Early percutaneous mitral commissurotomy vs. conventional management in asymptomatic moderate mitral stenosis

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Received 3 October 2011; revised 9 December 2011; accepted 15 December 2011; online publish-ahead-of-print 13 January 2012

Aims
The optimal timing of percutaneous mitral commissurotomy (PMC) remains controversial in asymptomatic patients with moderate mitral stenosis (MS). We sought to compare the long-term outcomes of early preemptive PMC and a conventional treatment strategy.

Methods and results
From 1997 to 2007, we prospectively enrolled 244 consecutive asymptomatic patients (191 women, age 51 ± 11 years) with moderate rheumatic MS who were potential candidates for early PMC. The treatment groups were not randomly assigned and the choice of early PMC or conventional treatment for each patient was at the discretion of the attending physician. The primary endpoint was defined as the composite of cardiovascular mortality, cerebral infarction, systemic embolic events, and PMC-related complications. In the PMC group, there were no procedure-related deaths and mitral valve area was increased from 1.26 ± 0.11 to 2.07 ± 0.28 cm² immediately after PMC ($P < 0.001$). During a median follow-up of 8.3 years, there were 3 cardiovascular deaths and 5 cerebral infarctions in the PMC group ($n = 106$) compared with 16 cardiovascular deaths, 12 cerebral infarctions, and 7 systemic embolic events in the CONV group ($n = 138$). The estimated actuarial 11-year event-free survival rate was 89 ± 4% in the PMC group and 69 ± 5% in the CONV group ($P < 0.001$) but not significantly different in those without atrial fibrillation and previous embolism (86 ± 5% in the PMC group and 79 ± 6% in the CONV group at 11 years, $P = 0.28$). For the 62 propensity score-matched pairs, the risk of cardiovascular endpoint was significantly lower in the PMC than in the CONV group (hazard ratio: 0.327; 95% CI: 0.112–0.954; $P = 0.041$).

Conclusion
In asymptomatic patients with moderate MS and favourable valve morphology, the clinical benefits of early PMC may outweigh the risks associated with early intervention, but prospective randomized trials are required to confirm the efficacy of early PMC.

Keywords
Mitral stenosis • Percutaneous mitral commissurotomy • Echocardiography • Survival

Introduction
Although percutaneous mitral commissurotomy (PMC) has been accepted as an effective treatment for symptomatic patients with moderate or severe mitral stenosis (MS), most asymptomatic patients are not candidates for PMC owing to the small but inherent procedure-related risks.1,2 Asymptomatic patients with MS show good survival rates up to 10 years, but there was a sudden deterioration precipitated by atrial fibrillation or embolism in half of the patients.3–5 Both European and American guidelines have discouraged intervention in patients with mild MS but have recommended PMC for asymptomatic selected patients with significant pulmonary hypertension, high thrombo-embolic risk,1,2 or severe MS,4 and controversies about indications for PMC exist in
asymptomatic patients with moderate MS. Although the potential benefits of early preemptive PMC in asymptomatic patients should be balanced against the real risks related to the procedure, no studies have compared early PMC and a conventional management strategy in asymptomatic patients with moderate MS. Because the success rates of PMC were improved to more than 95% in ideal patients from highly selected centers1 and early PMC may decrease the occurrence of embolism,2 we sought to examine the hypothesis that early PMC is associated with an improved clinical outcome by significantly decreasing embolic events compared with conventional treatment.

