVDd was measured in the parasternal long-axis view by M-mode transthoracic echocardiography. The LVEF was calculated by the modified Simpson method. The severity of MR was graded based on color Doppler images as follows: 1+, mild; 2+, moderate; 3+, moderately severe; and 4+, severe. The coaptation distance of the mitral valve was calculated by averaging values measured in 2- and 4-chamber apical views in mid-systole by B-mode transthoracic echocardiography.[5] The interpapillary muscle distance was also measured in the short axis view at the papillary muscle level in end-diastole. The coaptation distance and interpapillary muscle distance were obtained only from preoperative and postoperative echocardiography. For stage 2 and 3 patients, quantitative gated scintigraphy and magnetic resonance imaging were performed to assess the LV volume (end-systolic volume index), and the size and location of the myocardial scar lesion. The size of the scar was judged by surgeons qualitatively. LV volume assessment was done before and after surgery, but not regularly at follow-up.

Operative procedures

All the procedures were performed through a median sternotomy using standard cardiopulmonary bypass. Subsequent procedures were performed under cardiac arrest with moderate hypothermia. After declamping, we took enough time for the myocardium to recover from cardioplegic arrest with empty heart beating assisted by cardiopulmonary bypass. Therefore, longer cardiopulmonary bypass time was required than for other standard cardiac procedures. Mitral annuloplasty was performed using a semirigid (Physioring or Physioring II, Edwards Lifesciences, Irvine, California, USA) or rigid (Rigid Saddle Annuloplasty Ring, St. Jude Medical, Inc., St. Paul, Minnesota, USA) annuloplasty ring. The ring was undersized for those who underwent annuloplasty alone (stage 1) or true-sized for those who underwent annuloplasty plus PMA (stages 2 and 3). The patients with extensive mitral valve tethering (coaptation distance ≥10 mm or interpapillary muscle distance ≥30 mm) were indicated for PMA (stages 2 and 3) in which both the anterior and posterior papillary muscles were gathered using pledgetted mattress sutures of 3-0 polypropylene.[6] PMA was performed principally through an LV incision or through the mitral or aortic valve depending on whether left ventriculoplasty was concomitantly performed (stage 3) or not (stage 2), respectively. In stage 2 patients, however, a small LV incision was created if they had a small apical myocardial scar and PMA was performed through the incision followed by linear closure of it. In recent cases, the approximated papillary muscles were also suspended to the mitral annulus using 4-0 polytetrafluoroethylene sutures. The patients who had a large LV (LVDd ≥65 mm) with a large scar lesion were indicated for left ventriculoplasty (stage 3) to exclude scar lesions, reduce the LV volume, and restore the LV shape. Overlapping left ventriculoplasty[7] or partial left ventriculectomy[8] was selected for an anteroseptal or inferoposterior scar lesion, respectively. Coronary artery bypass grafting (CABG) was performed if the patient had untreated and significant coronary lesions. The Maze procedure, tricuspid annuloplasty and aortic valve replacement were performed when needed. Tricuspid annuloplasty was indicated even for mild regurgitation if the patients had severely deteriorated LV function or pulmonary hypertension. Perioperative hemodynamic instability refractory to medical control was treated with percutaneous cardiopulmonary support and intraaortic balloon pumping.

Statistical analyses

Continuous variables were expressed as mean ± standard deviation and categorical variables as numbers and percentages. Preoperative and postoperative data were compared using the Wilcoxon signed-rank test. Intergroup comparisons were conducted using the Kruskal-Wallis test for continuous data and the chi-square test or Fisher's exact test for categorical data as appropriate. Postoperative mortality and freedom from recurrence of MR were estimated using the Kaplan–Meier method, and differences among groups were assessed by the log-rank test. A two-sided P value <0.05 was considered to indicate statistical significance in all the tests. All analyses were performed using IBM SPSS Statistics (version 20, IBM Corporation, Somers, New York, USA).

Results

Patients' baseline characteristics

Table 2 shows the patients' baseline characteristics. The mean age of the study subjects was 63 ± 11 years (range, 32 to 85) and 67 (74%) were male. The baseline New York Heart Association (NYHA) functional class was III/IV for 61 (68%) patients and became more severe as the clinical stage progressed (P <0.001).

