

Percutaneous balloon valvotomy for patients with severe mitral stenosis

IGOR PALACIOS, M.D., PETER C. BLOCK, M.D., SERGIO BRANDI, M.D., PABLO BLANCO, M.D., HUMBERTO CASAL, M.D., JOSE I. PULIDO, M.D., SIMON MUNOZ, M.D., GABRIEL D'EMPAIRE, M.D., MIGUEL A. ORTEGA, M.D., MARSHALL JACOBS, M.D., AND GUS VLAHAKES, M.D.

ABSTRACT Thirty-five patients with severe mitral stenosis underwent percutaneous mitral valvotomy (PMV). There were 29 female and six male patients (mean age 49 ± 3 years, range 13 to 87). After transseptal left heart catheterization, PMV was performed with either a single- (20 patients) or double- (14 patients) balloon dilating catheter. Hemodynamic and left ventriculographic findings were evaluated before and after PMV. There was one death. Mitral regurgitation developed or increased in severity in 15 patients (43%). One patient developed complete heart block requiring a permanent pacemaker. PMV resulted in a significant decrease in mitral gradient from 18 ± 1 to 7 ± 1 mm Hg ($p < .0001$) and a significant increase in both cardiac output from 3.9 ± 0.2 to 4.6 ± 0.2 liters/min ($p < .001$) and in mitral valve area from 0.8 ± 0.1 to 1.7 ± 0.2 cm² ($p < .0001$). Effective balloon dilating diameter per square meter of body surface area correlated significantly with the decrease in mitral gradient but did not correlate with the degree of mitral regurgitation. There was no correlation of age, prior mitral commissurotomy or mitral calcification with hemodynamic results. PMV is an effective nonsurgical procedure for patients with mitral stenosis, including those with pliable valves, those with previous commissurotomy, and even those with mitral calcification.

Circulation 75, No. 4, 0-0, 1987.

ALTHOUGH the prevalence of rheumatic mitral stenosis has markedly decreased in the United States,¹ rheumatic heart disease is still common in underdeveloped and developing countries, accounting for 25% to 40% of all cardiovascular diseases.^{2,3} Surgical mitral commissurotomy is a low-risk surgical technique that results in symptomatic and hemodynamic improvement in selected patients. Percutaneous mitral valvotomy (PMV) or valvotomy via femoral cutdown using a balloon dilating catheter has recently been used in a small number of patients⁴⁻⁸ as an alternative to surgical mitral commissurotomy. This study reports the results to PMV in 35 patients with severe mitral stenosis.

Materials and methods

Patients. The patient population included 35 patients who presented with severe, symptomatic mitral stenosis. There were

six male and 29 female patients, mean age 49 ± 3 years, (range 13 to 87). Three patients were in NYHA class IIa, four class IIb, 21 class III, and seven class IV. Twenty-six patients were in normal sinus rhythm and nine had atrial fibrillation. Patients with left atrial thrombus shown on echocardiography were excluded.

All patients underwent right and left heart catheterization, measurement of cardiac output, and cine left ventriculography. Severity of mitral regurgitation was graded qualitatively from 1+ to 4+ as previously described.⁹ Selective coronary arteriography was performed in 24 patients and showed normal coronary arteries. Four patients had mild aortic valve disease. Three patients had previously undergone surgical mitral commissurotomy and had mitral restenosis. Severity of mitral valve calcification was graded qualitatively from 1+ to 4+ by its fluoroscopic appearance (1+ calcification barely visible to 4+ dense, multiple valvular opacification). Four patients had previously undergone aortic valve replacement. Ten patients underwent PMV at the Hospital Universitario de Caracas (Caracas, Venezuela), and 25 patients at the Massachusetts General Hospital (Boston). The protocol for the investigation was approved by the human studies committees at both hospitals. The same operators (I. P. and P. C. B.) were involved in all cases and the techniques used were identical.

