Comparison of Outcomes of Mitral Valve Repair for Leaflet Prolapse with Advanced versus Mild/Moderate Myxomatous Degeneration

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Summary

There is limited information on long-term outcomes of mitral valve repair for mitral regurgitation (MR) caused by different degrees of myxomatous degeneration. The aim of this study was to compare the surgical results of patients with advanced and mild/moderate myxomatous mitral valve degeneration (MVD). We identified 130 patients (25 advanced and 105 mild/moderate MVD patients) who underwent mitral valve repair for MR and were pathologically diagnosed as myxomatous degeneration. Follow-up was 100% complete (mean length, 5.1 ± 1.8 years). Survival differed significantly between the advanced and mild/moderate MVD groups (76.0 ± 9.7% versus 95.0 ± 5.4% at 8 years, \( P < 0.001 \)). The univariate predictors of mortality were advanced myxomatous degeneration, recurrent MR, and early series (surgeries before 2011). The mild/moderate MVD group had higher freedom from a moderate or severe MR rate compared with the advanced MVD group (77.4 ± 4.5% versus 50.5 ± 10.2% at 7 years, \( P = 0.003 \)). Multivariable Cox analysis revealed advanced myxomatous degeneration and residual MR as independent predictors of recurrent moderate or severe MR. A total of 25 patients (19.2%) had persistent atrial fibrillation (AF) after repair. In multivariate analysis, advanced myxomatous degeneration was found to be an independent predictor of postoperative persistent AF.

In conclusion, the long-term outcomes of mitral valve repair in patients with advanced MVD are poorer than in those with mild/moderate MVD. Advanced myxomatous degeneration is an independent predictor of recurrent moderate or severe MR and postoperative persistent AF in MVD patients performing repair, which deserves more attention before and after surgery.

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Key words: Mitral regurgitation, Pathology of valve, Recurrent mitral regurgitation

Degenerative mitral valve disease is the most common cause of surgical severe mitral regurgitation (MR) in Western countries, affecting 2-3% of the general population. The major functional abnormality related to degenerative mitral valve disease is leaflet prolapse. Mitral valve repair is considered to be the preferred surgical treatment for degenerative MR. The etiology of degenerative diseases should be highlighted in mitral valve repair since it has some important surgical implications. However, few trials in the mitral valve repair literature have focused on the relationship between the etiology of degenerative diseases and outcomes after surgery.

Myxomatous degeneration is the most common cause of mitral valve prolapse (MVP). Previous studies have reported that advanced myxomatous degeneration of the mitral valve is associated with increased risk of reoperation and recurrent MR. Nevertheless, etiologic differentiations in these studies are mainly based on clinical patterns and gross appearances. There has been limited data combining pathologic analysis and surgical inspection to classify the degree of myxomatous degeneration. Little is known regarding the outcomes of advanced versus mild/moderate myxomatous mitral valve degeneration (MVD) on survival, reoperation, recurrent MR, and arrhythmia. These 2 classifications may have different outcomes, because advanced MVD is a more generalized degeneration of the valve.

The aims of the present study were to compare out-
comes of patients performing mitral valve repair for leaflet prolapse with advanced and mild/moderate myxomatous degeneration, and to determine predictors of mortality, reoperation, recurrent MR, and arrhythmia.

**Methods**

**Subjects:** From August 2008 to February 2015, mitral valve repair for mitral valve prolapse (MVP) was performed in 225 consecutive patients by the same surgeon (S.W.). Eligible patients were those who underwent isolated mitral valve repair for pure MR and were diagnosed as myxomatous degeneration by 2 experienced pathologists independently. We excluded patients with mitral stenosis; concomitant aortic valve surgery; previous cardiac surgery; connective tissue disorders; MR caused by congenital or ischemic heart disease; and pericardial or myocardial disease. Ultimately, 130 patients were identified in our work. This study was approved by the local ethics committee and conducted according to the Declaration of Helsinki. All patients provided written informed consent.

