Long-Term Clinical and Echocardiographic Outcome of Percutaneous Mitral Valvuloplasty
Randomized Comparison of Inoue and Double-Balloon Techniques

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OBJECTIVES
The purpose of the present study was to compare the long-term clinical and echocardiographic results of the Inoue and the double-balloon techniques.

BACKGROUND
The large randomized trial comparing the extent of commissurotomy and the long-term results between the double-balloon and Inoue balloon techniques has not been reported.

METHODS
We conducted a prospective, randomized trial comparing two procedures in 302 consecutive patients who underwent percutaneous mitral valvuloplasty (PMV) using Inoue (n = 152; group I) or double-balloon technique (n = 150, group D) between 1989 and 1995. The sample size was planned to provide the study with approximately 80% power for the detection of a 10% difference between the two groups.

RESULTS
There were no significant differences in baseline characteristics between the two groups. Immediately after PMV, mitral valve area (MVA) increased from 0.9 ± 0.2 to 1.8 ± 0.3 cm² in group I and from 0.9 ± 0.2 to 1.9 ± 0.3 cm² in group D. No significant differences existed between the two groups in terms of development of commissural splitting, commissural mitral regurgitation (CMR), moderate to severe mitral regurgitation (MR) and MVA after PMV. The successful immediate results (MVA ≥ 1.5 cm² and MR ≤ 2) were achieved in 127 (84%) patients of group I and 122 (81%) patients of group D (p = NS). Annual clinical and echocardiographic evaluation was completed for 290 (96%) patients with mean follow-up of 51 ± 27 months. Adverse events occurred in 19 (13%) patients of group I (3 deaths, 7 mitral valve replacements, 5 repeat PMV, 2 NYHA class ≥ 3, 2 technical failures) and 16 (11%) patients of group D (2 deaths, 10 mitral valve replacements, 3 repeat PMV, 1 NYHA class ≥ 3). Estimated actuarial seven-year event-free survival was 75 ± 7% in group I and 82 ± 6% in group D (p = NS). Estimated actuarial seven-year restenosis-free survival was 67 ± 7% in group I and 76 ± 6% in group D (p = NS). On multivariate analysis, unsuccessful immediate result (p < 0.001) and absence of CMR (p < 0.01) were independently related with events. Absence of CMR and smaller mitral valve area after PMV were independently related with restenosis (p < 0.001).

CONCLUSIONS
The Inoue and double-balloon techniques were equally effective in commissurotomy and produced similar, excellent long-term results. The achievement of complete commissurotomy with development of CMR or larger post-PMV mitral valve area is important to optimize the long-term results of PMV. (J Am Coll Cardiol 2000;35:169–75) © 1999 by the American College of Cardiology

Percutaneous mitral valvuloplasty (PMV) using the double-balloon and Inoue balloon techniques has been accepted as an effective procedure for treatment of severe mitral stenosis (MS) (1–6), and both techniques yielded clinical and hemodynamic improvements on immediate and short-term results after PMV (7–12). However, large randomized trials comparing the long-term results of the double-balloon technique and the Inoue balloon technique have not been reported to date. Previous studies suggest that commissural splitting is the major determinant of successful PMV (13–15). Because the dilating instruments are different between the double-balloon and Inoue balloon techniques, the dilating force applied to the fused commissure and the extent of commissural splitting after PMV may be different. It has also not been known whether commissurotomy should be extensive enough to cause the development of commissural mitral regurgitation (CMR) or limited only to split fused commisure without causing the development of CMR.
Anatomical restenosis as determined by echocardiography was not always associated with recurrence of symptoms, and the time to restenosis was difficult to determine clinically. Both echocardiographic and clinical follow-up are necessary to assess the true incidence of restenosis after successful PMV, but only a few studies have reported the results of echocardiographic follow-up for two years (16–18). The primary goal of this prospective randomized trial was to compare the extent of commissurotomy, immediate and long-term clinical, echocardiographic results between double-balloon and Inoue balloon techniques, and a secondary goal was to relate the extent of commissurotomy after PMV with the clinical events and echocardiographic restenosis.