Surgical procedures

Table 3 summarizes the operative procedures. PMA was performed for stage 2 and 3 patients, of whom 9 (35%) patients in stage 2 underwent it through a small LV incision. Most stage 3 patients (85%) underwent overlapping left ventriculoplasty, though partial left ventriculectomy was performed for 5 (15%) patients. Concomitant CABG was performed for 82 (91%) patients, though 8 were not indicated for it because of previous percutaneous coronary intervention or CABG in 6, a history of vasospastic myocardial infarction in 1, and single vessel disease without viability in 1.

Changes of cardiac parameters

Table 4 summarizes preoperative, postoperative and follow-up cardiac parameters. The preoperative NYHA functional class was significantly smaller in stage 1 patients than in the others. The LV remodeling and systolic dysfunction became more severe as the clinical stage progressed with significant differences in LVDd and LVEF among stage 1, 2 and 3 patients. In contrast, the preoperative MR grade did not significantly differ among the groups. Postoperatively, the NYHA functional class,

Table 2 Patients' baseline characteristics

	Stage 1 (N = 30)	Stage 2 (N = 26)	Stage 3 (N = 34)	P values
Age, years	66 ± 10	60 ± 13	62 ± 12	0.08
Male, n (%)	17 (57%)	23 (86%)	27 (80%)	0.020
Diabetes, n (%)	14 (47%)	14 (54%)	11 (32%)	0.24
Dialysis, n (%)	3 (10%)	4 (15%)	6 (18%)	0.70
Atrial fibrillation, n (%)	7 (23%)	3 (12%)	6 (18%)	0.58
History of VT, n (%)	2 (7%)	2 (8%)	8 (24%)	0.12
Previous CABG, n (%)	4 (13%)	1 (4%)	4 (12%)	0.46
Previous PCI, n (%)	8 (27%)	5 (19%)	18 (53%)	0.015
NYHA functional class III/IV, n (%)	11 (37%)	20 (77%)	30 (88%)	<0.001
Inotropic support, n (%)	1 (4%)	5 (19%)	6 (18%)	0.24
Coronary artery lesions, n (%)				
Left main	8 (27%)	3 (12%)	5 (15%)	0.33
Left anterior descending	28 (93%)	23 (89%)	30 (88%)	0.75
Left circumflex	25 (83%)	24 (92%)	26 (77%)	0.31
Right coronary	26 (87%)	24 (92%)	28 (82%)	0.54
Medical treatment, n (%)				
Beta-blocker	5 (17%)	15 (60%)	14 (41%)	0.004
ACE inhibitor or ARB	9 (30%)	18 (72%)	18 (53%)	0.004

ACE: angiotensin-converting enzyme; ARB: angiotensin II receptor blocker; CABG: coronary artery bypass grafting; NYHA: New York Heart Association; PCI = percutaneous coronary intervention; VT: ventricular tachyarrhythmia

Table 3 Operative procedures

	Stage 1 (N = 30)	Stage 2 (N = 26)	Stage 3 (N = 34)	P values
Mitral annuloplasty	30 (100%)	26 (100%)	34 (100%)	n/a
Ring size, mm	26 ± 5	27 ± 1	27 ± 1	0.70
Papillary muscle approximation, n (%)	0	26 (100)	34 (100%)	<0.001
Papillary muscle suspension, n (%)	0	17 (65%)	17 (50%)	<0.001
Overlapping left ventriculoplasty, n (%)	0	0	29 (85%)	<0.001
Partial left ventriculectomy, n (%)	0	0	5 (15%)	0.039
CABG, n (%)	29 (97%)	25 (96%)	28 (82%)	0.11
No. of distal anastomoses	3.2 ± 1.3	3.5 ± 1.4	2.8 ± 1.8	0.32
Tricuspid annuloplasty, n (%)	8 (28%)	17 (65%)	24 (71%)	0.001
Aortic valve replacement, n (%)	2 (8%)	6 (23%)	1 (3%)	0.039
Maze, n (%)	8 (28%)	1 (4%)	4 (12%)	0.045
Cardiopulmonary bypass time, min	243 ± 62	301 ± 81	260 ± 71	0.031
Crossclamp time, min	139 ± 30	186 ± 45	152 ± 42	<0.001
Urgent operation, n (%)	1 (3%)	2 (8%)	2 (6%)	0.86
Redo surgery, n (%)	5 (17%)	1 (4%)	4 (12%)	0.31
Circulatory support, n (%)				
Preoperatively required				
IABP	1 (3%)	2 (8%)	8 (24%)	0.044
PCPS	0	0	1 (3%)	1.0
Intraoperatively required				
IABP	1 (3%)	3 (12%)	5 (15%)	0.30
PCPS	0	0	1 (3%)	1.0