We differentiated between advanced and mild/moderate myxomatous degeneration on the basis of clinical pattern, operative inspection and pathologic analysis. Advanced myxomatous degeneration of the mitral valve was defined as (1) both leaflets were thickened (≥ 3 mm), voluminous, and aneurysmal; (2) the mitral annulus diameter in systole was 40 mm or larger; (3) the chordae tendineae were thick and obviously myxomatous; and (4) diffuse histopathologic alternations of the valve tissue. Advanced MVD was present in 25 patients (19.2%). The remaining 105 patients (80.8%) were classified as having mild/moderate MVD. Preoperative characteristics are listed in Table I. Mitral annular diameter was significantly larger in patients with advanced MVD. Patients with mild/moderate MVD were significantly older and had more posterior leaflet prolapse.

**Surgical techniques:** For repair of prolapsed leaflets, reconstructive techniques described by Carpentier and others were used. Posterior leaflet prolapse was treated with leaflet resection with or without sliding plasty, and chordal replacement with Gore-Tex and expanded polytetrafluoroethylene sutures was added as a supplementary procedure, if necessary. Anterior leaflet prolapse was preferentially corrected by artificial chordal replacement.
Figure 1. Echocardiographic, operative and pathologic photo of patients with MVP. 

A: Severe prolapse of mitral valve with severe MR was observed in 2-dimensional image during systole. B: Histologic sections of mitral valve showing myxomatous degeneration in the leaflet. C: MVP is characterized by multi-segment prolapse and excess leaflet tissue. D: Repair technique included resection, sliding plasty, and ring annuloplasty. MVP indicates mitral valve prolapse; and MR, mitral regurgitation.

Table II. Perioperative Data

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Advanced MVD (n = 25)</th>
<th>Mild/moderate MVD (n = 105)</th>
<th>p</th>
</tr>
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<tbody>
<tr>
<td>Leaflet resection</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anterior leaflet</td>
<td>1 (4%)</td>
<td>4 (4%)</td>
<td>0.663</td>
</tr>
<tr>
<td>Posterior leaflet</td>
<td>20 (80%)</td>
<td>90 (86%)</td>
<td>0.477</td>
</tr>
<tr>
<td>Chordal resection</td>
<td>7 (28%)</td>
<td>11 (10%)</td>
<td>0.023</td>
</tr>
<tr>
<td>Chordal replacement</td>
<td>12 (48%)</td>
<td>33 (31%)</td>
<td>0.118</td>
</tr>
<tr>
<td>Ring annuloplasty</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rigid, complete</td>
<td>11 (44%)</td>
<td>35 (33%)</td>
<td>0.316</td>
</tr>
<tr>
<td>Semi-rigid, complete</td>
<td>5 (20%)</td>
<td>31 (30%)</td>
<td>0.339</td>
</tr>
<tr>
<td>Flexible, complete</td>
<td>6 (24%)</td>
<td>27 (26%)</td>
<td>0.860</td>
</tr>
<tr>
<td>Flexible, partial</td>
<td>3 (12%)</td>
<td>12 (11%)</td>
<td>0.584</td>
</tr>
<tr>
<td>Other procedures</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tricuspid valve repair</td>
<td>14 (56%)</td>
<td>61 (58%)</td>
<td>0.849</td>
</tr>
<tr>
<td>Coronary artery bypass grafting</td>
<td>0 (0%)</td>
<td>13 (12%)</td>
<td>0.053</td>
</tr>
<tr>
<td>Maze procedure</td>
<td>3 (12%)</td>
<td>7 (7%)</td>
<td>0.296</td>
</tr>
<tr>
<td>Cardiopulmonary bypass pump time (minutes)</td>
<td>116.1 ± 24.4</td>
<td>115.1 ± 37.8</td>
<td>0.902</td>
</tr>
<tr>
<td>Aortic cross clamp time (minutes)</td>
<td>85.3 ± 20.0</td>
<td>83.9 ± 29.2</td>
<td>0.815</td>
</tr>
<tr>
<td>ICU length of stay (hours)</td>
<td>39.1 ± 24.1</td>
<td>43.5 ± 25.9</td>
<td>0.451</td>
</tr>
<tr>
<td>Hospital length of stay (days)</td>
<td>23.3 ± 17.1</td>
<td>19.6 ± 8.6</td>
<td>0.218</td>
</tr>
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</table>

Data are expressed as mean ± SD for continuous data or number (percent) for categorical data. MVD indicates myxomatous mitral valve degeneration; and ICU, intensive care unit.

