Introduction

Mitral valve prolapse (MVP) is a valvular abnormality and a common cause of mitral regurgitation (MR) [1, 2]. Natural history of MVP is heterogeneous and can vary from benign with a normal life expectancy to adverse with significant morbidity or mortality [3, 4]. Although the rate of serious complications is not high, some known risk factors are defined by both clinical and echocardiographic findings [1, 3-5]. A poor prognosis is associated with MVP complicated by atrial or ventricular arrhythmias, congestive heart failure (CHF), moderate to severe MR, chordal rupture, and infective endocarditis. To date, mitral valve repair may provide long-term survival and a life expectancy for patients similar to that of the general population [6-8]. The timing of such surgery is therefore crucial for patient survival, indicating the need to predict the progression of MVP by close echocardiography follow-up studies.

The predisposing factors for severe MR include aging, male sex, severity of MR, prolapsed posterior mitral leaflet (PML), thickened mitral leaflet, and holo systolic murmur [9-14]. Site-related difference in prolapsed leaflets could also be a predictor for clinical outcome, with posterior leaflet prolapse often cited as a considerable risk for the incidence and progression of MR [12, 13, 15]. However, there is little data on the progression of mild to moderate MR, and its relationship to the site of prolapsed leaflets and prognosis of MVP patients in reference to the development of complications and cardiac events. Furthermore, the differences in the clinical outcome among distinct prolapsed seg-
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Materials and methods

We reviewed 65092 echocardiographic records of the Keio University Hospital from 1999 to 2007 and identified the patients who had mitral valve prolapse. Of these records, 3793 had mitral valve prolapse with at least mild mitral regurgitation. Prolapse of the anterior mitral leaflet (AML) was observed in 1733 cases, PML prolapse in 1378, and both AML and PML prolapse was observed in 682 cases. The number of the cases were counted from echocardiographic records and it included more than one record of the same patients who had echocardiography exams several times during follow-up period. Records also showing rheumatic heart disease, congenital heart disease, myocardial infarction, cardiomyopathy (DCM and HCM), Marfan syndrome, more than moderate aortic regurgitation, or infectious endocarditis were excluded. In addition, patients with no, trivial, or severe mitral regurgitation were excluded. From the remaining records, we identified the patients who were followed up for more than 1 year and examined echocardiography at least twice at interval of more than one year. We enrolled all of the patients of mitral valve prolapse who met all these conditions and criteria which were mentioned above. For these enrolled patients, we retrospectively examined the clinical data including sex, date of birth, medical history, ECG, medication, history of hospitalization for CHF, and previous mitral valve surgery. The ethical committee of Keio University School of Medicine approved our study protocol.

Echocardiographic studies

Two-dimensional (2D) and color Doppler echocardiography was performed using commercially available ultrasound systems. Prolapsed leaflets on 2D echocardiography was defined as a superior protrusion of the mitral leaflets into the left atrium, with an annular overshoot of leaflets > 2 mm in the long axis view [2]. Left ventricular end-diastolic diameter (LVEDD), left ventricular end-systolic diameter (LVESD), and left atrial diameter (LAD) measurements were done by M-mode echocardiography guided by 2D echocardiography [16]. Pulmonary artery systolic pressure (PASP) was estimated from the tricuspid regurgitant velocity and IVC diameter was measured to estimate right atrium (RA) pressure [17]. Repeated echocardiographic examinations were performed based on clinical judgment.

The severity of mitral regurgitation was estimated semiquantitatively by color Doppler echocardiography, with the degree of mitral regurgitation based on area. Mild MR was diagnosed by small, central jets occupying < 20% of the left atrium (LA) and moderate MR was diagnosed by central jets occupying < 40% of the LA or no existence of wall-impinging jets swirling in LA [18, 19]. Vena contracta widths were measured and severe MR was diagnosed if the width was > 7 mm [16].

Anatomical disruption to any part of the mitral apparatus results in an eccentric direction of the regurgitation jet with an orientation opposite in direction to the affected leaflet. In this study, the prolapsed mitral valve section was identified using a combination of 2D echocardiography for prolapse existence and color Doppler echocardiography for MR jet direction [20]. Carpentier’s widely recognized nomenclature describes three posterior leaflet scallops [the lateral (P1), middle (P2), and medial (P3)] and three anterior segments [the lateral (A1), central (A2), and medial (A3)] [21, 22]. The cases were then sorted into three groups: anterior mitral valve prolapse (AML), posterior mitral valve prolapse (PML), and AML & PML prolapse.

