Serial Echocardiographic Evaluation of Restenosis After Successful Percutaneous Mitral Commissurotomy

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This study was designed to determine predictors of restenosis after successful percutaneous mitral commissurotomy (PMC) and its relationship to late clinical outcome.

The restenosis rate after PMC and its relationship to late clinical outcome is poorly defined. Serial echocardiography was performed in 310 patients who underwent PMC. Restenosis, defined as mitral valve area (MVA) $<1.5$ cm$^2$ and $\geq50\%$ loss of initial MVA increase, was determined by both two-dimensional (2D) and Doppler echocardiography. Clinical, echocardiographic and cardiac catheterization variables were evaluated to determine predictors of restenosis. The relationship between restenosis and major adverse clinical events (death, repeat PMC or mitral valve replacement) and functional status was assessed.

Acute procedural success occurred in 206 patients (66%), who were then followed for restenosis. The cumulative restenosis rate was approximately 40% at six years after successful PMC (44% by 2D and 40% by Doppler MVA). The only independent predictor of restenosis was echocardiographic score (restenosis at five years was 20% for score $<8$ vs. 61% for score $\geq8$, $p < 0.001$). The decline in MVA and occurrence of restenosis was gradual and progressive during the follow-up period. Procedural results and baseline factors predicted event-free survival. Restenosis by 2D MVA was related to adverse events or New York Heart Association functional class 3 to 4 symptoms, but restenosis was not an independent predictor of clinical outcome by multivariate analysis.

Restenosis is a common, gradual and progressive occurrence after successful PMC and is predicted by higher echocardiographic score. Restenosis is related to late adverse clinical outcome, though clinical outcome remains best predicted by the acute procedural results of PMC. (J Am Coll Cardiol 2002;39:328–34) © 2002 by the American College of Cardiology

Percutaneous mitral commissurotomy (PMC) using the Inoue balloon is an effective treatment for patients with mitral stenosis (MS) and suitable valve morphology. Restenosis after PMC has been evaluated in a number of studies, with an incidence ranging from 4% to 39% (1–6). This variability reflects the different definitions of restenosis, duration and consistency of follow-up and/or small cohorts of patients in previous studies.

Furthermore, the relationship between restenosis and long-term clinical outcome is not well defined. Iung et al. (7) have recently reported that restenosis occurred in 97% of patients with poor functional results (New York Heart Association [NYHA] functional class III or IV symptoms) after PMC. However, because restenosis was not evaluated for the entire patient population, its relationship to functional status is unclear. The objectives of this study were to: 1) determine the rate of restenosis by annual serial echocardiography after successful PMC; 2) determine the variables related to restenosis; and 3) assess the relationship between restenosis and long-term clinical outcome after successful PMC.

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Manuscript received June 11, 2001; revised manuscript received September 4, 2001, accepted October 18, 2001.

METHODS

Study population. From 1990 to 1999, 310 consecutive patients with symptomatic MS and mitral valve area (MVA) $<1.5$ cm$^2$ underwent Inoue balloon (Toray Inc., Tokyo, Japan) PMC at our institution. Informed consent was obtained from all patients in accordance with a protocol approved by the Institutional Review Board of Duke University Medical Center. Patients with mitral regurgitation (MR) higher than Sellers grade 2+ by left ventricular (LV) angiography (8) or evidence of left atrial (LA) thrombus by transesophageal echocardiography did not undergo PMC. Baseline characteristics are depicted in Table 1.

Catheterization data and PMC procedure. The technique of Inoue balloon PMC (9) and our protocol of data collection at the time of PMC (10) have previously been described. Standard hemodynamic measurements of the right and left heart, including simultaneous measurement of LA and LV pressures, were made before and immediately after the procedure using fluid-filled catheters. The transmitral pressure gradient was determined by computerized planimetry of the LA and LV diastolic pressure difference. Cardiac output was determined by the Fick method and MVA was calculated using the Gorlin and Gorlin formula, with an empiric constant of 40 (11). The average diastolic
area of three beats was used for patients in sinus rhythm; the average of 10 beats was used to calculate the Gorlin valve area for patients in atrial fibrillation. After the procedure, a right heart oximetry series was performed to evaluate for residual left-to-right shunting after withdrawal of the balloon catheter from the interatrial septum. When a left-to-right shunt of >1.3 was observed (n = 29, 9%), the calculated systemic blood flow was substituted for the cardiac output in the Gorlin formula. Biplane left ventriculography was performed before and after the procedure and MR severity was graded using the Sellers classification (8).