Percutaneous mitral valvotomy. PMV was performed with a cardiac surgical suite on standby. Right heart catheterization was performed percutaneously from the right internal jugular vein with a thermodilution Swan-Ganz catheter. An indwelling 18-gauge Teflon catheter was placed percutaneously in the left radial artery to monitor systemic blood pressure. Transseptal left heart catheterization was performed from the right common

From the Cardiac and Cardiac Surgery Units of the Massachusetts General Hospital, Harvard Medical School, Boston, and the Cardiac and Cardiac Surgery Units of the Hospital Universitario, Caracas, Venezuela.

Address for correspondence: Igor Palacios, M.D., Cardiac Unit, Massachusetts General Hospital, Boston, MA 02114.

Received April 3, 1986; revision accepted Jan. 8, 1987

Presented at the 59th Annual Scientific Sessions of the American Heart Association, Dallas, 1986.

femoral vein with a No. 8 F Mullins transseptal sheath and dilator (USCI, Billerica, MA) and a modified Brockenbrough needle. Systemic anticoagulation was achieved by 100 U/kg heparin.

Single-balloon valvotomy was performed in 20 patients as previously described by Lock et al.^{5,6} (figure 1). In 14 patients balloon valvotomy was performed with a combination of two balloon dilating catheters. Double-balloon PMV was done differently than reported by Zaibag et al.⁸ in that the two balloon dilating catheters were introduced through the same femoral vein and atrial punctures. When double-balloon PMV was performed, a second 260 cm long exchange wire was passed through the same atrial puncture parallel to the first wire through a special double-lumen sheath (Mansfield, Mansfield, MA). The special double-lumen sheath was then removed, leaving the two guidewires behind. The interatrial septum was dilated with an 8 mm balloon dilating catheter (Mansfield) to allow passage of larger valvotomy balloon catheters. One valvotomy balloon catheter was advanced over one of the guidewires through the left atrium and positioned across the mitral valve. A second balloon dilating catheter was then passed parallel to the first one over the other guidewire. The two valvotomy balloon catheters were then inflated simultaneously by hand until the indentation of the balloon due to the stenotic mitral valve disappeared (figure 2). Inflation-deflation time was approximately 15 sec. Regardless of whether the single- or double-balloon valvotomy technique was used, multiple balloon inflations were done to ensure that the balloon catheters were in correct position across the mitral valve.

Single-balloon PMV was performed in 20 patients. A 25 mm (4.9 cm²) balloon was used in 17 patients, a 20 mm (3.4 cm²) balloon in two, and a 15 mm (1.77 cm²) balloon in one. Double-balloon PMV was performed in 14 patients. Two 15 mm diameter (4.02 cm²) balloon valvotomy catheters were used in four patients, two 18 mm (5.78 cm²) in two patients, a combination of a 15 and a 20 mm balloon catheter (5.51 cm²) in two patients, and a combination of a 25 and 15 mm balloon catheter (7.33 cm²) in six patients.

Immediately after PMV, the balloon valvotomy catheters were removed and the hemodynamic measurements were repeated. Thereafter cine left ventriculography in the right antero-

or oblique projection was performed in all patients to evaluate the severity of mitral regurgitation. Finally, a right heart oximetric study was performed to assess left-to-right shunting through the atrial septum. The procedure was completed in each of the patients in less than 2 hours and was tolerated well with minimal discomfort. Hemostasis of the venous puncture was easily achieved at the end of the procedure by direct compression of the right femoral vein.

After PMV the patients were transferred to an intensive care unit and monitored. Most patients were discharged 24 hr after the procedure.

Hemodynamic measurements. Right and left heart pressures, mitral gradient, and cardiac output were measured before and after PMV (figures 2 and 3). Cardiac output was determined by thermodilution in most patients. However, when tricuspid valve regurgitation was present, the green dye technique with injection in the main pulmonary artery and sampling in a peripheral artery was employed. When left-to-right shunting occurred after PMV, systemic blood flow was obtained according to the Fick principle (superior vena cava oxygen content was used as the mixed sample). Mitral valve area was calculated by the Gorlin formula. Simultaneous mean pulmonary arterial pressure, mean left atrial pressure, and cardiac output determination allowed calculation of pulmonary vascular resistance.