CABG: coronary artery bypass grafting; IABP: intraaortic balloon pumping; PCPS: percutaneous cardiopulmonary support

LVDd and MR grade significantly decreased in all 3 groups, but LVEF improved only in stage 3 patients. The preoperative LV end-systolic volume index was extremely large in both stage 2 and 3 patients (101 ml/min^2 and 132 ml/min^2, respectively) and significantly decreased after surgery (36% and 40% decreases, respectively). At the latest follow-up, the NYHA functional class had not significantly changed in stage 1 and 2 patients, though it became worse in stage 3 patients. At that time, the NYHA functional class was class II or less in 100%, 100% and 79% of stage 1, 2 and 3 patients, respectively (P = 0.05). Although there was no significant change in

Table 4 Changes of cardiac parameters

	Stage 1 (N = 30)	Stage 2 (N = 26)	Stage 3 (N = 34)	P values
Heart failure status				
NYHA functional class				
Preoperative	2.5 ± 0.7	3.1 ± 0.7	3.3 ± 0.7	0.001
Postoperative	1.1 ± 0.4*	1.6 ± 0.9*	1.6 ± 0.8*	0.23
Follow-up	1.1 ± 0.4*	1.4 ± 0.5*	1.8 ± 0.8*§	0.028
Left ventricular parameters				
LV end-diastolic diameter, mm				
Preoperative	56 ± 7	66 ± 5	70 ± 7	<0.001
Postoperative	50 ± 5*	57 ± 6*	62 ± 8*	<0.001
Follow-up	52 ± 9*	59 ± 7*	65 ± 9*	<0.001
LV ejection fraction (%)				
Preoperative	45 ± 12	32 ± 9	27 ± 9	<0.001
Postoperative	46 ± 13	34 ± 8	36 ± 14*	0.001
Follow-up	47 ± 12	42 ± 11*§	33 ± 14*	0.005
LV end-systolic volume index (ml/m^2)				
Preoperative	–	101 ± 24	132 ± 56	0.030
Postoperative	–	67 ± 22*	74 ± 28*	0.29
Reduction rate (%)	–	36 ± 15	40 ± 15	–
Mitral valve parameters				
Mitral regurgitation grade				
Preoperative	2.9 ± 0.8	3.0 ± 1.0	2.9 ± 1.1	0.93
Postoperative	0.5 ± 0.5*	0.3 ± 0.4*	0.4 ± 0.6*	0.54
Follow-up	1.4 ± 1.1*§	1.2 ± 1.0*§	0.8 ± 0.6*§	0.11
Coaptation distance (mm)				
Preoperative	7 ± 2	9 ± 2	10 ± 4	0.006
Postoperative	7 ± 2	4 ± 2*	3 ± 3*	0.004
Interpapillary muscle distance (mm)				
Preoperative	24 ± 3	30 ± 6	31 ± 7	0.005
Postoperative	21 ± 2*	8 ± 7*	5 ± 7*	<0.001

*P <0.05 compared with baseline parameters, §P <0.05 compared with postoperative parameters

LV: left ventricle; NYHA: New York Heart Association

LVDd at the latest follow-up compared with the postoperative value, LVEF significantly improved in stage 2 patients.

The severity of mitral valve tethering (coaptation distance and interpapillary muscle distance) was significantly greater in stage 2 and 3 patients than in stage 1 patients, though the parameters were significantly improved only in stage 2 and 3 patients who underwent PMA.

Postoperative mortality

The 30-day and hospital mortality rates of the study subjects were 3% and 12%, respectively. A total of 37 patients died during a mean follow-up time of 3.4 ± 2.8 years. Cardiac-related deaths were observed for 16 patients. Non-cardiac causes of death were infection (septicemia) for 7, pulmonary disease for 6, cerebrovascular disease for 3, gastrointestinal disease for 2, multiple organ dysfunction for 1, malignancy for 1 and suicide for 1. The hospital mortality rates did not significantly differ among stage 1, 2, and 3 patients (10%, 12%, and 15%, respectively, P = 0.92). The all-cause and cardiac-related mortality rates were comparable among the 3 groups (P = 0.61 and 0.92, respectively) (**Fig. 1**). The 3-year rates of freedom from all-cause mortality were 73%, 73%, and 66% for stage 1, 2, and 3 patients, respectively. In contrast, the rates of freedom from cardiac-related mortality were 89%, 89%, and 89%, respectively.