**METHODS**

**Study population.** From September 1989 to December 1995, a total of 302 consecutive patients (77 men, mean age 41 ± 11 years) were randomly assigned to either the double-balloon method (n = 150; group D) or the Inoue balloon method (n = 152; group I). The criteria for inclusion in the study were defined as moderate to severe MS (mitral valve area [MVA] ≤1.2 cm²) patients with symptomatic New York Heart Association (NYHA) functional class II to IV, atrial fibrillation, pulmonary hypertension, or previous history of embolism. Patients with total echocardiographic score >10, mitral regurgitation (MR) ≥grade 3, left atrial thrombi or significant aortic valvular disease were excluded. Informed consent was obtained from all patients, and the study protocol was approved by the ethical committee of our institution.

**PMV.** After cardiac catheterization confirmed severe MS without significant MR, the randomization envelope was opened. The PMV was performed using either the double-balloon or the Inoue balloon technique as previously described (12). Every procedure was done by two experienced physicians (S.J.P. and S.W.P.), and conventional hemodynamic parameters were monitored. To minimize the effects of the balloon size and dilation technique on the extent of commissurotomy, we chose the same size balloon and the same dilation technique in both PMV groups. Balloon size was chosen to obtain the value of effective balloon dilating area/body surface area (EBDA/BSA) at approximately 4 cm²/m², and one-step dilation was performed in both techniques (12).

**Echocardiographic evaluation.** Two dimensional echocardiography and Doppler color flow imaging were performed in all patients on the day before and 24 h after PMV, using a Hewlett-Packard Sonos 1000 or 2500 imaging system equipped with a 2.5-MHz transducer. Transesophageal echocardiography was also carried out in all patients to exclude left atrial thrombus. All the echocardiographic examinations were recorded on super VHS videotapes and reviewed by two experienced physicians (D.H.K. and J.K.S.). The morphological features of the mitral valve were categorized as previously described (19), and the total echocardiographic score was obtained by adding the score for each of the following individual morphologic features: leaflet mobility, thickness, calcification, and subvalvular lesions. The MVA was measured by direct planimetry of mitral orifice before PMV. Mitral regurgitation was detected and semiquantitatively graded with color flow imaging (20).

On the next day after PMV, the MVA was measured by direct planimetry, and successful immediate results of PMV were defined as MVA ≥1.5 cm² and MR grade ≤2. Commissural splitting after PMV was determined from examination of the parasternal short-axis view and defined as either an increased apparent opening angle of either commissure (15) or increased leaflet separation associated with an increased transverse diameter of the orifice, or both (17). The extent of the commissurotomy by PMV was quantified by the increase of transverse diameter of the orifice and the development of CMR. Development of CMR was determined from examination of the parasternal short-axis view and the apical two-chamber view by two independent observers (D.H.K. and J.K.S.), and CMR was defined as MR originating from medial or lateral commissure on color flow imaging and regarded as an index of complete commissural splitting (Fig. 1). The two observers disagreed as to whether CMR occurred in nine (3%) cases, and the final decision was reached based on the presence or absence of CMR in the follow-up echocardiographic study performed one year later.

**Follow-up studies.** Clinical follow-up was performed at two months and six months after PMV and every year until December 1997. Clinical data were collected either during patient visits to the department or by telephone interviews. The primary end points were defined as the clinical events of death, mitral surgery, repeat PMV, and deterioration of NYHA functional class ≥3. Echocardiographic follow-up data were obtained at one-year intervals until December 1997. The secondary end point was echocardiographic restenosis defined as a MVA ≤1.5 cm² with loss of initial gain in MVA ≤50%. Clinical and echocardiographic follow-up was completed for 287 patients (96%) with a
mean follow-up period of 51 ± 27 months (up to eight years).

Statistical analysis. The long-term incidence of clinical events after PMV in patients with favorable morphology of mitral valve ranges from 5% to 10% (21–23). Approximately 150 patients are needed in each group to detect a 10% difference between two groups with a power of 80% and a type I error of 5% (two-sided). The primary analysis of clinical and echocardiographic outcomes was based on the intention-to-treat principle. Numerical values were expressed as mean ± SD. Continuous variables were compared using the Student unpaired t test. The chi-square test compared frequency ratios between groups. Kaplan-Meier analysis was used to determine survival rate, event-free survival rate and restenosis rate. Differences in survival rates between the two groups were examined with the log-rank test. The clinical and echocardiographic variables were evaluated by Cox regression analysis to identify predictors of event-free survival and restenosis. The variables included in the analysis were age, gender, pre-PMV NYHA class, cardiac rhythm, balloon technique, echocardiographic score, pre- and post-PMV MVA and transmitral gradients, development of commissural splitting and CMR, and achievement of immediate successful result after PMV.