Statistical analysis. Hemodynamic variables before and after PMV were compared by the Hotelling t^2 test for multivariate generalization of the paired t test. Differences were considered significant at $p < .05$. Values are expressed as \pm SEM. Effective balloon dilating diameter was determined by geometrical analysis and normalized by square meter of body surface area. Effective balloon dilating diameter per square meter of body surface area was correlated with mitral gradient reduction and with degree of mitral regurgitation using linear regression analysis. Patient age, prior surgical commissurotomy, and mitral valve calcification were correlated with mitral gradient reduction by multiple regression analysis.

Results

All patients were documented by cardiac catheterization to have severe mitral stenosis. Before PMV,

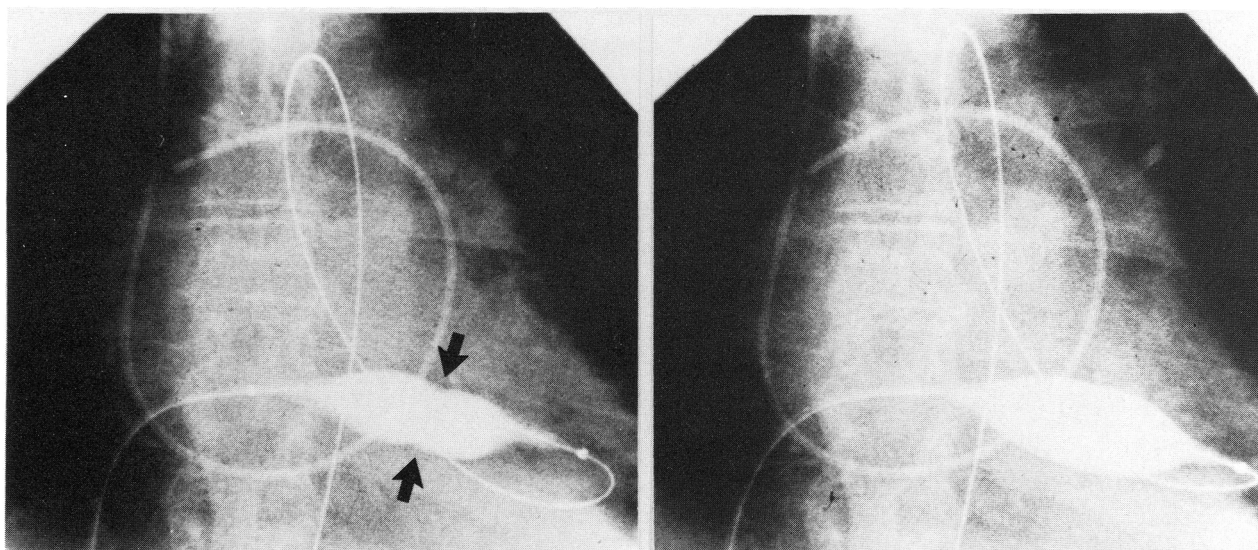


FIGURE 1. Single-balloon PMV. Cineangiograms of a single 25 mm balloon dilating catheter inflated in a mitral valve. Arrows point to the indentation of the balloon produced by the stenotic mitral valve. A guidewire passes through the atrial septum into the left atrium, through the left ventricle and aortic valve, to the distal descending aorta.