and supplemented by triangular resection in some cases. Elongation of chordae was repaired with chordal reconstruction including chordal replacement, chordal shortening, or chordal transfer. An annuloplasty ring was used in all cases to complete the repair (Figure 1). The surgical procedures are detailed in Table II.
In addition, all patients received intraoperative transesophageal echocardiography after termination of cardiopulmonary bypass. The necessity of a second pump run for repeat repair was determined depending on the transesophageal echocardiography findings. No patient left the operating room with MR more than mild. Patients were routinely treated with anticoagulants during the first 3 months after repair. Moreover, anticoagulants would be continuously used if they had atrial fibrillation (AF) or flutter.

**Patient evaluation and follow-up:** All patients underwent preoperative echocardiography within 6 months before surgery. The degree of MR was assessed semiquantitatively and classified as none, trace, mild, moderate, and severe based on regurgitant jet length and area. All patients underwent 12-lead electrocardiograms after admission. During postoperative hospital stay, arrhythmia was documented through continuous cardiac monitoring by 5-lead telemetry. Electrocardiograms and electrocardiographic Holter monitoring were performed when necessary to confirm the diagnosis. Electrocardiograms were routinely obtained and checked daily during hospitalization after operation. Ventricular arrhythmia was defined as the presence of any of the following: premature ventricular contractions, couplets, and ventricular tachycardia.

Follow-up information was collected from clinic or telephone contact with patients by an investigator blinded to the degree of myxomatous degeneration. Echocardiograms were obtained at least every second year in most patients after discharge from our institution and others. Electrocardiograms were routinely performed and assessed at clinic. Death documentation was obtained from hospital medical records and phone conversations with family members. Cause of death was adjudicated by review of medical records. The follow-up data was obtained up to February 2017. The overall completeness of follow-up was 100%. The mean follow-up time was 5.1 ± 1.8 years (range, 1-8.5 years).

**Statistical analysis:** Comparison of normally distributed variables between groups was performed by an independent-sample t test. Non-normally distributed variables were compared by the Mann-Whitney U test. The chi-square test or Fischer exact test was used for categorically evaluated predictors of recurrent moderate or severe MR in the univariate analysis. Multivariable Cox analysis revealed advanced myxomatous degeneration, recurrent moderate or severe MR, and early series (surgical before 2011). However, the number of events was insufficient for multivariate analysis. A total of 3 patients required mitral valve reoperations: 2 for recurrent MR and 1 for endocarditis. All 3 patients survived. The mitral valve was repaired in 1 and replaced in 2 patients. Overall freedom from reoperation was 97.5 ± 1.4% at 8 years. The freedom from reoperation in the advanced MVD group was not significantly different from that in the mild/moderate MVD group (95.6 ± 4.3% versus 97.9 ± 1.4% at 8 years, P = 0.514).

**Residual MR:** All patients had received a postoperative transthoracic echocardiography before discharge. At discharge, residual MR was trace in 11.5% patients (15 of 130) and mild in 6.2% patients (8 of 130). The incidence of residual MR decreased from 34.0% (17 of 50) before 2011 to 7.5% (6 of 80) after 2011 (P < 0.001). Compared to the follow-up data, residual MR worsened in 13 patients (56.5%), stayed unchanged in 4 patients (17.4%), and improved in 6 patients (26.1%). The advanced MVD group had residual MR: 32.0% versus 14.3%, P = 0.041) than the mild/moderate MVD group.

**Recurrent MR:** During the follow-up period, 33 patients (25.4%) had developed recurrent moderate or severe MR. The freedom from moderate or severe MR was 78.9 ± 3.7% at 1 year, 73.6 ± 4.0% at 4 years, and 72.1 ± 4.2% at 8 years. Kaplan-Meier analysis revealed that the mild/moderate MVD group had higher freedom from moderate or severe MR rate compared with the advanced MVD group (77.4 ± 4.5% versus 50.5 ± 10.2% at 7 years, P = 0.003) (Figure 3). Advanced myxomatous degeneration, isolated anterior leaflet prolapse, cardiopulmonary bypass pump time, and residual MR were identified as risk factors for recurrent moderate or severe MR in the univariate analysis. Multivariable Cox analysis revealed advanced myxomatous degeneration and residual MR as independent predictors of recurrent moderate or severe MR (Table III).