RESULTS

Baseline characteristics. Three hundred and two patients were randomly assigned to group I or to group D. Baseline clinical, echocardiographic and hemodynamic characteristics of the study population are summarized in Table 1. No significant differences existed between group I and group D patients in terms of age, gender ratio, NYHA functional class, cardiac rhythm, total echocardiographic score, MVA and mitral valve gradient.

Immediate outcome. Percutaneous mitral valvuloplasty was completed successfully in all 150 patients of group D and in 149 of 152 patients of group I; one death during emergency operation after unsuccessful balloon deflation and two cases of unsuccessful mitral valve crossing occurred in group I. In group I, the total procedure time was 41 ± 16 min, which was significantly shorter than that of group D (50 ± 17 min, p < 0.01). The balloon size was similar in both techniques: the mean value of EBDA/BSA was 3.9 ± 0.3 cm²/m² in both groups. In group I, the mean height of the patients was 159 ± 8 cm, the mean BSA was 1.57 ± 0.15 m², and the diameter of the balloons ranged from 24 to 30 mm. The actual balloon size adjusted by BSA in group I was significantly larger than the recommended initial reference size adjusted by height (27.9 ± 1.0 vs. 25.9 ± 0.8 mm, p < 0.001). The PMV resulted in a significant increase of MVA from 0.9 ± 0.2 to 1.8 ± 0.3 cm² (p < 0.001) in group I, and from 0.9 ± 0.2 to 1.9 ± 0.3 cm² (p < 0.001) in group D, and a significant decrease of transmitral pressure gradient in both groups (16 ± 6 to 7 ± 3 mm Hg [p < 0.001] in group I and 17 ± 7 to 6 ± 4 mm Hg [p < 0.001] in group D). There were no significant differences between the two groups in terms of MVA and mean mitral gradient after PMV. MVA ≥1.5 cm² was achieved in 137 (90%) patients of group I and 132 (88%) patients of group D (p = NS). Of the patients who had a MVA ≥1.5 cm²,

Figure 1. Both commissural splitting and commissural mitral regurgitation after successful PMV on parasternal short axis view (A and B) and apical two-chamber view (C). The arrows indicate split commissures (A) and origination of MR from both commissures (B and C). IVS, interventricular septum; LA, left atrium; LV, left ventricle; MV, mitral valve; MVO, mitral valve orifice; RV, right ventricle.

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<th>Table 1. Baseline Characteristics of Patients Who Underwent Inoue or Double-Balloon Percutaneous Mitral Valvuloplasty</th>
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NYHA = New York Heart Association; MVA = mitral valve area; PAP = pulmonary arterial pressure. Continuous variables are expressed as mean ± SD.
MR grade ⩾ 3 occurred in 10 patients of group I and 10 patients of group D. Thus, the successful immediate results were achieved in 127 (84%) patients of group I and 122 (81%) patients of group D (p = NS). The multiple logistic regression analysis identified lower total echo score and larger pre-PMV MVA as the independent predictors of successful immediate results (p < 0.001).

**Commissural splitting.** Splitting of one or both commissures was observed in 147 (97%) patients of group I and 143 (95%) patients of group D (p = NS). Commissural splitting was observed in 246 of 249 patients with a successful immediate outcome and in 24 (80%) of 30 patients with post-PMV MVA < 1.5 cm² (p < 0.001). The extent of commissurotomy was evaluated using the change of transverse diameter of mitral valve orifice and development of CMR after PMV. The mean changes in transverse diameter of mitral valve orifice after PMV were 0.6 ± 0.2 cm in group I and 0.6 ± 0.3 cm in group D, and the increase of transverse diameter by PMV was not significantly different between the two groups. Commissural mitral regurgitation was observed in 78 (51%) patients of group I and 80 (53%) patients of group D. The severity of CMR was grade 2 in 148 (94%) patients and grade 3 in 10 (6%) patients. No patients with grade 3 of CMR required operation.