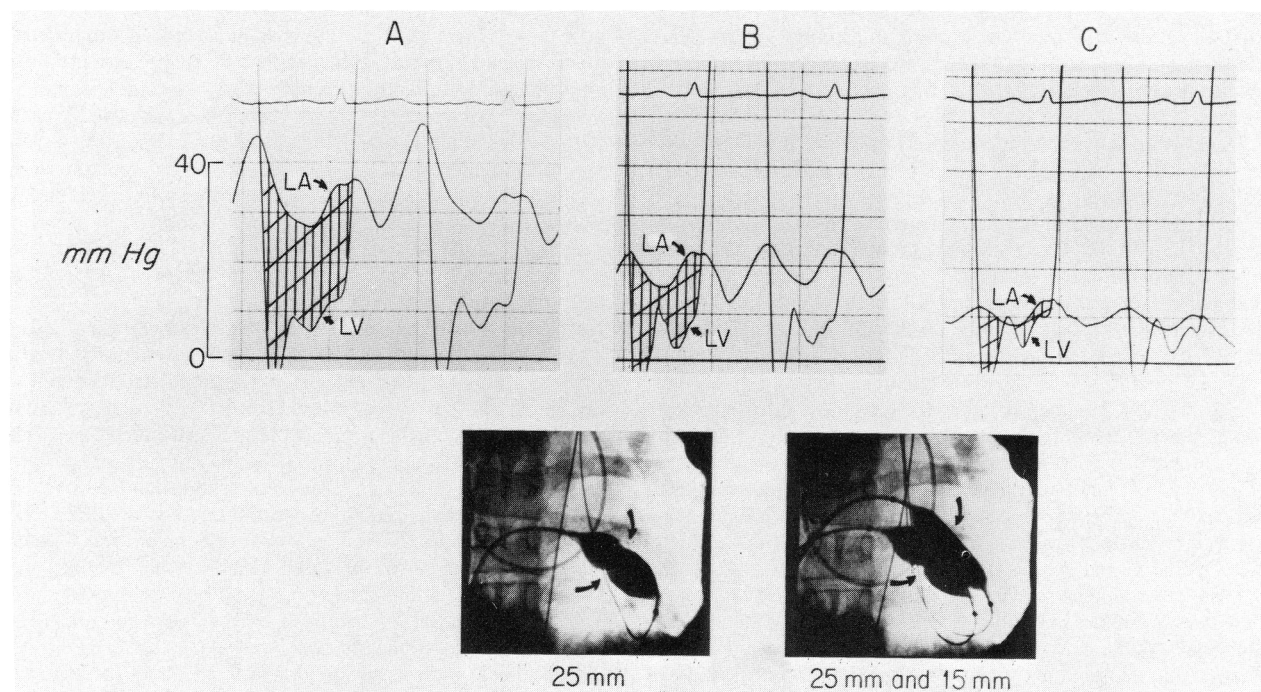


FIGURE 2. Double balloon PMV. Cineangiograms of a single 25 mm balloon dilating catheter (*bottom left*) followed by PMV with a combination of two (25 and 15 mm) balloon dilating catheters (*bottom right*). Hemodynamic measurements before (A) and after single- (B) and double- (C) balloon PMV are above. LV = left ventricular pressure; LA = left atrial pressure.

the average mitral valve gradient was 18 ± 1 mm Hg and the average cardiac output was 3.9 ± 0.2 liters/min, giving an average mitral valve area of 0.8 ± 0.1 cm². Pulmonary artery hypertension was present in all patients. The average mean pulmonary arterial pressure was 41 ± 2 mm Hg. The corresponding mean pulmonary vascular resistance was 338 ± 45 dyne-sec-cm⁻⁵. Before PMV, 1+ mitral regurgitation was present in nine patients and 2+ in one patient. Mitral valve calcification was present in 16 patients (1+ in five, 2+ in four, 3+ in six, and 4+ in one).

Hemodynamic changes produced by PMV. The changes in hemodynamic variables produced by PMV in the 35 patients are shown in figures 4 and 5. The average mitral valve area increased from 0.8 ± 0.1 to 1.7 ± 0.2 cm² ($p < .0001$). PMV resulted in a significant decrease in mitral gradient from 18 ± 1 to 7 ± 1 mm Hg ($p < .0001$) and a significant increase in cardiac output from 3.9 ± 0.2 to 4.6 ± 0.2 liters/min ($p < .001$) (figure 4).