Methods

Study population
A prospective registry, commenced in 1997 and using a standard case report form, has included all consecutive patients with rheumatic MS undergoing echocardiography at our hospital. Case report forms, including patient demographics, clinical presentation, and echocardiographic data, were stored in an electronic database.8 Comorbidity was assessed using the Charlson comorbidity scale, which assigns weights to specific comorbid disease states.9 Clinical and echocardiographic follow-up data on study patients were collected annually and entered into the database. From 1997 to 2007, we enrolled 244 consecutive asymptomatic patients (191 women; mean age 51 ± 11 years) with moderate rheumatic MS, who had favourable mitral valve (MV) morphology for PMC without the presence of left atrial thrombi or moderate to severe mitral regurgitation (MR). According to the recommendations of the 2006 American College of Cardiology/American Heart Association (ACC/AHA) guidelines,1 the exclusion criteria were defined as patients with exertional dyspnea, total echocardiographic score > 10,10 bicommissural calcification,11,12 moderate to severe MR, left atrial thrombi, moderate to severe aortic stenosis and aortic regurgitation, left ventricular ejection fraction (LVEF) < 50%, Doppler-estimated pulmonary artery systolic pressure (PAP) > 50 mmHg at rest or > 60 mmHg with exercise, and those who were not candidates for early PMC based on age > 70 years or the presence of coexisting malignancies. Patients with new onset of atrial fibrillation were also excluded and referred for PMC, but four asymptomatic patients with paroxysmal atrial fibrillation were included. In patients with non-specific symptoms, symptom-limited treadmill exercise test and exercise Doppler echocardiography were selectively performed to evaluate their symptoms.

The treatment groups were not randomly assigned and the choice of early PMC or conventional treatment for each patient was at the discretion of the attending physician, who explained the potential benefits of early PMC and procedural risks in detail and considered the preferences of individual patients most importantly. Whereas a conventional strategy was chosen for 138 patients (CONV group), early elective PMC was performed on 106 patients (PMC group) within 3 months of initial echocardiographic evaluation. Patients with atrial fibrillation or prior embolic events were effectively anticoagulated with warfarin. Informed consent was obtained from each patient and the study protocol was approved by the ethics committee of our institution.

Percutaneous mitral commissurotomy
Percutaneous mitral commissurotomy was performed by experienced interventional cardiologists using the Inoue balloon technique as described previously.10 During the procedure, conventional haemodynamic parameters were monitored. A successful immediate result was defined as a mitral valve area (MVA) > 1.5 cm² without the development of significant MR, such as moderate to severe MR or non-commisural MR related to leaflet laceration and significant subvalvular damage.13

Echocardiographic evaluation
Echocardiographic evaluation was performed at baseline and immediately after PMC. All patients underwent two-dimensional echocardiography and Doppler colour flow imaging using a Hewlett-Packard Sonos 2500 or 5500 imaging system equipped with a 2.5 MHz transducer (Hewlett-Packard, Andover, MA). The dimensions of the left ventricle (LV) and left atrium (LA) were measured from parasternal M-mode acquisitions. Morphologic features of the MV were categorized as described previously.14 and total echocardiographic score was obtained by adding the scores for leaflet mobility, thickness, calcification, and subvalvular lesions. The MVA was measured by direct planimetry of the mitral orifice, and MS severity was graded as mild, moderate, or severe when MVA was > 1.5, 1.0–1.5, or < 1.0 cm², respectively.1 The severity of mitral and tricuspid regurgitation was assessed semiquantitatively or using quantitative methods and classified as mild, moderate, or severe.16 Pulmonary artery systolic pressure was estimated by continuous wave Doppler with the simplified Bernoulli equation \[ 4 \times (\text{peak velocity of tricuspid regurgitation})^2 \].16 Transosseophageal echocardiography was performed to detect left atrial thrombi in all patients of the PMC group and in 74 (54%) patients of the CONV group (P < 0.001). In the CONV group, 80% of patients with atrial fibrillation and 41% of those in sinus rhythm underwent transosseophageal echocardiography. No left atrial thrombi were observed in both groups. Diverse spontaneous echo contrast was observed in 2 (2.5%) of 80 patients with sinus rhythm and in 13 (50%) of 26 patients with atrial fibrillation in the PMC group, and in none of 38 patients with sinus rhythm and 14 (39%) of 36 patients with atrial fibrillation in the CONV group, respectively. Echocardiographic follow-up evaluation was performed annually and completed for 213 (87%) patients with a median follow-up of 5.0 years (interquartile range 2.4–9.2 years). Echocardiographic restenosis was defined as a recurrence of moderate MS (MVA ≤ 1.5 cm²) after PMC.