Complications and cardiac events

Events such as CHF, mitral valve surgery, echocardiographic evidence of worsening MR, and newly developed chordal ruptures were noted. New onset of atrial fibrillation (AF) by ECG was also noted as a complication. We compared changes in echocardiographic measurements such as LVEDD, LVESD, LAD, and estimated PASP during follow up among the AML prolapse, PML prolapse, and AML & PML prolapse groups.

Statistical analysis

Descriptive statistics (mean ± SD or frequency (percentage)) for the demographic and baseline characteristics were summarized by three MVP groups (AML prolapse, AML & PML prolapse and
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PML prolapse. Survival function for each clinical outcome was estimated by means of the Kaplan-Meier method and was compared between the MVP groups with the Log-rank test. Average of continuous variables was compared between groups with ANOVA model (Turkey’s adjustment). In the subgroup analysis, Fisher’s exact test was used to compare binary endpoints between groups. Data was analyzed using SPSS17.

Results

Table 1 details the baseline characteristics of the 128 patients who were followed up for more than 1 year. Of these, 59 had AML prolapse only, 47 had PML prolapse only, and 22 had both AML & PML prolapse. The mean age was 47 ± 17 years for AML prolapse, 57 ± 20 years for PML prolapse, and 61 ± 14 years for AML & PML prolapse. There was no difference in follow-up length between these three groups. (p = 0.37). The baseline echocardiographic data including LVEDD, LVESD, LAD, PASP, MR grade, and the presence of chordal rupture are also shown in Table 1.

Table 2 indicates the sites of MVP. The lateralsided leaflets in both AML and PML were less frequently prolapsed, compared with medial or central leaflets. Figure 1 shows transition of MR grade by semiquantitative analysis of color Doppler echocardiography. Of PML prolapse patients, 11 (56%) with mild MR at baseline wors-
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...ended in MR grade during follow up, compared to 4 (13%) AML prolapse patients with mild MR, and 1 (11%) AML & PML prolapse patients.

Table 3 and Figure 2 showed that average time to mitral valve surgery differed significantly among AML prolapse, PML prolapse, and AML & PML prolapse patients (AML 104.5 months, PML 88.8 months, AML & PML 83.9 months, \( P = 0.04 \)), average time to new occurrence of atrial fibrillation (AML 97 months, PML 73.4 months, AML & PML 88.8 months, \( P = 0.02 \)), echocardiographic evidence of new chordal rupture (\( P < 0.001 \)), and worsening of MR (AML 90.7 months, PML 73.9 months, AML & PML 88.9 months, \( P = 0.01 \)) also differed significantly among these three groups. Average time to admission due to CHF did not differ among these three groups.

<table>
<thead>
<tr>
<th>Baseline MR grade</th>
<th>Follow-up MR grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>AML prolapse (n=59)</td>
<td>Mild : 31</td>
</tr>
<tr>
<td></td>
<td>Moderate : 28</td>
</tr>
<tr>
<td></td>
<td>AML &amp; PML prolapse (n=22)</td>
</tr>
<tr>
<td></td>
<td>Moderate : 13</td>
</tr>
<tr>
<td>PML prolapse (n=47)</td>
<td>Mild : 16</td>
</tr>
<tr>
<td></td>
<td>Moderate : 31</td>
</tr>
</tbody>
</table>

**Table 3.** Event occurrence and mean survival time free from the event

<table>
<thead>
<tr>
<th>Event</th>
<th>AML prolapse</th>
<th>AML &amp; PML prolapse</th>
<th>PML prolapse</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>Survival, mo</td>
<td>95%CI, mo</td>
<td>Survival, mo</td>
</tr>
<tr>
<td>CHF admission</td>
<td>4</td>
<td>99.9</td>
<td>94.3-105.5</td>
</tr>
<tr>
<td>MV surgery</td>
<td>1</td>
<td>104.5</td>
<td>101.5-107.4</td>
</tr>
<tr>
<td>New AF</td>
<td>5</td>
<td>97</td>
<td>89.7-104.3</td>
</tr>
<tr>
<td>Chordal rupture</td>
<td>1</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Worsening of MR</td>
<td>11</td>
<td>90.7</td>
<td>83.6-97.8</td>
</tr>
</tbody>
</table>

Data are presented as occurrence and survival time as mean (mo, month) and 95% CI (confidence interval). In the analysis of new onset of atrial fibrillation, patients who had atrial fibrillation at baseline were excluded. In the analysis of new onset of chordal rupture, patients who had chordal rupture at baseline were excluded. AML anterior mitral leaflet, PML posterior mitral leaflet, CHF congestive heart failure, MV mitral valve, AF atrial fibrillation, MR mitral regurgitation.
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**Table 4. Comparison of mean alternation of echocardiographic measurements during follow up**