PMV resulted in a significant decrease in mean pulmonary arterial pressure from 41 ± 2 to 27 ± 2 mm Hg ($p < .0001$). Mean left atrial pressure decreased from 27 ± 2 to 14 ± 1 ($p < .0001$). The calculated pulmonary vascular resistance decreased significantly from 338 ± 45 to 260 ± 33 dyne-sec-cm⁻⁵ ($p < .001$) (figure 5).

Symptomatic improvement after PMV occurred in

all but two patients. Twenty patients were judged to be in NYHA class I and 12 class II. Of the two patients who did not improve, one died 3 weeks after PMV from heart failure. The other patient underwent successful mitral valve replacement. All the improved patients are alive except one, who died of sepsis (likely related to drainage of a dental abscess) 2 weeks after PMV.

Mitral regurgitation. Of the nine patients with 1+ mitral regurgitation before PMV, there was no change in four patients. In four patients the severity of mitral regurgitation increased from 1+ to 2+ and in one patient from 1+ to 4+. The patient with 4+ mitral regurgitation has not required surgery, has not developed cardiomegaly, and is in NYHA class I 8 months after PMV. The severity of mitral regurgitation increased to 3+ in the patient who had 2+ severity before PMV. New mitral regurgitation occurred in nine patients. In seven patients the severity was graded 1+ and in the other two patients 2+. There were no factors (severity of mitral valve calcification, effective balloon dilating diameter, age, prior surgical commissurotomy) that would predict which patients would develop or experience more severe mitral regurgitation.

Oximetric studies performed immediately after PMV demonstrated a small left-to-right shunt through the interatrial communication in four patients. The pul-