Follow-up and endpoints
All study patients regularly visited their attending physicians at 3 month interval for maintenance of anticoagulation therapy or every year for annual re-evaluation. Patients in the CONV group who became symptomatic during follow-up were referred for PMC or MV surgery. Data were collected until December 2010, during annual visits to the echocardiography laboratory and by detailed annual review of all medical records or telephone interviews. Deaths were classified as cardiovascular or non-cardiovascular on the basis of medical records. For the eight (3%) patients lost to follow-up, data on vital status, dates, and causes of death were obtained from the Korean National Registry of Vital Statistics. The primary endpoint of the study was defined as the composite of cardiovascular mortality, cerebral infarction, systemic embolic events that occurred during follow-up and PMC-related complications; procedural mortality and urgent MV surgery. Diagnosis of embolic event was based on clinical symptoms, signs, and computerized tomography scans. A specific diagnosis of cerebral infarction was confirmed by an experienced neurologist and additional brain magnetic resonance imaging was performed if indicated.
Statistical analysis
Categorical variables are presented as numbers and percentages and were compared by the use of the chi-square test and Fisher’s exact test. Continuous variables are expressed as mean ± SD and were compared using Student’s unpaired and paired t-test or the Mann–Whitney U test, as appropriate. Analysis of clinical endpoint was performed on an intention-to-treat basis and two cardiac deaths and one cerebral infarction that occurred after MV replacement were counted in endpoints. Event-free survival curves were constructed with Kaplan–Meier estimates and compared by the use of the log-rank test. For the Kaplan–Meier analysis, we analysed all clinical events by time to first event. To reduce the effect of treatment selection bias and potential confounding in this observational study, we performed rigorous adjustment for the differences in baseline characteristics using propensity score matching.17 The propensity scores were estimated without regard to outcome variables, using multiple logistic regression analysis. All prespecified covariates were included in the full non-parsimonious models for treatment with early PMC vs. conventional strategy (Table 1). The discrimination and calibration ability of the propensity score model was assessed by means of the C-statistic and the Hosmer–Lemeshow statistic. To develop the propensity score-matched pairs without replacement (a 1:1 match), the Greedy 5→1 digit match algorithm was used as described previously.18 After propensity score matching, the baseline covariates were compared between the two groups with the paired t-test or the Wilcoxon signed-rank test for continuous variables, and the McNemar test or marginal homogeneity test for categorical variables (Supplementary material online, Table S2). In the propensity score-matched cohort, the risks of clinical endpoints were compared using Cox regression models with robust standard errors that accounted for the clustering of matched pairs. To compare hazard rates of outcomes between the PMC and CONV groups, weighted Cox proportional hazards regression models were also constructed using the inverse probability of treatment-weighted (IPTW) method,19 with weights for patients receiving early PMC being the inverse of (1 – propensity score) and weights for patients receiving CONV treatment being the inverse of propensity score. All reported P-values were two-sided, and a P < 0.05 was considered statistically significant. SAS software, version 9.1 (SAS institute, Inc, Cary, NC), was used for statistical analyses.