<table>
<thead>
<tr>
<th></th>
<th>AML prolapse</th>
<th>AML&amp;PML prolapse</th>
<th>PML prolapse</th>
<th>AML vs. AML&amp;PML</th>
<th>PML vs. AML</th>
<th>PML vs. AML&amp;PML</th>
</tr>
</thead>
<tbody>
<tr>
<td>ΔLVEDD, cm</td>
<td>0.07 ± 0.04</td>
<td>0.04 ± 0.06</td>
<td>0.23 ± 0.04</td>
<td>n.s</td>
<td>0.02</td>
<td>0.01</td>
</tr>
<tr>
<td>ΔLVESD, cm</td>
<td>0.06 ± 0.04</td>
<td>0.05 ± 0.06</td>
<td>0.22 ± 0.04</td>
<td>n.s</td>
<td>0.02</td>
<td>n.s</td>
</tr>
<tr>
<td>ΔLAD, cm</td>
<td>0.36 ± 0.05</td>
<td>0.05 ± 0.09</td>
<td>0.4 ± 0.07</td>
<td>0.02</td>
<td>n.s</td>
<td>0.01</td>
</tr>
<tr>
<td>ΔPASP, mmHg</td>
<td>5</td>
<td>5</td>
<td>9.4</td>
<td>n.s</td>
<td>0.01</td>
<td>n.s</td>
</tr>
</tbody>
</table>

Data are presented as mean ± SE. AML anterior mitral leaflet, PML posterior mitral leaflet, LVEDD left ventricular end-diastolic dimension, LVESD left ventricular end-systolic dimension, EF ejection fraction, LAD left atrial diameter, PASP pulmonary artery systolic pressure.

**Table 5. Subanalysis of PML prolapse**

<table>
<thead>
<tr>
<th></th>
<th>P2 (n = 30)</th>
<th>P1 or P3 (n = 16)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHF admission</td>
<td>4 (13)</td>
<td>4 (25)</td>
<td>0.32</td>
</tr>
<tr>
<td>MV surgery</td>
<td>4 (13)</td>
<td>2 (13)</td>
<td>0.93</td>
</tr>
<tr>
<td>New AF</td>
<td>6 (20)</td>
<td>7 (44)</td>
<td>0.09</td>
</tr>
<tr>
<td>Chordal rupture</td>
<td>13 (43)</td>
<td>3 (18)</td>
<td>0.09</td>
</tr>
<tr>
<td>Worsening of MR</td>
<td>12 (40)</td>
<td>6 (38)</td>
<td>0.89</td>
</tr>
</tbody>
</table>

Data are presented as occurrences (percentage). PML posterior mitral leaflet, P1: lateral scallop, P2: middle scallop, P3: medial scallop. CHF congestive heart failure, MV mitral valve, AF atrial fibrillation, MR mitral regurgitation.

**Figure 3.** Comparison of mean alternation of echocardiographic measurements during follow up. *P < 0.05 vs. AML; †P < 0.05 vs. AML; ‡P < 0.05 vs. AML & PML; AML: anterior mitral leaflet; PML: posterior mitral leaflet; LVEDD, left ventricular end-diastolic dimension; LVESD, left ventricular end-systolic dimension; EF, ejection fraction; LAD, left atrial diameter; PASP, pulmonary artery systolic pressure.

During the follow-up period, the increases in LVEDD, LVESD, and estimated PASP were significantly greater in patients with PML prolapse than in those with AML or AML & PML. (ΔLVEDD (cm); AML: + 0.07, PML: + 0.23, AML & PML: + 0.04, PML vs. AML P = 0.02, PML vs. PML & AML P = 0.01, ΔLVESD (cm); AML: + 0.06, PML: + 0.22, AML & PML: + 0.05, AML vs. PML P = 0.02, ΔLAD (cm); AML: 0.36, PML: 0.4, AML & PML: 0.05, AML vs. AML & PML P = 0.02, PML vs. AML & PML P = 0.01; Table 4 and Figure 3).

**Discussion**

This study focused on a subset of MVP patients with mild to moderate MR, since severe MR
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...itself would be a predisposing factor for poor prognosis of MVP patients [5, 9, 14]. Occurrence of complications such as AF, CHF, chordal rupture, and cardiac events including mitral valve surgery, infective endocarditis, cerebral infarction, and cardiac death were investigated, and site-related differences in clinical outcomes including progression of MR, occurrence of complications, and cardiac events were elucidated. Our data demonstrated that the complications such as CHF, mitral valve surgery, new onsets of AF and chordal rupture occurred more frequently in patients with PML prolapse compared with AML or AML & PML prolapses. Echocardiographic evidence of worsening of MR was also significantly more frequent in patients with PML prolapse. In addition, LV size, LA size, and estimated PASP were more highly increased in PML prolapses. These data indicated that the PML prolapse has a higher risk for cardiac complications and MR progression, compared with AML or AML & PML prolapses.