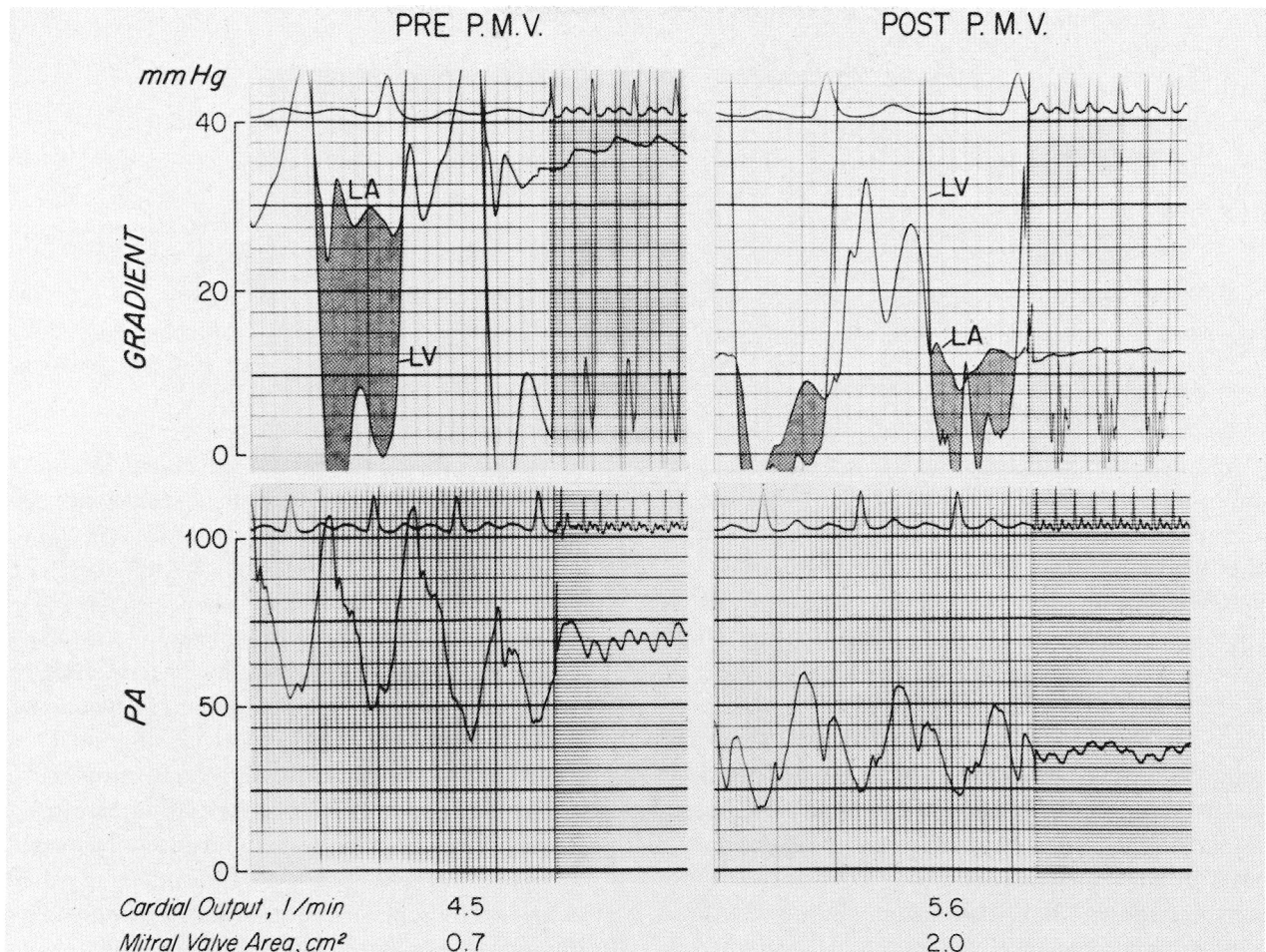


FIGURE 3. Hemodynamic measurements before and after single-balloon PMV in one patient. PA = pulmonary arterial pressure; other abbreviations as in figure 2.

monary-to-systemic blood flow ratios in these four patients were 1.9:1, 1.6:1, 1.5:1, and 1.7:1. Repeat oximetry 24 hr after PMV showed no evidence of atrial shunting in any patient.

Effect of balloon size. Regression analysis showed a significant relationship between effective balloon dilating diameter per square meter of body surface area and gradient reduction. This relationship is described

by the regression equation ($MG = 2.96 (EBDd/m^2) + 2.04$ ($p < .02$), where MG - mitral gradient reduction after PMV and $EBDd/m^2$ - effective balloon dilating diameter per square meter. The correlation coefficient between the two variables was .40. Regression analysis did not demonstrate any correlation between effective balloon dilating diameter per square meter and degree of mitral regurgitation produced by PMV.

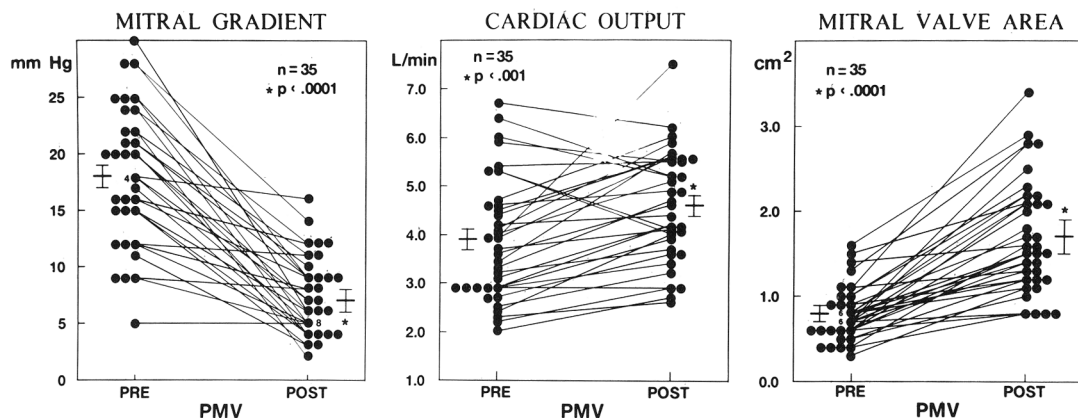


FIGURE 4. Changes in the hemodynamic determinants of mitral valve area produced by PMV.

