

Clinical Effect of Left Ventricular Dysfunction in Patients with Mitral Stenosis after Mitral Valve Replacement

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Background: Mitral stenosis (MS) remains one of the important heart diseases. There are many factors that influence the clinical outcomes, and little is known about how left ventricular (LV) dysfunction clinically affects the prognosis of the patient with MS after mitral valve replacement (MVR). We reviewed our clinical experiences of MVR in patients with MS who had LV dysfunction. **Methods:** Between January 1991 and January 2013, 110 patients with MS who underwent MVR were analyzed and divided into two groups according to ejection fraction (EF). Group 1 (EF≤45%) included 13 patients and group 2 (EF>45%) included 97 patients. **Results:** Thromboembolism occurred in 8 patients after MVR (group 1: n=3, 23.1%; group 2: n=5, 5.2%) and its incidence was significantly higher in group 1 than in group 2 (p=0.014). There were 3 deaths each in groups 1 and 2 during follow-up. The overall rate of cardiac-related death in group 1 was significantly higher than in group 2 (group 1: n=3, 23.1%; group 2: n=3, 3.1%; p=0.007). The cumulative survival rate at 1 and 15 years was 83.9% and 69.9% in group 1 and 97.9% and 96.3% in group 2 (p=0.004). The Cox regression analysis revealed that survival was significantly associated with postoperative stroke (p=0.011, odds ratio=10.304). **Conclusion:** This study identified postoperative stroke as an adverse prognostic factor in patients with MS after MVR, and as more prevalent in patients with LV dysfunction. Postoperative stroke should be reduced to improve clinical outcomes for patients. Preventive care should be made in multiple ways, such as management of LV dysfunction, atrial fibrillation, and anticoagulation.

Key words: 1. Mitral valve
2. Mitral valve stenosis
3. Heart failure
4. Stroke

Introduction

Mitral stenosis (MS) remains one of the major mitral valve diseases, although its incidence rate has gradually been reduced in developed countries. The main pathology of MS is a mechanical stenosis of the mitral valvular orifice. Pressure in the left atrium (LA) is chronically elevated and inappropriate pre-

load in the left ventricle (LV) is due to the stenosis between the LA and the LV. As a result, these lead to pulmonary hypertension and heart failure, both adversely influencing the clinical course of the patient [1-3]. It is generally accepted that the LV function is usually spared in patients with MS due to a relatively low preload. However, patients with MS who have LV dysfunction are frequently encountered in

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Table 1. Preoperative patient characteristics

| Characteristic | Group 1 (n=13) | Group 2 (n=97) | p-value |
|-------------------------------------|----------------|----------------|---------|
| Age (yr) | 52.6±9.9 | 51.0±9.1 | 0.564 |
| Sex (male:female) | 6:7 | 30:67 | 0.347 |
| Body surface area (m ²) | 1.55±0.21 | 1.59±0.15 | 0.448 |
| New York Heart Association class | 3.0±0.6 | 2.7±0.7 | 0.106 |
| Follow-up period (mo) | 95.0±79.0 | 97.3±74.5 | 0.920 |
| Hypertension | 0 | 9 (9.3) | 0.380 |
| Coronary artery disease | 0 | 1 (1.0) | 1.000 |
| Stroke | 2 (15.4) | 35 (36.1) | 0.212 |
| Atrial fibrillation | 13 (100.0) | 75 (77.3) | 0.055 |
| Ejection fraction (%) | 38.7±5.5 | 58.9±6.4 | 0.000 |
| Left atrium dimension (mm) | 57.8±9.9 | 54.8±9.2 | 0.301 |
| LV end systolic dimension (mm) | 47.5±6.3 | 32.8±4.9 | 0.000 |
| LV end diastolic dimension (mm) | 56.2±9.4 | 48.5±5.6 | 0.022 |

Values are presented as mean±standard deviation or number (%). LV, left ventricle.

the clinical field, and little is known about how the clinical course of the patient following mitral valve replacement (MVR) is affected. The objectives of this study were to evaluate the clinical outcomes of MVR in patients with MS who have LV dysfunction.