Recurrence of MR

Recurrence of MR ≥2+ was observed in 23 (26%) patients (10, 8 and 5 patients in stages 1, 2 and 3, respectively), of whom 5 had grade 3+ or higher MR (3, 1 and 1, respectively). Two of the 5 patients had recurrence early after PMA due to dehiscence of sutures (penetration of the pledgets for 1 and infective endocarditis for 1). The remaining 3 patients had recurrence of MR ≥3+ at 18 months, 2 years and 5 years after reduction annuloplasty. Reoperation for recurrent MR was performed

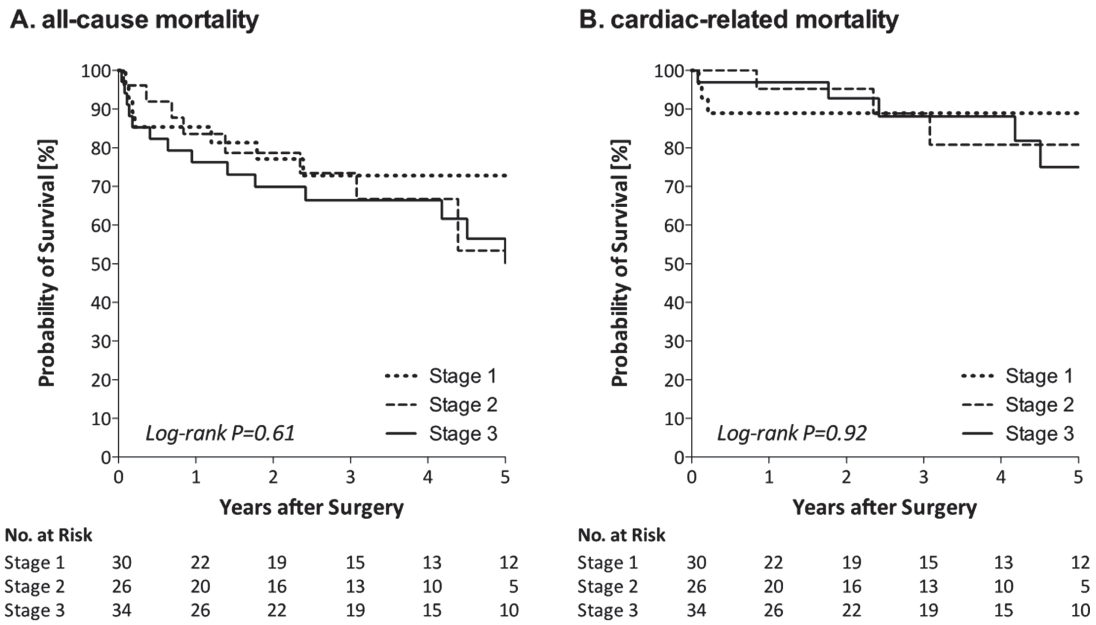

Fig. 1 Kaplan-Meier curves for patients with different clinical stages of ischemic mitral regurgitation for all-cause (**A**) and cardiac-related (**B**) mortality.

for 3 patients. The surgical procedures performed for reoperation were mitral valve replacement for 1 patient and PMA for 2. The rate of freedom from grade ≥2+ recurrence tended to be lower for stage 2 patients than for the others (P = 0.09). However, the rate of freedom from recurrence of MR ≥3+ and that from reoperation were comparable among the 3 groups (P = 0.50 and 0.58, respectively). The 3-year rates of freedom from recurrence of MR ≥3+ were 87%, 95%, and 97% for stage 1, 2, and 3 patients, respectively.

Discussion

The indication for mitral valve repair of ischemic MR remains controversial because its benefit has not been clearly proven.[9] Although reduction annuloplasty is a standard surgical procedure for ischemic MR, the application of additional or alternative surgical procedures should be considered according to the severity of the underlying ventricular disease because the severity of mitral valve tethering and LV remodeling affects the result of reduction annuloplasty.[5] However, the surgical strategy for those whose condition is unfavorable for reduction annuloplasty alone is not well established. Mitral valve replacement and chordal cutting could be candidates but their superiority to annuloplasty alone, especially for those whose LV remodeling has progressed, has not been proven.[10,11] In contrast, submitral procedures could be a preferable approach as several studies have advocated their effectiveness.[12–17]