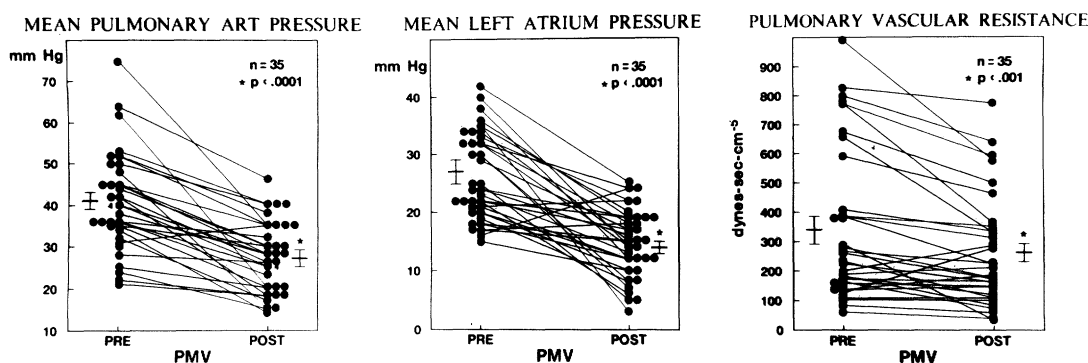


FIGURE 5. Changes in the hemodynamic determinants of pulmonary vascular resistance produced by PMV.

Multiple regression analysis did not identify age, prior surgical commissurotomy, or mitral valve calcification as predictors of the changes in mitral gradient after PMV.

Complications. There was one death associated with PMV. This death occurred after emergency mitral valve replacement in a 78-year-old woman who became hypotensive when an unsuccessful attempt was made to cross the stenotic mitral valve with an 8 mm balloon dilating catheter. Mitral valve replacement was uneventful. At surgery, she was found to have severe mitral stenosis and adherent, laminated left atrial thrombus. After mitral valve replacement the patient could not be weaned from cardiopulmonary bypass because of profound right heart failure. No autopsy was performed.

One patient developed a transient episode of liver dysfunction 3 days after PMV. Although the liver scan was normal and her prothrombin time was in the therapeutic range, a thromboembolic episode may have accounted for this complication.

Two patients developed complete heart block requiring temporary ventricular pacing. In one patient normal atrioventricular conduction returned 8 hr later. The other patient, who had advanced underlying intraventricular conduction disease, needed a permanent pacemaker.

Moderate-to-severe mitral regurgitation occurred in one patient. The severity of mitral regurgitation remained unchanged at follow-up angiography and the patient did not require valve replacement.

Discussion

This study demonstrates that PMV produces immediate hemodynamic changes and clinical improvement in a wide variety of patients with mitral stenosis, including those with pliable mitral valves, those with previous surgical commissurotomy, and even those with mild-to-moderate mitral valve calcification.

Although patients with pliable valves without severe mitral valve calcification and without subvalvular disease would appear to be the best candidates for PMV, the presence of a rigid and/or calcified mitral valve or a previous mitral commissurotomy did not, in this group of patients, result in a worse outcome.

PMV resulted in immediate hemodynamic changes: (1) a significant decrease in diastolic transvalvular mitral gradient and pulmonary arterial pressure and, (2) a significant increase in cardiac output and mitral valve area. These hemodynamic changes are in agreement with previous reports of a small number of patients⁴⁻⁸ and support the belief that PMV is an effective palliative method for relieving mitral stenosis. The hemodynamic changes produced by PMV were not influenced by age, prior surgical commissurotomy, or valvular calcification.

Although PMV resulted in an increase in mitral valve area in all of our patients, six patients had suboptimal results (17%). Although PMV produced an increase (0.5 ± 0.1 to 0.8 ± 0.0 cm²) in mitral valve area in four of these patients, the hemodynamic results were suboptimal because the post-PMV valve area remained below the "critical" mitral valve area of 1.0 cm².¹⁰ Hemodynamic results were also suboptimal in two patients with a post-PMV mitral valve area greater than 1.0 cm² but in whom PMV failed to increase valve area by more than 25%. By these criteria successful PMV was performed in 28 patients (80%).