Methods

1) Patients

A total of 110 patients with MS underwent MVR at Dong-A University Hospital between January 1991 and January 2013. The patients' ages ranged from 25 to 67 years (mean 51.2±9.2 years). Seventy-four patients were female (67.6%) and the mean follow-up period was 76.8±62.5 months. Patients who underwent MVR with a bioprosthesis or concomitant aortic valve replacement were excluded because of advanced age and small number of cases. Based on the ejection fraction (EF), 110 patients were divided into two groups: group 1 (EF≤45%, n=13), group 2 (EF>45%, n=97). A value of EF 45% was used for the definition of LV dysfunction because the left ventricular end diastolic dimension (LVEDD) increased at this point (LVEDD >55 mm). All patients were put on anticoagulation therapy after MVR in keeping with regular monitoring of the prothrombin time-international normalized ratio (PT-INR; maintained within the range of 2.0 and 3.0). The preoperative patient characteristics are summarized in Table 1.

Table 2. Operative data

| Variable | Group 1 | Group 2 | p-value |
|---|-----------|------------|---------|
| Cardiopulmonary bypass time (min) | 94.8±24.4 | 99.1±26.3 | 0.594 |
| Aortic cross clamp time (min) | 66.0±24.8 | 71.7±23.5 | 0.432 |
| Mechanical valves (Carbomedic:OnX:TEKNA:others) | 8:3:3 | 51:10:6:30 | |
| Concomitant procedure | | | |
| Maze | 7 (53.8) | 32 (33.0) | 0.140 |
| Tricuspid annuloplasty | 4 (30.8) | 40 (41.2) | 0.469 |
| Left atrium thrombectomy | 9 (69.2) | 29 (29.9) | 0.010 |

Values are presented as mean±standard deviation or number (%).

2) Surgical technique

Standard median sternotomy was performed and cardiopulmonary bypass was established with ascending aortic cannulation and bicaval cannulation. Cold blood cardioplegia was administered for heart arrest and protection. The mitral valve was exposed through a left atriotomy in the interatrial groove and examined, and the anterior leaflet was excised with preservation of the posterior leaflet. The mechanical valve was then implanted. Concomitant procedures included a maze procedure with LA appendectomy, tricuspid annuloplasty, and LA thrombectomy (Table 2).

3) Statistical analysis

All data were analyzed with IBM SPSS ver. 21.0 (IBM Co., Armonk, NY, USA). Continuous values were expressed as mean±standard deviation and categorical values as percentages. Categorical values were compared by the chi square test and continuous values by the Student unpaired t-test. The Kaplan-Meier test was used to estimate the rates of survival and freedom from reoperation as well as from post-operative thromboembolism. The log-rank test was used to determine statistical differences between groups. Significance on late death was assessed by Cox regression analysis.

Results

The median follow-up period was 59 months (group 1, 52 months; group 2, 70 months). Both groups were similar with respect to age, New York Heart Association class, and follow-up period, but statistically different in the incidence of preoperative atrial fibrillation (AF). The male ratio was higher in group

Table 3. Echocardiographic parameters before and after the operation

| Variable | Preoperative | Postoperative | p-value |
|----------------|--------------|---------------|---------|
| Group 1 | | | |
| EF (%) | 36.8±5.7 | 50.9±14.3 | 0.011 |
| LVESD (mm) | 47.3±6.8 | 38.9±7.9 | 0.019 |
| LVEDD (mm) | 54.7±9.5 | 51.8±6.2 | 0.389 |
| LAD (mm) | 55.7±10 | 47.9±6.7 | 0.008 |
| Group 2 | | | |
| EF (%) | 58.8±5.9 | 59.8±5.7 | 0.186 |
| LVESD (mm) | 33.0±4.8 | 33.0±6.6 | 0.982 |
| LVEDD (mm) | 48.8±5.5 | 48.7±6.6 | 0.915 |
| LAD (mm) | 55.3±9.7 | 50.0±10.0 | 0.000 |