<table>
<thead>
<tr>
<th>Table 1 Baseline characteristics of patients (percutaneous mitral commissurotomty group) who underwent early elective percutaneous mitral commissurotomty and those (CONV group) who underwent conventional treatment strategy</th>
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<tr>
<td><strong>PMG group</strong></td>
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<tr>
<td>(n = 106)</td>
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<tr>
<td>Age (years)</td>
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<tr>
<td>Gender (female)</td>
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<tr>
<td>Body surface area (m²)</td>
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<tr>
<td>Smoking</td>
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<td>Diabetes</td>
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<td>Hypertension</td>
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<td>Atrial fibrillation</td>
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<td>Paroxysmal</td>
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<td>Permanent/persistent</td>
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<td>Previous embolism</td>
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<td>Cholesterol (mg/dL)</td>
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<tr>
<td>Comorbidity index</td>
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<td>LA dimension (mm)</td>
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<tr>
<td>LVEF (%)</td>
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<tr>
<td>MVA (cm²)</td>
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<tr>
<td>Planimetry</td>
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<tr>
<td>Pressure halftime method</td>
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<tr>
<td>Mean mitral gradient (mmHg)</td>
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<tr>
<td>Tricuspid regurgitation ≥ moderate</td>
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<tr>
<td>PAP (mmHg)</td>
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<td>Total echo score</td>
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LA, left atrium; LVEF, left ventricular ejection fraction; MVA, mitral valve area; PAP, pulmonal artery systolic pressure.

Results

Baseline characteristics
A comparison of baseline clinical and echocardiographic characteristics of the PMC and CONV groups is shown in Table 1. There were no significant differences between the two groups in terms of gender, body surface area, smoking, diabetes mellitus, atrial fibrilation, previous embolism, cholesterol level, comorbidity index, left atrial dimension, LVEF, mitral gradient, and significant tricuspid regurgitation. However, age (P < 0.001), prevalence of hypertension (P = 0.008), total echo score (P = 0.04), and MVA (P < 0.001) were significantly higher, and PAP lower (P = 0.006) in the CONV group than in the PMC group. Propensity score matching for the entire population yielded 62 matched pairs of patients (Supplementary material online, Table S2). In the matched cohort, there were no significant between-group differences for any covariates.

Comparison of outcomes between the PMC and CONV groups
Percutaneous mitral commissurotomty was completed successfully in all 106 patients of the PMC group without procedural mortality. The PMC resulted in a significant increase in MVA from 1.26 ± 0.11 to 2.07 ± 0.28 cm² (P < 0.001), and a significant decrease in mitral gradient from 8.2 ± 3.0 to 5.3 ± 1.7 mmHg (P < 0.001). MVA > 1.5 cm² was achieved in 105 (99%) patients, and severe MR occurred in 2 (2%) patients; no patient required urgent surgery. Thus, successful immediate results were achieved in 103 (97%) patients.

The median follow-up was 8.8 years (interquartile range 5.7–11.2 years) in the PMC group and 8.0 years (interquartile range 5.1–11.4 years) in the CONV group (P = 0.420). During follow-up, there were 3 cardiovascular and 4 non-cardiovascular deaths in the PMC group and 16 cardiovascular and 3 non-cardiovascular deaths in the CONV group. The estimated actuarial 11-year cardiovascular mortality rates were 5 ± 3% in the PMC group and
15 ± 4% in the CONV group (P = 0.011). The risk of cardiovascular mortality was significantly lower in the PMC group than in the CONV group (hazard ratio: 0.220; 95% CI: 0.058–0.832; P = 0.026) on adjusted multivariable analysis using the IPTW method. Among the 62 propensity score-matched pairs, the risk of cardiovascular mortality was significantly lower in the PMC group than in the CONV group (hazard ratio: 0.220; 95% CI: 0.058–0.832; P = 0.026). The causes of non-cardiac deaths were malignancy in five patients and pneumonia and liver cirrhosis in one patient each. The causes of cardiovascular deaths in the CONV group were stroke in seven patients, congestive heart failure in three, acute myocardial infarction in three, sudden cardiac death in two, and operative mortality after late MV replacement in one. The causes of cardiovascular deaths in the PMC group were stroke, congestive heart failure, and acute myocardial infarction in one patient each.