**Atrial fibrillation:** AF was documented in 31 of the 130 patients (23.8%) before repair. The maze procedure was performed in 10 patients and was effective in terminating AF during the follow-up in 5 patients. Postoperative AF occurred in 44 of the 130 patients (33.8%), in which 25 patients had persistent AF. In univariate analysis, advanced myxomatous degeneration, isolated anterior leaflet prolapse, preoperative left atrial diameter, and recurrent moderate or severe MR were identified as the risk factors of persistent AF after surgery. In multivariate analysis of these risk factors, advanced myxomatous degeneration (odds ratio [OR] 6.767, 95% confidence interval [CI] 2.153 to 21.276, P = 0.001) and preoperative left atrial diameter (OR 1.119, 95% CI 1.045 to 1.198, P = 0.001)
Figure 2. Kaplan-Meier estimates of survival rate for patients with advanced or mild/moderate MVD. MVD indicates myxomatous mitral valve degeneration.

Number at risk
Mild/moderate MVD 105 105 105 97 70 51 33 22 8
Advanced MVD 25 24 23 21 17 11 6 5 2

Figure 3. Kaplan-Meier estimates of freedom from moderate or severe MR for patients with advanced or mild/moderate MVD. MVD indicates myxomatous mitral valve degeneration; and MR, mitral regurgitation.

Number at risk
Mild/moderate MVD 105 86 84 77 52 40 26 16
Advanced MVD 25 16 13 12 10 5 1 1
were found to be independent predictors of postoperative persistent AF. During the follow-up, there were no significant differences in strokes and mortality between patients with and without persistent AF after repair.

**Discussion**

The present study provides information on outcomes of patients who underwent mitral valve repair for leaflet prolapse with myxomatous degeneration. This study found, for the first time, advanced MVD patients had significantly lower survival and more persistent AF after mitral valve repair compared with mild/moderate MVD patients. In addition, the present study identified advanced myxomatous degeneration as an independent predictor of recurrent MR in MVD patients who underwent repair, as previously reported.9)

For degenerative mitral valve disease, Carpentier and associates defined the key differentiating factors between Barlow disease and fibroelastic deficiency. However, Carpentier’s group also found it difficult to differentiate them.10) Previous investigators concluded that sometimes the valve may share characteristics of both diseases.11) In later work, Eriksson and colleagues investigated the etiologic differences based on the degree of myxomatous degeneration in the valve. In addition, the histopathologic findings had been taken into consideration to analyze the prognosis in their work.12)

It is generally accepted that mitral valve repair is related with low operative mortality, excellent long-term durability, and improved survival.13) A previous study with a small number of events (n = 3) indicated similar survival between advanced and mild/moderate MVD groups. Nevertheless, the follow-up time between these 2 groups was significantly different.14) The present study with more events, which presented identical follow-up times between the groups, demonstrated lower survival in the advanced MVD group compared with the less advanced MVD group. We found that advanced myxomatous degeneration was a predictor of mortality by means of univariate analysis. In the present study, advanced myxomatous degeneration has been found to be associated with more bileaflet prolapse, multi-segmental prolapse, and chordae elongations. These findings may underlie more extensive and complex mitral valve repair. Thus, we suspect the complexity of valve lesions and repair techniques may impact the long-term outcomes. In previous studies, advanced myxomatous degeneration was identified as a predictor of recurrent MR and reoperation.15,20) Suri and colleagues demonstrated that recurrent MR following degenerative mitral valve repair was associated with adverse left ventricular remodeling and late death.21) Therefore, it is reasonable to consider that the degenerative process is progressive and is not arrested by mitral valve repair. Although the number of events in our series was too limited to draw a strong conclusion, progression of the degenerative process may influence the long-term survival. Further studies with a larger number of patients are warranted to clarify if advanced myxomatous degeneration is an independent predictor of mortality after repair and the underlying mechanisms.