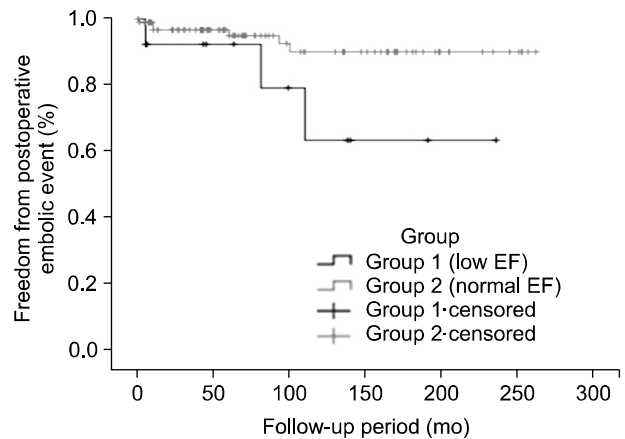
Values are presented as mean±standard deviation. EF, ejection fraction; LVESD, left ventricular end-systolic dimension; LVEDD, left ventricular end-diastolic dimension; LAD, left atrial dimension.

1 than in group 2 (Table 1).

Transthoracic echocardiography was performed in all patients preoperatively, as well as postoperatively, before discharge. All parameters except the LVEDD improved substantially in all patients in group 1 after MVR, while the parameters in group 2 were unchanged (Table 3).

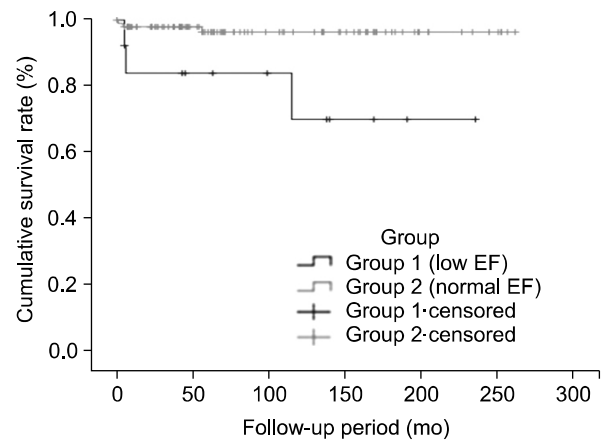
There were a total of 9 postoperative thromboembolic events in 9 patients. Each of these 9 cases developed cerebral infarction, which in one case was accompanied by a concomitant superior mesenteric artery thrombosis. Two patients in group 1 showed a low EF postoperatively (27%, 43%) and died due to cerebral infarctions. The occurrence of postoperative thromboembolic events was significantly higher in group 1 than in group 2 (3 in group 1, 23.1%; 6 in group 2, 6.2%; p=0.019). The actuarial freedom from postoperative thromboembolic events at 1, 5, and 10 years was 92%, 92%, and 63% in group 1 and 97%, 95%, and 90% in group 2; these were statistically different between the two groups (log-rank test, p=0.049) (Fig. 1).

Cardiac-related death occurred in 3 patients each in groups 1 and 2. The causes of death in group 1 were cerebral infarction in 2 patients (no maze procedure) and heart failure in 1 patient. The causes of death in group 2 were constrictive pericarditis in 1 patient, intracerebral hemorrhage in 1 patient, and subdural hematoma in 1 patient. Actuarial overall survival rate at 1, 5, and 10 years was 83.9%, 83.9%, and 69.9% in group 1 and 97.9%, 96.3%, and 96.3%



| At risk | 0 | 50 | 100 | 150 |
|---------|----|----|-----|-----|
| Group 1 | 12 | 8 | 5 | 2 |
| Group 2 | 96 | 63 | 37 | 27 |

Fig. 1. Actuarial freedom from thromboembolic events. EF, ejection fraction.



| At risk | 0 | 50 | 100 | 150 |
|---------|----|----|-----|-----|
| Group 1 | 12 | 8 | 6 | 3 |
| Group 2 | 96 | 64 | 39 | 28 |

Fig. 2. The actuarial survival rate of group 1 and group 2. EF, ejection fraction.

in group 2 with a significant difference between the two groups (log-rank test p=0.004) (Fig. 2).