**Clinical and echocardiographic follow-up.** Clinical and echocardiographic evaluations were performed immediately before PMC, then 24 h, six months, one year and yearly thereafter. Clinical assessment included a detailed history and physical examination with determination of functional class (K. B. K.) before the clinical assessment. Two-dimensional (2D) and Doppler echocardiographic examinations were performed with a commercially available phased-array sec-

**Table 1.** Baseline Characteristics of the Study Population

<table>
<thead>
<tr>
<th></th>
<th>Total Population (n = 310)</th>
<th>Successful PMC (n = 206)</th>
<th>Unsuccessful PMC (n = 104)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>52 ± 13</td>
<td>50 ± 13</td>
<td>54 ± 13</td>
</tr>
<tr>
<td>Female gender</td>
<td>265 (85%)</td>
<td>170 (82%)</td>
<td>95 (91%)</td>
</tr>
<tr>
<td>NYHA functional class</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>3 (1%)</td>
<td>2 (1%)</td>
<td>1 (1%)</td>
</tr>
<tr>
<td>2</td>
<td>82 (26%)</td>
<td>57 (28%)</td>
<td>25 (24%)</td>
</tr>
<tr>
<td>3</td>
<td>199 (64%)</td>
<td>134 (65%)</td>
<td>65 (63%)</td>
</tr>
<tr>
<td>4</td>
<td>26 (8%)</td>
<td>13 (6%)</td>
<td>12 (12%)</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>102 (33%)</td>
<td>61 (30%)</td>
<td>41 (39%)</td>
</tr>
<tr>
<td>Prior commissurotomy</td>
<td>52 (17%)</td>
<td>30 (14%)</td>
<td>22 (21%)</td>
</tr>
<tr>
<td>Mitral valve area, cm²</td>
<td>1.1 ± 0.2</td>
<td>1.1 ± 0.2</td>
<td>1.0 ± 0.2</td>
</tr>
<tr>
<td>Mitral valve echo score</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mobility</td>
<td>2.2 ± 0.7</td>
<td>2.1 ± 0.7</td>
<td>2.4 ± 0.7</td>
</tr>
<tr>
<td>Thickening</td>
<td>2.5 ± 0.8</td>
<td>2.4 ± 0.8</td>
<td>2.7 ± 0.7</td>
</tr>
<tr>
<td>Calcification</td>
<td>2.6 ± 0.8</td>
<td>2.5 ± 0.8</td>
<td>2.8 ± 0.7</td>
</tr>
<tr>
<td>Subvalvular thickening</td>
<td>1.5 ± 0.8</td>
<td>1.5 ± 0.7</td>
<td>1.7 ± 0.9</td>
</tr>
<tr>
<td>Total score</td>
<td>8.8 ± 2.3</td>
<td>8.5 ± 2.2</td>
<td>9.5 ± 2.3*</td>
</tr>
<tr>
<td>Mitral regurgitation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>186 (60%)</td>
<td>137 (67%)</td>
<td>49 (48%)</td>
</tr>
<tr>
<td>1</td>
<td>97 (31%)</td>
<td>56 (27%)</td>
<td>41 (40%)</td>
</tr>
<tr>
<td>2</td>
<td>21 (7%)</td>
<td>10 (5%)</td>
<td>10 (10%)</td>
</tr>
</tbody>
</table>

*p < 0.05 for comparison between successful and unsuccessful PMC.

NYHA = New York Heart Association; PMC = percutaneous mitral commissurotomy.

**Statistical analysis.** Continuous data are reported as mean ± standard deviation and categorical variables as the number and percentage of patients. Differences in categorical factors and procedural outcomes are compared using a Pearson chi-square test. Differences in procedural outcomes for continuous variables were compared using paired t test. A p value <0.05 was considered statistically significant. Univariable comparisons of baseline and preprocedural factors and postprocedural outcomes were made using Excel 97. All other statistical analyses were performed using SAS Version 6.12 (SAS Institute, Cary, North Carolina).

Restenosis after successful PMC was assessed at six months, one year and yearly thereafter. To determine predictors of this binary outcome, a generalized linear model was applied. This model assumed a binomial distribution with a logit link function and applied repeated measures of the data over time. Once a patient met the definition of restenosis, restenosis was assumed for all subsequent follow-up intervals at which data were collected on the
patient. A backward selection technique was applied to determine the set of baseline and postprocedural factors that were multivariably predictive of restenosis.