**Follow-up.** There were two patient deaths in group I: one patient died at three months after PMV during mitral valve replacement due to flail mitral valve with severe MR, and the other patient with post-PMV MVA of 1.2 cm² died four years after PMV. In patients of group D, there were two deaths from seven years and seven years after PMV. The survival rate at seven years was 97 ± 2% in group I and 99 ± 1% in group D (p = NS). In group I, mitral valve replacement was performed in seven cases, repeat PMV in five cases and deterioration of NYHA functional class ⩾ 3 occurred in two cases during mean follow-up of 51 ± 26 months. In group D, mitral valve replacement occurred in 10 cases, repeat PMV in three cases and deterioration of dyspnea in one case during mean follow-up of 50 ± 28 months. The atrial septal defects with left-to-right shunt on color flow imaging persisted in four patients of group I and 10 patients of group D (p = NS) during follow-up. No patient required early or late surgical closure due to left-to-right interatrial shunt. The cerebral infarctions occurred in one patient of group I and in three patients of group D during follow-up. The probability of event-free survival in group I was 97 ± 2% at three years, 91 ± 3% at five years and 75 ± 7% at seven years and in group D, 98 ± 1% at three years, 92 ± 3% at five years and 82 ± 6% at seven years, respectively (Fig. 2A). Cox regression analysis demonstrated that echocardiographic score, pre- and post-PMV MVA, development of CMR and commissural splitting, calcification of mitral valve and achievement of immediate successful result after PMV were significantly related with the incidence of events at follow-up. Multiple Cox stepwise regression analysis identified that immediate unsuccessful result (p < 0.001) and absence of CMR (p < 0.01) after PMV were directly and independently related with the clinical events.

Among 249 patients with successful immediate results after PMV (MVA ≥ 1.5 cm² and MR grade ≤ 2), echocardiographic restenosis occurred in 22 (17%) patients of group I and in 16 (13%) patients of group D during follow-up.
The estimated actuarial seven-year restenosis-free survival rate was 67 ± 6% in group I and 76 ± 6% in group D, respectively (p = NS) (Fig. 2B). Multiple stepwise Cox regression analysis identified that absence of CMR and smaller post-PMV MVA were the only two independent predictors of echocardiographic restenosis (p < 0.001).

The estimated actuarial seven-year event-free survival rate (84 ± 6%) in patients with successful immediate results after PMV was significantly better than that in patients with poor immediate results due to insufficient valve opening or severe MR (54 ± 9%) (Fig. 3). The estimated actuarial seven-year event-free survival was also significantly different between the patients with restenosis (43 ± 12%) and those without restenosis (92 ± 3%). As decrease in MVA occurred gradually after PMV, no patients with echocardiographic restenosis required emergency reinterventions due to abrupt deterioration of symptoms. The symptomatic improvement by PMV persisted in 29 (63%) of 46 patients with restenosis. These asymptomatic patients with restenosis had a significantly larger MVA at follow-up study than did those who needed mitral valve surgery or PMV (1.2 ± 0.1 cm² vs. 0.9 ± 0.2 cm², p < 0.001).

Development of CMR was the significant independent predictor of event-free and restenosis-free survival, and the serial post-PMV MVAs were significantly different between the patients with and without CMR after PMV (Fig. 4). The annual decrease of post-PMV MVA was also significantly smaller in the patients with, than those without, CMR (0.06 ± 0.12 vs. 0.12 ± 0.16 at one year, p < 0.001; 0.03 ± 0.07 vs. 0.06 ± 0.10 at two years, p = 0.005; 0.02 ± 0.05 vs. 0.07 ± 0.10 at three years after PMV, p < 0.001, respectively). Among 39 patients with CMR ≥2, CMR decreased in 13 (33%) cases, did not change in 22 (57%) cases, and progressed to moderate MR in four (10%) cases. Progression to severe MR requiring mitral valve surgery was not observed in follow-up studies.