To estimate the survival effect of the maze procedure, the survival rate was obtained for each group. In group 1, the actuarial overall survival rate at 1 and 10 years was 66.7% and 50.0%, respectively, in patients who did not undergo maze procedure and 100% and 100% in patients who did undergo the procedure. The survival rate in patients who underwent the maze procedure was more favorable than

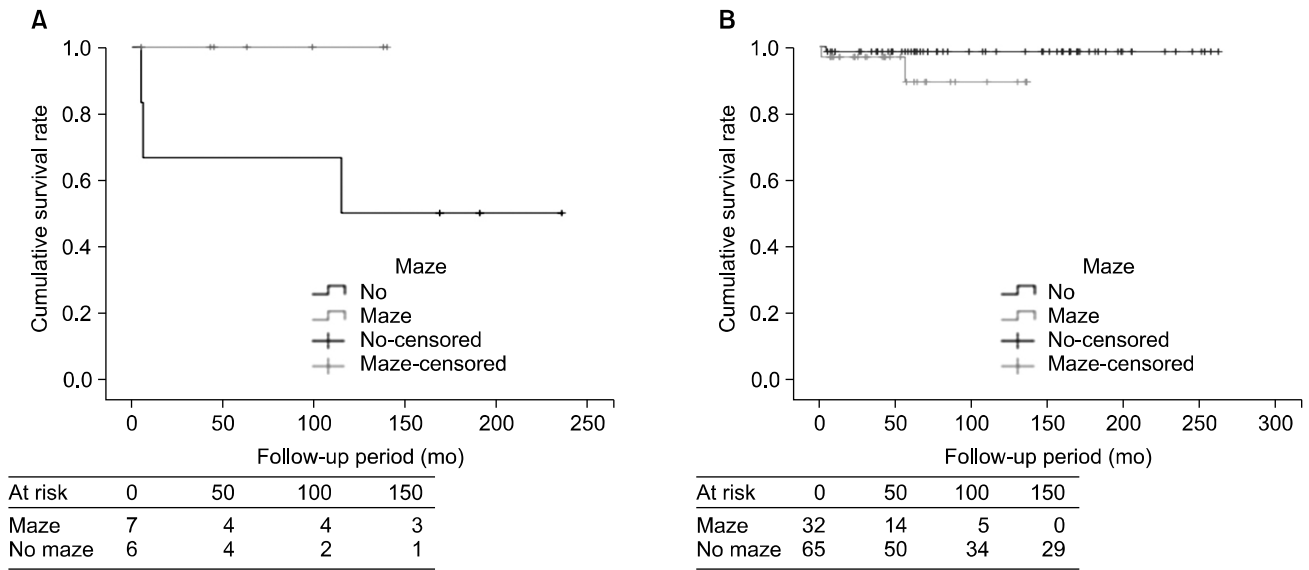


Fig. 3. Survival effect of the maze procedure for each group. (A) Survival functions in group 1. (B) Survival functions in group 2.

in patients who did not undergo the maze procedure; however, there was no statistical difference between the two groups (log-rank test $p=0.095$). In group 2, the actuarial overall survival rate at 1 and 10 years was 98.5% and 98.5% in patients who did not undergo the maze procedure and 96.9% and 89.4%, respectively, in patients who did. There was no significant survival difference between the two groups (log-rank test $p=0.144$) (Fig. 3).