Long-term event-free survival was estimated using a Cox proportional hazards model. The assumption of proportional hazards was evaluated and no factor greatly violated this assumption. The association of this outcome with baseline and postprocedural factors was evaluated using a stepwise variable selection technique. The variables evaluated were age, gender, NYHA functional class, previous surgery, total echocardiographic score, atrial fibrillation; preprocedural MVA, MR, mean atrial pressure, mitral gradient and LA pressure and postprocedural MVA, MR, mitral gradient and LA pressure. Forward stepwise variable selection techniques were used on the baseline and preprocedural variables and postprocedural variables separately. The results of these two models were combined and forward stepwise selection was again used to develop the final model. The association between restenosis and long-term event-free survival was tested using restenosis as a time-dependent covariate. This was evaluated initially by univariate analysis and subsequently by multivariate analysis including those factors found to be associated with survival.

RESULTS

Procedural results. For the total patient population (n = 310), PMC resulted in an increase in MVA from 1.1 ± 0.2 cm² to 1.7 ± 0.5 cm² (p < 0.001) and a reduction in mean transmitial gradient from 12.5 ± 4.8 mm Hg to 6.8 ± 3.3 mm Hg (p < 0.001). The mean Sellers MR grade increased from 0.5 ± 0.6 to 0.9 ± 1.0 (p < 0.001) after PMC.

Successful PMC, as defined above, was accomplished in 206 (66%) patients. For the patients with successful PMC, mean MVA increased from 1.1 ± 0.2 cm² to 1.9 ± 0.4 cm² (p < 0.001) and mean MR increased from Sellers grade 0.4 ± 0.6 to 0.6 ± 0.7 (p < 0.001) after the procedure. Percutaneous mitral commissurotomy was defined as unsuccessful because of residual mitral stenosis (MVA <1.5 cm²) in 77 (25%) patients and the presence of severe (3 or 4+) MR in 27 (9%) patients. Baseline characteristics of patients who had successful PMC compared with unsuccessful PMC are depicted in Table 1. In general, patients who had successful PMC were younger (p = 0.016), more often men (p = 0.020), had lower total echocardiographic score (p < 0.001) and had less angiographic MR before PMC (67% with no baseline MR in the successful group compared with 48% in the unsuccessful group; p = 0.002).

Event-free survival. The median follow-up duration for the patient population was 3.3 years. There were 69 major adverse clinical events in the entire cohort (11 deaths, 58 mitral valve replacement surgeries). Two of the 11 deaths (18%) were cardiac. Within the group with successful PMC, 30 major events occurred during clinical follow-up: 2 deaths (1 cardiac) and 28 mitral valve replacements (13 for predominant MS, 10 for predominant MR and 5 for combined MS/MR). In the unsuccessful PMC group, 39 major events occurred: 9 deaths and 30 mitral valve replacements (17 for predominant MR, 10 for predominant MS and 3 for combined MS/MR). The median time to major event after successful PMC was 978 days (25th to 75th percentile, 455 to 1,727 days) compared with 62 days (25th to 75th percentile, 10 to 329 days) after unsuccessful PMC. Event-free survival for patients with successful PMC compared with unsuccessful PMC is shown in Figure 1. Patients with successful PMC had a three-year event-free survival of 88% compared with 63% after unsuccessful PMC (five-year event-free survival 81% vs. 54%, respectively).

For the total patient population, multivariable logistic regression analysis demonstrated that the pre- and postprocedural predictors of event-free survival were post-PMC mitral gradient (X² = 28.9, p < 0.001), post-PMC MR severity (X² = 16.5, p < 0.001) and prior surgical commissurotomy (X² = 6.8, p = 0.009). In the group who had a successful PMC procedure, independent predictors of event-free survival were post-PMC mitral gradient (X² = 7.2, p = 0.007), post-PMC LA pressure (X² = 6.2, p = 0.013) and echocardiographic score (X² = 2.8, p = 0.095). When NYHA functional class III or IV symptoms was considered a major end point, the multivariate model yielded the following predictors: echocardiographic score (X² = 11.6, p = 0.001), baseline NYHA functional class (X² = 11.4, p < 0.001), post-PMC mitral gradient (X² = 7.8, p = 0.005) and age (X² = 7.1, p = 0.007).