Kamei et al. [15] associated PML prolapse with increased risk of cardiovascular complication, although compared to our study, their study population was much younger (mean age was 28 ± 15 years in AML prolapse and 41 ± 18 years in PML prolapse). Kim et al. [13] reported in 1996 that moderate to severe MR was more frequent in patients with PML prolapse and the occurrence of complications (such as AF or CHF) was significantly greater in the prolapsed posterior leaflet than AML prolapse by univariate logistic regression analysis. In addition Fukuda et al. [12] reported in 1995 that PML prolapse was a predisposing factor for severe MR. According to the literature more broadly, the most frequent site of mitral valve prolapse is the posterior middle scallop, [1, 23, 24] and chordal rupture is most frequently associated with the middle scallop of the posterior leaflet in surgically excised valves [25, 26]. Our results were consistent with these reports and supported that PML prolapse confers a higher risk of poor outcome.

Mitral valve repair for MR due to MVP is associated with excellent long-term survival [6-8]. According to the AHA/ACC guidelines in 2006, patients with chronic severe MR with symptoms, mild to moderate LV dysfunction, and an end-systolic diameter greater than 40 mm are class I indications for MV repair [2]. Class IIa indications are asymptomatic patients with preserved LV function and new-onset of AF or pulmonary hypertension [2]. One prospective study revealed that asymptomatic patients with severe MR could be safely followed up until either symptoms occur or currently recommended cut-off values for LV size, LV function, or pulmonary hypertension are reached [27]. However, during the follow up of patients with MV prolapse, it is important to judge the best timing of surgery and not to miss the correct window. The present study indicated that MVP patients with PML prolapse should be more carefully followed up, including cases with mild MR.

Several risks are associated with serious complications. Patients with depressed left ventricular systolic function and moderate to severe MR at baseline have a higher overall mortality rate than those with normal ejection fraction and mild to moderate MR [1, 3, 5, 10]. Mild to moderate MR at baseline, AF, age older than 50 years, flail leaflet, and LA enlargement are known risk factors for cardiovascular morbidity [5].

One of the most important complication of MVP is MR, which may result from either progressive myxomatous degeneration or chordal rupture [1]. Subanalysis of PML prolapse cases in the present study revealed that new onset of chordal rupture tended to occur more frequently in P2 prolapse (43%) compared with prolapse at P1 or P3 (18%), as indicated in Table 5. In contrast, new onset of AF and admission for CHF occurred more frequently in P1 or P3 scallop prolapse, compared with P2, while there were no differences in mitral valve surgery or worsening of MR severity among locations of PML, as indicated in Table 5. Since a prolapse of P1 or P3 scallop regions would produce eccentric MR jets toward pulmonary veins, blood return from pulmonary veins to LA might be locally perturbed and direct physical stimulation of pulmonary veins by MR jets might induce pulmonary extrasystole, a common cause of atrial fibrillation, resulting in increased pressure on pulmonary veins and new onset of AF. Even though our current data did not show significant differences in occurrence of the cardiac events by P1, P2, or P3, it is possible that the direction of MR jet caused by prolapsed mitral valve leaflets could have more specific effects such as chordal rupture and AF. Both chordal rupture and AF are important indicators of clinical consequences in MVP patients, and further studies focused on site-related differences in clinical events are currently underway to predict the prognosis of MVP patients during follow up.
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Our results also showed that during the follow up, changes in LV enlargement, LA diameter, and PASP were significantly greater in the PML prolapse cases, compared with AML or AML & PML prolapses. These results are compatible with those of previous studies indicating that PML prolapse confers a poor prognosis. Therefore, precise diagnosis of the prolapsed segments in mitral leaflets might help to predict the occurrence of cardiac complications and events.

This study had some limitations. First, a retrospective study may not be suitable for risk stratification of MVP by the location of prolapsed mitral valve. Accordingly, a prospective study is underway to confirm the present data. Second, quantitative analysis by the proximal isovelocity surface area (PISA) method or pulsed Doppler quantitative flow method were not performed, because acceleration flow of regurgitant flow could not generally be detected in mild MR cases.

In conclusion, patients with PML prolapse showed worse clinical outcomes compared with AML prolapse and AML & PML prolapse patients. Precise regional evaluation of prolapsed leaflets may predict the future occurrence of cardiac complications and events.

Acknowledgments

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