To further evaluate the concomitant maze procedure, patients were divided according to that procedure, irrespective of group membership (i.e., group 1 and group 2). Excluding 22 patients who had no pre-operative AF, 39 patients underwent the maze procedure (maze procedure group) and 49 did not (no maze procedure group). Postoperative thromboembolic events developed less frequently in patients who underwent the maze procedure (maze procedure 2, 4.1%; no maze procedure 7, 7.9%; $p=0.021$).

There were 5 postoperative episodes of anticoagulation-related hemorrhage (0 in group 1, 5 in group 2). The reasons for hemorrhage were trauma in 3 patients and over-anticoagulation in 2 patient. Subdural hematomas developed in 4 patients who experienced hemorrhage. This included 2 patients (maze procedure group) who experienced syncope during follow-up care, which caused a fall and subsequent head injury that developed into a subdural hematoma.

A total of 5 patients required reoperation (1 in

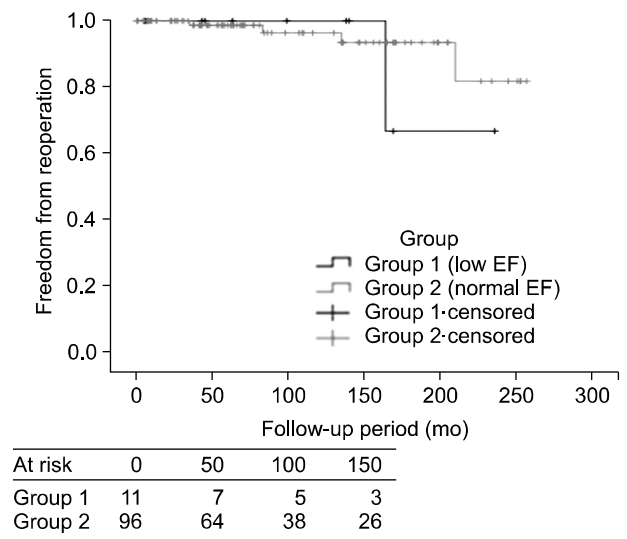


Fig. 4. Actuarial freedom from reoperation. EF, ejection fraction.

group 1, 4 in group 2). Reasons for reoperation were valve thrombosis in 2 patients and stuck valve by remnant tissue or growth in Pannus ingrowth in 3 patients. The actuarial freedom from reoperation at 1, 10, and 15 years was 100%, 100%, and 66.7% in group 1 and 100%, 96.4%, and 93.5% in group 2, respectively; there was no significant statistical difference between the two groups (log-rank test $p=0.567$) (Fig. 4).

Cox regression analyses revealed that a patient's survival was significantly associated with postopera-

tive stroke ($p=0.011$, odds ratio=10.304), but was not significantly associated with low EF, LA >60 mm, pulmonary hypertension, age >60 years, or maze operation.

Discussion

MS is one of the most common forms of heart valve disorder and a major reason for MVR. Cardiac output is usually reduced in the patients with MS not by LV myocardial dysfunction but by inappropriate preload and irregular heart rhythm, which are expected to improve after MVR. It is usually understood that LV function is spared in patients with MS due to relatively low preload, compared with mitral regurgitation. However, impaired LV function is frequently encountered in patients with MS in clinical situations; little is known about how the impaired LV function clinically affects the prognosis of the patient with MS after MVR. Rheumatic carditis and chronic low preload or reactive high afterload and enlargement of right ventricle may be the causes of impaired LV function [4-6]. In this series, the patients with LV dysfunction had a generally enlarged LV and no history of hypertension, ischemic heart disease, or right ventricular enlargement. Therefore, rheumatic carditis and primary cardiomyopathy were considered to be the most likely causes of impaired LV function.