The long-term freedom from moderate or severe recurrence of MR was 64.9 ± 5.6% in Flameng’s series at 10 years16) and 81 ± 2% in David’s group at 10 years.17) The freedom from moderate or severe MR in our patients was 72.1 ± 4.2% at 8 years. The incidence of residual MR was greater in the advanced MVD group than in the mild/moderate MVD group in our study. Advanced myxomatous degeneration usually involves multi-segmental prolapse and diffuse valve tissue. In this study, the higher incidence of residual MR is probably due to extensive leaflet resection and complex leaflet remodeling procedures in the advanced MVD group. In line with evidence from previous records, advanced myxomatous degeneration and residual MR were demonstrated to be related to a higher risk of recurrent MR. We suspect that the degenerative process is progressive and is not arrested by mitral valve repair. Minimizing residual MR by improving our techniques will be essential to prevent recurrent MR. Currently, there is no appropriate method to treat the progression of degenerative process. However, it is worth noting that some trials have raised the possibility that the progression could potentially be controlled by therapies that reduce the overexpression of transforming growth factor-beta (TGF-β).22) We believe that patients with advanced MVD should be differentiated before surgery and monitored with regular echocardiograms to assess valve and left ventricular function during the follow-up.

The frequency of AF occurred before repair was 23.8% in our study. This rate is in the range reported in the literature.23,24) Postoperative persistent AF did not increase the risk of thromboembolic events and mortality in our patients. This is likely because all patients in AF were treated with oral anticoagulants. David and colleagues found advanced myxomatous degeneration to be related with a higher risk of new-onset AF after surgery.25) Similarly, advanced myxomatous degeneration was an independent predictor of postoperative persistent AF in our study. This association may be mediated by recurrent MR.

### Table III. Multivariate Analysis of Risk Factors for Recurrent Moderate or Severe MR

<table>
<thead>
<tr>
<th>Variable</th>
<th>HR (95% CI)</th>
<th>P</th>
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<tbody>
<tr>
<td>Isolated anterior leaflet prolapse</td>
<td>1.591 (0.672-3.769)</td>
<td>0.291</td>
</tr>
<tr>
<td>Advanced MVD</td>
<td>2.120 (1.013-4.437)</td>
<td>0.046</td>
</tr>
<tr>
<td>Cardiopulmonary bypass pump time</td>
<td>1.008 (0.998-1.018)</td>
<td>0.101</td>
</tr>
<tr>
<td>Residual MR</td>
<td>3.376 (1.614-7.063)</td>
<td>0.001</td>
</tr>
</tbody>
</table>

HR indicates hazard ratio; CI, confidence interval; MVD, myxomatous mitral valve degeneration; and MR, mitral regurgitation.
increased hemodynamic burden, and left atrial remodeling.\textsuperscript{26,27} In addition, the abnormal biological pathways involved in MVD may play a role in promoting AF.\textsuperscript{24,28} TGF-β upregulation appears to have an important role in various signaling pathways in the pathogenesis of MVP and AF. We are measuring TGF-β value in MVP patients to explore the exact mechanisms linking advanced myxomatous degeneration and AF.

Our study could have several potential limitations to address. First, the present study included MVD patients from a single tertiary center. Surgeries were performed by a single surgeon. The results are not applicable to other forms of MR. Second, this study is subject to the limitations inherent in a retrospective study. Preoperative transesophageal echocardiograms were not routinely performed to assess displacement of the mitral annulus. Some echocardiographic data, such as left atrial volume, trans-mitral flow velocities, and proximal isovelocity surface area size was incomplete. Third, during the follow-up, echocardiograms were obtained from different institutions, and the interpretation of the results may have been inconsistent. Finally, the number of patients and duration of follow-up were limited. This might account for some non-significant factors. In summary, a multi-center, large sample size, and prospective study may be required to evaluate the long-term outcomes.

In conclusion, the long-term outcomes of mitral valve repair in patients with advanced MVD are poorer than in those with mild/moderate MVD. In addition, the present study identified advanced myxomatous degeneration as an independent predictor of recurrent moderate or severe MR and postoperative persistent AF in MVD patients performing repair. The degenerative process is progressive. Evaluation of myxomatous degeneration may influence surgical timing. In addition, it must be emphasized that advanced myxomatous degeneration requires careful evaluation before and after surgery.

Disclosures

Conflicts of interest: None.

References