Suspension of the papillary muscle towards the mitral annulus using papillary muscle relocation[12,13] or the RING+STRING technique[14] is an effective approach to correct tethering at the submitral level. However, this procedure cannot reduce posterior and outward tethering as much as apical tethering because the papillary muscles are retracted toward the mitral annulus. Therefore, it might be insufficient for patients with tethering that has progressed more posteriorly and outwardly such as those with a greater LV sphericity index.[18] In contrast, papillary muscle approximation is a procedure that can radically correct mitral valve tethering, especially in the outward and posterior directions, by direct repositioning of the displaced papillary muscles.[6] Various procedures based on the same concept have been presented,[15-17] with favorable results for rare recurrence of MR, LV volume reduction, and improvement of sphericity indices and LVEF.[19] Recently, we have adopted papillary muscle suspension for all patients with papillary muscle approximation to achieve balanced repositioning of the papillary muscles in the apical, posterior, and outward directions. Although we initially suspended the approximated papillary muscles to the center of the posterior mitral annulus, we changed the direction of the suspension towards the anterior annulus aiming at more effective reduction of the posterior tethering. Such relocation

of the papillary muscles can result in a reduction of leaflet tension and restoration of normal leaflet motion. Therefore, we adapt a true-sized annuloplasty ring for mitral valve repair with PMA because a downsized annuloplasty ring may not be necessary after the correction of mitral valve tethering.

The parameters indicating progression of LV remodeling also predict unsuccessful repair with reduction annuloplasty alone. Braun et al. reported that the extremely dilated LV (LVDd ≥65 mm) was associated with mortality and precluded reverse LV remodeling after mitral valve repair with CABG.[20] They also referred to the need of ventricular procedures for such patients. In our cohort, however, the possible difference in either all-cause or cardiac-related mortality between those with LVDd ≥65 mm and <65 mm was not evident (P = 0.27 and 0.37, respectively). The outcomes in group 3 patients (with left ventriculoplasty) were comparable to those in group 2 patients (without left ventriculoplasty) although the former had more severe LV remodeling. We believe that additional left ventriculoplasty can be effective for such patients in terms of improvement of postoperative LV function and survival. Indeed, only the group 3 patients had improvement of LVEF early after surgery. Because their systolic function did not continue to improve during follow-up as it did in group 2 patients, possibly due to the severity of LV remodeling, the acute surgical reverse remodeling by left ventriculoplasty may have had a great impact on the postoperative outcomes in such patients. Mandeger et al. demonstrated that left ventriculoplasty with PMA was associated with more effective control of MR and further improvement of LVEF and sphericity indices than reduction annuloplasty alone.[21] The survival benefit of left ventriculoplasty for those with ischemic heart failure is controversial because it was denied in a randomized control trial.[22] However, it is understandable that the study could not prove the benefit of left ventriculoplasty because the patients in the study had less severe LV remodeling (the LV end-systolic volume index was 83 ml/m^2), although left ventriculoplasty was suggested to be beneficial for those with a severely dilated LV (LV end-systolic volume index >100 ml/min^2).[23] In contrast, despite the comparable survival, the heart failure status in group 3 was impaired at the latest follow-up compared with the other 2 groups. This suggested the limitation of surgical repair for such patients. For those with further progression of LV remodeling, an LV assist device or heart transplantation should be considered.

Considering the results of previous reports, it is clear that the outcome of surgical repair of ischemic MR with reduction annuloplasty alone will become worse as LV remodeling progresses. Therefore, our finding that the patients with different degrees of severity of LV remodeling had comparable results for mortality, durability of repair, and freedom from reoperation, demonstrated the possibility that additional subvalvular and ventricular procedures could improve the results of mitral valve repair for those with severe LV remodeling. Though this study enrolled only a small number of patients with respect to the length of study period because of the rarity of the patients with this etiology, there was no learning curve, and no significant differences in the all-cause and cardiac-related survival rates (P = 0.78 and P = 0.75, respectively) between the patients in the early (≤2006, n = 42) and late (>2007, n = 48) era. In addition, we compared patients with different surgical procedures for different conditions of the disease. A further study comparing the procedures among patients with the same condition will be required to verify our results.

Conclusion

Additional submitral and ventricular procedures can compensate for the possible impairment of the outcomes after annuloplasty alone for ischemic MR in those with severe LV remodeling and tethering.

Disclosure Statement

There is no conflict of interest.

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