The relationship between echocardiographic restenosis after successful PMC and clinical outcome was investigated using unadjusted and adjusted 2D and Doppler MVA. Although restenosis defined by Doppler MVA was not related to clinical outcome, restenosis by 2D echocardiography was found to be associated with time to major events after successful PMC (X² = 5.9, p = 0.015) (Fig. 2). Restenosis by 2D MVA was more strongly related to time to major events or NYHA functional class III or IV symptoms (X² = 9.0, p = 0.003) by univariable analysis. However, when adjusted for pre- and post-PMC clinical, echocardiographic and catheterization variables, neither method independently predicted clinical outcome. Additionally, because the definition of restenosis may be somewhat arbitrary, three other criteria were investigated: MVA ≤1.5 cm² and >75% loss of PMC gain, MVA as a proportion of immediate post-PMC MVA, and absolute MVA. However, none of these predicted major events or functional class III or IV symptoms after adjustment for pre- and post-PMC variables.

Echocardiographic follow-up and restenosis. Among the subset of patients with successful PMC, 25 of 206 (12%) did not have an echocardiographic measurement of MVA by either 2D or Doppler methods during follow-up. In addition, 22 patients (11%) did not have adequate 2D measurement of MVA.

After successful PMC, MVA as measured by 2D echo-
Cardiography (planimetry) decreased by an average of 0.08 cm²/year. Mitral valve area by Doppler echocardiography decreased by an average of 0.06 cm²/year. Comparison between the two echocardiographic methods after PMC demonstrated a progressive, gradual decrease in MVA over time with both 2D and Doppler measurements. Likewise, the percentage of patients who met the definition of restenosis was similar and progressive for both MVA measures over time (approximately 6% to 7% per year). Thus, at six-year follow-up, approximately 40% of patients had evidence of echocardiographic restenosis by either 2D or Doppler MVA. During the follow-up period, the distribution of MR severity did not change after successful PMC.

Multivariable logistic regression analysis was performed to determine predictors of restenosis after successful PMC using the following variables: age, gender, baseline functional status, prior commissurotomy, cardiac rhythm, echocardiographic score, MVA (pre-PMC), mitral gradient (pre-PMC), MR (pre-PMC), mean pulmonary artery pressure (pre-PMC), MVA (post-PMC), mitral gradient (post-PMC) and MR (post-PMC). Only echocardiographic score was found to predict restenosis (z = 3.42; p < 0.001). Restenosis as a function of echocardiographic score is depicted in Figure 3. Patients with a baseline echocardiographic score <8 (n = 73) had a five-year restenosis rate of 20% compared with 61% for those with total score ≥8.

**DISCUSSION**

In the present study, serial echocardiography was performed in a large, consecutive cohort of patients undergoing Inoue balloon PMC in order to define the incidence and clinical implications of restenosis. The results demonstrate that after successful PMC, restenosis was: 1) a gradual and progressive process during long-term follow-up; 2) predicted only by baseline echocardiographic score; and 3) related to poorer long-term outcome but less important than acute procedural results and baseline variables for predicting event-free survival. To our knowledge, this is the largest North American cohort of patients undergoing PMC and followed by serial clinical and echocardiographic evaluations in order to define the clinical implications of restenosis. This study is unique in its evaluation of mitral valve restenosis in relation to baseline and postprocedural variables.

Restenosis after PMC. Restenosis after PMC has been evaluated in prior studies, but the reported rates have been quite variable. This variability is related to multiple factors, including different definitions of restenosis, durations of follow-up, techniques for measuring MVA and methods of sampling within a given cohort of patients.

The definition of restenosis in the present study was that most widely used in the literature (2–4,6). This definition (MVA <1.5 cm² and ≥50% loss of initial gain in MVA) thereby limits the assessment of restenosis to the subgroup...
of patients who had had successful PMC results (specifically, post-PMC MVA ≥1.5 cm²). Because procedural results have been found to be the strongest predictor of event-free survival in the present and prior studies (6,15), the issue of restenosis is less clinically relevant for those patients who do not meet this definition of acute procedural success. Indeed, clinical follow-up of the subset of patients with unsuccessful PMC results demonstrated a high rate of adverse events within the first year, as a consequence of severe mitral regurgitation or inadequate relief of mitral stenosis. On the other hand, the issue of restenosis is a common clinical consideration in the follow-up of patients after successful PMC.

Changes in MVA and restenosis rates in this study were similar and consistent for both 2D and Doppler echocardiographic measures of MVA. Using either measure of MVA, restenosis occurred in approximately 40% of patients six years after successful PMC. Although this percentage may seem high, Hernandez et al. (6) reported a similar rate of restenosis (39% at seven years) in their European cohort.

