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

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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. 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. 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, or severe MS, 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 manage-
ment 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 centres1 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, in-
cluding patient demographics, clinical presentation, and echocardi-
ographic 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 echocardi-
ographic follow-up data on study patients were collected annually and
entered into the database. From 1997 to 2007, we enrolled 244 con-
secutive 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/Ameri-
can Heart Association (ACC/AHA) guidelines,1 the exclusion criteria
were defined as patients with exertional dyspnoea, total echocardiog-
graphic 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 fibrilla-
tion 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 ben-
efits of early PMC and procedural risks in detail and considered
the preferences of individual patients most importantly. Whereas a con-
ventional 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 fib-
ribilation 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 immedi-
ately after PMC. All patients underwent two-dimensional echocardiog-
raphy 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.16 and total echocardiographic score was
obtained by adding the scores for leaflet mobility, thickness, calcifica-
tion, and subvalvular lesions. The MVA was measured by direct planim-
etry 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, re-
spectively.1 The severity of mitral and tricuspid regurgitation was
assessed semiquantitatively or using quantitative methods and classified
as mild, moderate, or severe.15 Pulmonary artery systolic pressure was
estimated by continuous wave Doppler with the simplified Bernoulli
equation \( P \times \frac{v^2}{2} \) where \( v \) is the peak velocity of tricuspid regurgitation.16 Transoeso-
ophageal 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 fibr-
illation and 41% of those in sinus rhythm underwent transoesophageal
echocardiography. No left atrial thrombi were observed in both
groups. Dense 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 evalu-
ation 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 symp-
tomatic during follow-up were referred for PMC or MV surgery. Data
were collected until December 2010, during annual visits to the echo-
cardiography laboratory and by detailed annual review of all medical
records or telephone interviews. Deaths were classified as cardiovas-
cular or non-cardiac 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 com-
plications; procedural mortality and urgent MV surgery. Diagnosis of
embolic event was based on clinical symptoms, signs, and computer-
ized tomography scans. A specific diagnosis of cerebral infarction
was confirmed by an experienced neurologist and additional brain
magnetic resonance imaging was performed if indicated.
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. 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, 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.

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 fibrillation, 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 commissurotomy 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

Table 1 Baseline characteristics of patients (percutaneous mitral commissurotomy group) who underwent early elective percutaneous mitral commissurotomy and those (CONV group) who underwent conventional treatment strategy

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>PMC group (n = 106)</th>
<th>CONV group (n = 138)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>48 ± 10</td>
<td>54 ± 10</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Gender (female)</td>
<td>89 (84%)</td>
<td>102 (74%)</td>
<td>0.06</td>
</tr>
<tr>
<td>Body surface area (m²)</td>
<td>1.60 ± 0.16</td>
<td>1.60 ± 0.16</td>
<td>0.86</td>
</tr>
<tr>
<td>Smoking</td>
<td>19 (18%)</td>
<td>14 (10%)</td>
<td>0.08</td>
</tr>
<tr>
<td>Diabetes</td>
<td>3 (3%)</td>
<td>9 (7%)</td>
<td>0.19</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1 (1%)</td>
<td>12 (9%)</td>
<td>0.008</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>26 (25%)</td>
<td>45 (33%)</td>
<td>0.17</td>
</tr>
<tr>
<td>Paroxysmal</td>
<td>3</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Permanent/persistent</td>
<td>22/1</td>
<td>44/0</td>
<td></td>
</tr>
<tr>
<td>Previous embolism</td>
<td>6 (6%)</td>
<td>15 (11%)</td>
<td>0.15</td>
</tr>
<tr>
<td>Cholesterol (mg/dL)</td>
<td>181 ± 38</td>
<td>176 ± 32</td>
<td>0.30</td>
</tr>
<tr>
<td>Comorbidity index</td>
<td>0.22 ± 0.54</td>
<td>0.23 ± 0.49</td>
<td>0.82</td>
</tr>
<tr>
<td>LA dimension (mm)</td>
<td>50 ± 7</td>
<td>51 ± 7</td>
<td>0.09</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>60 ± 7</td>
<td>59 ± 7</td>
<td>0.11</td>
</tr>
<tr>
<td>MVA (cm²)</td>
<td>1.26 ± 0.11</td>
<td>1.35 ± 0.12</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>PAP (mmHg)</td>
<td>35 ± 7</td>
<td>32 ± 7</td>
<td>0.006</td>
</tr>
<tr>
<td>Total echo score</td>
<td>7.2 ± 1.0</td>
<td>7.5 ± 1.3</td>
<td>0.04</td>
</tr>
</tbody>
</table>

LA, left atrium; LVEF, left ventricular ejection fraction; MVA, mitral valve area; PAP, pulmonary artery systolic pressure.
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: 0.309; 95% CI: 0.112–0.852; P = 0.023).
Early intervention in asymptomatic moderate MS

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. 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 event-free survival rates were significantly different in patients with atrial fibrillation or previous embolism (100% in the PMC group and 54 ± 8% in the CONV group at 11 years, P < 0.001), but not 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).

In the PMC group, 80 (75%) patients remained free of events and asymptomatic, and echocardiographic restenosis occurred in 9 patients, 6 of whom underwent repeat PMC (n = 3) or MV replacement (n = 3). The estimated actuarial restenosis rate was 9 ± 4% at 7 years and 16 ± 5% at 11 years. Immediately after PMC, severe MR developed in two patients and moderate MR in five, and during follow-up, progression of mild MR to moderate MR occurred in two, improvement of moderate MR to mild MR in one, and three patients underwent MV replacement; the indications for surgery were severe MR, infective endocarditis, and aggravation of tricuspid regurgitation in one patient each.

In the CONV group, 61 (44%) patients remained free of events and asymptomatic, and total echocardiographic score was significantly increased from 7.57 ± 1.27 to 8.80 ± 1.36 (P < 0.001) and 37 (27%) patients underwent late PMC (n = 12) or late MV replacement (n = 25) during follow-up. The indications for late surgery in the CONV group were development of LA thrombi (n = 8), unfavourable valve morphology for late PMC (n = 8), aggravation of tricuspid regurgitation (n = 5), progression of aortic valve disease (n = 3), and aggravation of MR (n = 1). In eight patients who underwent late MV replacement due to unfavourable MV morphology, echo score was increased significantly from at baseline 8.1 ± 0.6 to 11.0 ± 1.1 at the time of surgery (P = 0.010). 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 fibrillation. Systemic embolism 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 fibrillation.
atrial thrombi and the presence of atrial fibrillation is closely related to systemic embolism. 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. The rate of embolism including cerebral infarction in the CONV group was similar to the rates reported in the other studies, 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. Although PMC does not seem to affect persistency of atrial fibrillation, the performance of PMC was associated with a decrease in the risk of embolic events in 402 patients with MS and atrial fibrillation. 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, 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, 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. 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. The 2007 European Society of Cardiology guidelines extended the indications of PMC to patients at high thrombo-embolic risk. Although 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.

**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.

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