Systemic thromboembolism is one of the major causes of death in patients with MS [3] and the incidence rate is relatively high even after MVR because AF and a large LA remain. Its development may be closely related to impaired LV function. It has been reported that heart failure and AF cooperate with each other to cause occurrence and aggravation of systemic thromboembolism [7]. AF is more prevalent in cases of heart failure, and consequently, systemic thromboembolism increases [7]. Therefore, LV dysfunction can be recognized as a risk factor of systemic thromboembolism. This report confirms that AF was more prevalent and systemic thromboembolism occurred more frequently in patients with impaired LV function after MVR than in patients without impaired LV function. AF that remained postoperatively in patients with LV dysfunction caused postoperative stroke and affected patients' survival. Even if impaired LV function is not a direct cause of postoperative thromboembolism, it

might partially influence the development of postoperative thromboembolism. Although oral anticoagulants are effective in reducing stroke risk in AF, some patients still sustain stroke despite receiving oral anticoagulant therapy. The risk factors that contribute to stroke risk in AF include old age, moderate and severe renal impairment, previous stroke, hypertension, heart failure, and diabetes mellitus (DM) [8]. Because the patients in this study had few of those risk factors, AF and LV dysfunction played a more critical role in the development of postoperative systemic thromboembolism than other risk factors. In order to prevent systemic thromboembolism, it is crucially important to manage AF. Maze operation has been reported to decrease the incidence of cerebrovascular accidents (CVA) in patients with AF [9,10]. In this study, systemic thromboembolism occurred more frequently in patients who did not undergo the maze operation than in patients who did. The maze operation plays an important role in the prevention of systemic thromboembolism after MVR. When it comes to clinical effects of survival after maze procedure, the survival rate in patients with LV dysfunction who underwent the maze procedure was better than in patients with LV dysfunction who did not undergo the maze procedure; however, the difference does not reach statistical significance because of the small study population. With these considerations, when patients with MS and AF undergo MVR, it is essential to perform a maze procedure to achieve better long-term results.

Anti-coagulation related hemorrhage is one of the most frequent valve-related complications. It usually develops within 6 months postoperatively when the PT-INR is beyond the therapeutic level; intracerebral hemorrhage is the most fatal [11]. In this series, two patients died due to intracerebral hemorrhage and subdural hematoma more than 6 months postoperatively with therapeutic levels of anticoagulation. Thus, for the prevention of subsequent hemorrhages when anticoagulants are maintained within therapeutic range, every effort should be made to prevent inadvertent traumatic injury to patients.

Redo-MVR sometimes is required and may affect clinical outcomes according to its causes. Infective endocarditis and paravalvular leakage are known as the main causes of reoperation [12-14]. In this series, however, there were no cases of redo-MVR caused

by infective endocarditis or paravalvular leakage. All redo-MVRs were performed due to valve thrombosis or stuck valve; we did not find a definite relationship between LV dysfunction and redo-MVR.

The risk factors that affect the clinical outcomes in patients who undergo MVR vary. They include age, emergency based on surgery, DM, CVA, respiratory insufficiency, infective endocarditis, anticoagulation-related hemorrhage, and heart failure [15]. In our study, we found that postoperative stroke is one of the most important risk factors and affected survival in patients with MS. Postoperative stroke occurred in patients who showed no EF improvement rather than in patients with normal LV function after MVR. To reduce risk of a postoperative stroke, the maze operation should be performed. Heart rate and symptoms should be closely monitored to avoid postoperative syncope that may provoke traumatic complications. A careful management of heart failure is also needed.

This study is a retrospective analysis with all of its associated weaknesses. A larger sample size, especially a population with more cases with impaired LV dysfunction, would be necessary for a more confirmative clinical assessment. Data of late follow-up echocardiography were not included in our study due to incomplete follow-up of the patients.

In conclusion, postoperative stroke in patients with MS was one of the poor prognostic factors after MVR and was closely associated with AF and LV dysfunction. For survival, and to gain better outcomes, it is crucially important to prevent systemic thromboembolism in patients with LV dysfunction and postoperative AF after MVR. Management of heart failure is also necessary.

Conflict of interest

No potential conflict of interest relevant to this article was reported.

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