In the present study, only total echocardiographic score at baseline was found to predict restenosis. Although initially developed to assess the morphology of mitral valve as a predictor of procedural success (12), the echocardiographic score has recently been associated with restenosis as well (6,16). Calcification of the mitral valve, either leaflet or commissure involvement, has also been related to restenosis (4,17). Finally, in a study of 103 patients with mild MS who did not undergo PMC, Sagie et al. (18) found that the baseline echocardiographic score was a weak predictor of the rate of progression of MS. This association between the echocardiographic score and progression of MS or restenosis remains unexplained. One possibility is that higher echocardiographic score may reflect ongoing rheumatic involvement or an immunologic response with progressive valve injury. The gradual, progressive decline in MVA after PMC and lack of relationship between immediate post-PMC MVA and restenosis suggest that restenosis is an ongoing biological process and not simply a mechanical or "recoil" phenomenon.

**Restenosis and clinical outcome.** Our study demonstrated that restenosis defined by 2D echocardiographic measurement of MVA was related to late clinical outcome. However, this relationship between restenosis by 2D MVA and late clinical outcome was statistically weak. Although MVA continues to decline during long-term follow-up, event-free survival was excellent after successful PMC (81% at five years), demonstrating the disparity between the gradual process of restenosis and clinical outcome. The acute procedural results of PMC were the predominant predictors of event-free survival for both the entire cohort and the subgroup of patients with successful PMC. Thus, whereas univariable regression analysis found that restenosis defined by 2D MVA was associated with major adverse clinical events or impaired functional status, when adjusted for baseline factors and postprocedural results, restenosis was no
longer predictive of either major events or poorer functional status.

The disparity between restenosis and clinical outcome suggests that the hemodynamic benefits of successful PMC persisted beyond the point of restenosis as defined by this study. A greater reduction in MVA or duration of time may be necessary before recurrent symptoms develop. After PMC, LA stiffness has been shown to decline significantly (19), and this improvement in compliance may confer symptomatic benefit despite a reduction in MVA. In support of this hemodynamic change after PMC, our multivariate analysis found that LA pressure after successful PMC was an independent predictor of poor long-term clinical outcome. Alternatively, variability between measures of MVA may contribute to a higher perceived rate of restenosis (10,14), yet the rates of MVA decline and restenosis for both 2D and Doppler measures of MVA were remarkably similar. Longer clinical follow-up of the patients who experience restenosis may reveal a stronger association between restenosis and adverse clinical events and poor functional status.

This lack of association between restenosis and outcome also supports current guidelines for repeat echocardiography after successful PMC. The American Heart Association/American College of Cardiology Guidelines for the Management of Patients with Valvular Heart Disease state that after successful PMC, management of patients is similar to that of asymptomatic patients with mitral stenosis (20). Echocardiography is recommended initially after PMC to determine the effect or complications of the procedure, but thereafter only for patients with recurrent or worsening symptoms (20). Closer clinical follow-up of patients with echocardiographic scores ≥8 may be warranted after successful PMC because the restenosis rate is particularly high among these patients.

**Study limitations.** The immediate postprocedural MVA determined by Gorlin formula was used as the reference MVA for determination of restenosis. This measure was chosen because of the recognized inaccuracy of the Doppler MVA acutely after PMC (21). However, we have also separately evaluated restenosis and MVA decline using post-PMC 2D MVA as the reference MVA and found similar results to those reported above. Selection bias may have affected the clinical event rate during follow-up, because criteria to proceed with mitral valve replacement were clinically determined and not prespecified in the study. However, because restenosis by echocardiography did not independently predict time to clinical events or poor functional status, it is unlikely that surgery was performed primarily on the basis of the echocardiographic results.

**Conclusions.** Serial yearly echocardiographic assessment following PMC demonstrates that restenosis of the mitral valve is a common, gradual and progressive occurrence whereas the severity of MR does not change substantially.

![Figure 3. Freedom from restenosis by two-dimensional echocardiography after successful percutaneous mitral commissurotomy as a function of baseline echocardiographic score.](image-url)
Patients with lower baseline echocardiographic scores are less likely to experience restenosis. Although restenosis by 2D echocardiography is related to late adverse events after successful PMC, a disparity exists between echocardiographic restenosis and clinical outcome. The acute procedural results of PMC remain the strongest predictors of long-term clinical outcome.

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REFERENCES