DISCUSSION

Inoue versus double-balloon technique. The Inoue single-balloon technique differs from the double-balloon technique in several important aspects. The Inoue technique is easier to perform and needs shorter total procedure and fluoroscopic times (7,12,24), and in this study the procedure time was also significantly shorter in the Inoue balloon than
in the double-balloon technique. The dilating shape achieved in the Inoue balloon is circular and different from the elliptic dilating shape achieved in the double-balloon. It has not been known whether different dilating shapes in the two techniques might produce differences in extent of commissurotomy and whether that might result in different incidences of restenosis and cardiac events. There is controversy as to whether the Inoue and the double-balloon techniques provide similar immediate and long-term results (11,12,25–27). In this randomized trial, we compared clinical and echocardiographic results of the Inoue balloon and the double-balloon technique for up to eight years, and we minimized the effects of balloon size and dilation technique by choosing balloons with similar EBDAs and by using a one-step dilation technique in both groups. Our study demonstrates that the Inoue and double-balloon methods resulted in similar long-term outcomes in terms of survival, cardiac events and echocardiographic restenosis.

**Long-term outcomes.** In this study, the overall actuarial seven-year survival and event-free survival rates were excellent and might be better than those of others (22,23,28). The ages of our patients were 41 ± 11 years, and patients with severe deformity of mitral valve were excluded in this study. Because old age, high echocardiographic score, fluoroscopic calcification and commissural calcification are known as important risk factors for the immediate and long-term outcomes of PMV (29–32), these differences of clinical characteristics and mitral valve morphology in each study should be considered in comparison with the results of PMV.

We found that achievement of successful immediate results and development of echocardiographic restenosis after PMV were significantly related to long-term outcomes of PMV. Previous studies also reported post-PMV MVA and restenosis as significant independent predictors of the long-term results of PMV (6,31–33). Immediate success was related with clinical and echocardiographic characteristics of the patients, such as total echocardiographic score and pre-PMV MVA, but echocardiographic restenosis was more related to procedural variables, such as post-PMV MVA and development of CMR after PMV. These findings suggested that complete commissurotomy with larger MVA or CMR may prevent fibrous fusion of split commissure (34) and restenosis. Both the Inoue and double-balloon techniques obtained a similar extent of commissurotomy based on a similar incidence of CMR and the same change in MVA and transverse diameter of the mitral valve orifice after PMV. The similar extent of commissurotomy in both techniques may explain the similar long-term results in terms of restenosis and cardiac events.

The annual echocardiographic follow-up data suggested that the natural course of most CMR was benign during follow-up and that the rate of decrease in MVA after PMV was significantly slower in patients with CMR compared with those without CMR. Previous studies also reported that the mechanisms of development of MR after PMV were different for mild and severe MR. Mild MR was produced by complete commissurotomy, but severe MR was produced by leaflet tears or chordal rupture (35–37). The mechanism by which CMR maintains initial gain in MVA is unclear. The decrease in MVA after PMV may be related to fusion of split commissure and recoil of the stretch component. Complete commissurotomy and CMR might prevent immediate recoil and late fusion by preventing apposition of split commissures.

**Study limitations.** In this study we chose the same dilation technique and the same balloon size in both groups to differentiate the effects of dilating instruments from those of dilation technique and balloon size. In group I, the balloon sizes were larger than the initial reference balloon sizes adjusted by height, and the dilation technique was also different from the more commonly used stepwise dilation technique (38). For the patients with severe deformity of mitral valve, stepwise dilation with the smaller initial balloon size may have the advantage of avoiding occurrence of severe MR (21,38). Because we speculated that in the patients with favorable morphology of mitral valve, one-step dilation with the maximal recommended size of the balloon (39) could achieve commissurotomy in the largest number of patients without increasing the risk of severe MR and also decrease procedure time compared with stepwise dilation technique, the study population was limited to patients with an echocardiographic score ≤10, and one-step dilation technique was chosen in this study. It is also unclear whether the stepwise dilation technique would be better in long-term results than would the one-step dilation, because the stepwise dilation with inadequate initial inflation volume might decrease CMR as well as severe MR and result in ineffective commissurotomy and early restenosis due to recoil of stretched leaflets. It was reported that the incidence of severe MR was lower if balloon sizes were chosen so that EBDABSA ≤4 cm²/m² and the optimal EBDABSA was between 3.1 and 4.0 cm²/m² (39). The balloon size chosen in this study might be oversized for the patients with high echocardiographic score or high risk of post-PMV MR (40).

In conclusion, this study demonstrates that both the Inoue technique and the double-balloon technique were equally effective in commissurotomy and produced similar and excellent long-term results. Whether the PMV is performed using the Inoue balloon or the double-balloon technique, the achievement of complete commissurotomy with development of CMR or larger MVA is important in optimizing the long-term results of PMV.

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