During follow-up, non-fatal cerebral infarctions occurred in 12 patients of the CONV group and in 5 patients of the PMC group, and 7 systemic embolic events (3 renal, 2 popliteal, 1 brachial, and 1 spleen) occurred in the CONV group. The estimated actuarial 11-year embolism rate was 21 ± 5% in the patients with atrial fibrillation and 14 ± 3% in those with sinus rhythm, respectively (P = 0.08) (Figure 1A), but this rate was significantly lower in the PMC than in the CONV group (7 ± 3% vs. 23 ± 4%, P = 0.0013; Figure 1B). On adjusted multivariable analysis using the IPTW method, the risk of cerebral infarction or embolism was significantly lower in the PMC than in the CONV group (hazard ratio: 0.309; 95% CI: 0.112–0.852; P = 0.023). In the propensity score-matched pairs, the risk of cerebral infarction or embolism tended to be lower in the PMC group than in the CONV group (hazard ratio: 0.330; 95% CI: 0.101–1.076; P = 0.066).

In consequence, 35 (25%) patients in the CONV group and 8 (8%) in the PMC group attained the composite endpoint, and the estimated actuarial 11-year event-free survival rate was 89 ± 4% in the PMC group and 69 ± 5% in the CONV group, respectively (P < 0.001) (Figure 2A). Among the propensity-matched patients, the risk of cardiovascular endpoint was significantly lower in the PMC group than in the CONV group (hazard ratio:
Although late intervention, including MV replacement and late PMC, was not a pre-specified endpoint, we performed post hoc analysis to compare treatment groups in terms of late intervention. The estimated actuarial 11-year rates of MV replacement and late intervention (MV replacement or PMC) were 7% ± 3% and 11% ± 4% in the PMC group and 23% ± 4% and 35% ± 5% in the CONV group (P < 0.01 for each) (Figure 3A), and the estimated actuarial rates of endpoint or late intervention were significantly lower in the PMC than in the CONV group (22 ± 5 vs. 56 ± 5% at 11 years, P < 0.001; Figure 3B). In the propensity score-matched pairs, the risk of late intervention was significantly lower in the PMC group than in the CONV group (hazard ratio: 0.365; 95% CI: 0.147–0.906; P = 0.026). On Cox proportional hazard analysis, the CONV group was associated with endpoint or late intervention in patients without atrial fibrillation and previous embolism (hazard ratio: 2.162; 95% CI: 1.170–3.994; P = 0.012) as well as in patients with atrial fibrillation or previous embolism (hazard ratio: 22.18; 95% CI: 2.901–169.5; P = 0.002).

Discussion

The main results of this study in a cohort of 244 asymptomatic patients with moderate MS can be summarized as follows. Early PMC was associated with a significant reduction in the composite event rate of cardiovascular mortality, cerebral infarction, systemic embolic events, and PMC-related complications. The reduction in the long-term event rate associated with early PMC persisted in the propensity analysis and in the adjusted multivariable Cox analysis using the IPTW method that controlled for the inherent biases related to treatment selection and baseline prognostic heterogeneity.

Systemic embolism, involving the brain most frequently, occurs in 10–20% of patients with MS and is the second leading cause of death. Embolic events are thought to originate from left
atrial thrombi and the presence of atrial fibrillation is closely related to systemic embolism.2, 5 Although there is no debate on the efficacy of anticoagulation therapy in patients with MS and atrial fibrillation, anticoagulation alone does not offer complete protection to patients with significant MS.2, 6 The rate of embolism including cerebral infarction in the CONV group was similar to the rates reported in the other studies,3, 5 although all of our study patients with prior embolic events or atrial fibrillation were administered maintenance anticoagulation therapy. Furthermore, coagulation activity is increased in the LA in patients with significant MS even during anticoagulation.22 Although PMC does not seem to affect persistence of atrial fibrillation,20 the performance of PMC was associated with a decrease in the risk of embolic events in 402 patients with MS and atrial fibrillation.23 In the present study, the efficacy of PMC was directly compared with that of the conservative management in the prevention of embolism, and early PMC in asymptomatic patients with moderate MS was associated with better long-term event-free survival owing to a more effective decrease in the incidence of embolic events.

Compared with the previous outcome studies of PMC,2, 7, 20–23 the higher rate of successful immediate result and the lower long-term cardiovascular mortality rates and event rates observed in our PMC group might result from several possible factors. First, centre volume and patient selection consistently affect results, and patients with severe deformity of MV were excluded in the present study. Second, earlier intervention in patients with few or no symptoms might be more beneficial. In a series of 423 consecutive patients who underwent PMC while in New York Heart Association class 1 or 2, 21 95% were alive and 77% were asymptomatic after 9 years; these excellent long-term results were similar to those found in the present study. However, half of the patients with predominantly unfavourable characteristics for PMC required further intervention or died at 6 years after PMC.26 No randomized trials have been performed to ascertain the optimal timing of intervention in asymptomatic patients with significant MS, and the current ACC/AHA guidelines recommend PMC only in selected asymptomatic patients with significant pulmonary hypertension or new onset of atrial fibrillation.24 The 2007 European Society of Cardiology guidelines extended the indications of PMC to patients at high thrombo-embolic risk with previous history of embolism or with dense spontaneous contrast in LA.2 Both guidelines have declared against cardiac surgery in asymptomatic patients with MS. Although a conventional treatment strategy may decrease the number of PMC performed, the overall risk tended to increase in the CONV group, because more patients needed MV replacement instead of PMC during follow-up and MV replacement is associated with a prosthetic-related morbidity. The timing of intervention tends to be earlier in good candidates for PMC, and better insights into the embolic risk of MS and the performance of PMC at low risk may lead to consideration of PMC at an earlier stage of disease.21, 27

In summary, the present study suggests that the clinical benefits of early PMC may outweigh the risks associated with early intervention, and early intervention may be a valuable therapeutic option to further improve clinical outcomes in these asymptomatic MS patients.

Limitations

Comparison of treatment strategies for moderate MS is subject to the limitations inherent to non-randomized assignment, and such limitations may have significantly affected our results due to selection bias and unmeasured confounders. Prospective randomized trials are needed to reduce these biases between treatment groups. Although all study patients were enrolled consecutively in a prospectively designed registry for annual clinical and echocardiographic follow-up, the CONV group was older and had a higher incidence of hypertension and a higher echo score, and the PMC group had a smaller MV area and higher PAP. The proportion of patients who underwent transoesophageal echocardiography was significantly lower in the CONV group. These factors might have influenced on the decisions to perform PMC. To control for the inherent biases related to treatment selection and heterogeneity in baseline factors, we performed the propensity analysis and the adjusted multivariable Cox analysis using the IPTW method, both of which consistently showed significantly lower rates of cardiovascular endpoints in the PMC group. However, these techniques do not adjust for all potential confounders and event-free survival rates according to the treatment strategies were not significantly different in patients without atrial fibrillation and previous embolism. The present study also had a very high proportion of women and was a limited study in scope, in that it had numerous exclusion criteria. This study targeted a homogenous population with moderate MS and favourable morphology of MV, and the incidence of procedure-related complications was very low. The results are not applicable to low-volume centres, patients with mild MS, severe deformity of MV, or unfavourable commissural morphology. Morphologic evaluation of MV was performed with echocardiographic score only, not with commissural score.28

Conclusions

Compared with the conventional treatment, early PMC is associated with improved long-term event-free survival and may be a therapeutic option to further improve clinical outcomes in selected, asymptomatic patients with moderate MS, but prospective randomized trials are required to confirm the efficacy of early PMC.

Supplementary material

Supplementary material is available at European Heart Journal online.

Conflict of interest: none declared.

References

Early intervention in asymptomatic moderate MS