The rheumatic process deforms the mitral valve leaflets by contracture, shortening, fibrous thickening, calcification, and adherence of the commissures. In addition, in advanced stages there may be proliferation of fibrosis that shortens, fuses, and immobilizes the leaflets, chordae tendineae, and papillary muscles into a rigid funnel. The mechanism of successful PMV is splitting of the commissures toward the mitral annulus, resulting in commissural widening.¹¹ Despite adequate splitting of the commissures by PMV, mitral stenosis

could persist because of subvalvular disease. This could explain the residual mitral gradient after PMV in some of our patients and the less-than-perfect correlation between effective balloon dilating diameter and final hemodynamic improvement.

PMV performed with larger effective balloon diameters (double-balloon technique using a combination of a 15 and a 25 mm or two 20 mm balloon dilating catheters) appears to produce the greater decrease in mitral gradient and increase in mitral valve area. Suboptimal results were produced when a small effective balloon dilating diameter such as 1.77 cm² (15 mm balloon dilating catheter) was used alone. However, the correlation between effective balloon dilating diameter per square meter of body surface area and decrease in mitral gradient is less than perfect because of the wide range of hemodynamic results that occurred in patients in whom an effective balloon dilating diameter of only 4.91 cm² was used. Therefore it appears that PMV is most effective with balloon dilating diameter catheters larger than 4.91 cm². At present we recommend initial dilation of the mitral valve with an effective balloon dilating diameter of greater than 4.9 cm². If the hemodynamic results are suboptimal (residual mean diastolic mitral gradient of more than 8 mm Hg), repeat PMV should be done with a larger effective balloon dilating diameter. With current technology, large balloon areas are obtained only by using a double-balloon technique. We introduce the two balloon catheters through the same venous and atrial punctures, thereby decreasing the potential risks associated with two transseptal catheterizations.

PMV cannot be performed without risk. In skilled hands transseptal left heart catheterization when meticulously performed is safe, but a thorough understanding of the technique, its contraindications, and potential complications are needed before attempting PMV. Other potential complications of PMV include thromboembolic events, severe mitral regurgitation, left-to-right shunting through the created interatrial communication, and heart block. Although only one of our patients may have had a systemic embolus, one of the suspected major risks of PMV in patients with fibrillating atria and calcific mitral valves is systemic emboli. We feel that echocardiographic evaluation to identify atrial thrombus should be carried out in all candidates for PMV, and excluded patients in whom left atrial thrombus was identified. To minimize the risk of embolization, our patients with chronic atrial fibrillation received anticoagulants for at least 2 months before PMV.

Mitral regurgitation either increased or appeared in

15 (43%) patients after PMV. Although it was severe in one patient (3%), no patients required emergency mitral valve replacement for relief of mitral regurgitation. There were no factors that could predict which patients developed mitral regurgitation. Specifically, there was no correlation between balloon dilating diameter per square meter of body surface area and degree of mitral regurgitation.

Regardless of whether the single- or the double-balloon technique is utilized, the interatrial communication created by PMV is not hemodynamically significant. In only four patients (11%) a small left-to-right shunt was demonstrated immediately after PMV. However, in all of them the shunt could not be demonstrated 24 hr later.

Atrial and ventricular ectopy associated with catheter and balloon manipulations occurred frequently during PMV. Complete AV block occurred in two patients (6%) after PMV. Heart block was transient, requiring temporary ventricular pacing in one patient (3%). The other patient developed permanent complete AV block and required a permanent pacemaker (3%).

PMV was performed with a surgical suite on standby. Emergency mitral valve replacement was needed in one patient. Although mitral valve replacement was uneventful, the patient could not be weaned from cardiopulmonary bypass and died from right heart failure. This patient accounted for the only death technically associated with PMV (3%) that occurred in our study.

Although open mitral valve commissurotomy with cardiopulmonary bypass to allow direct visualization of the mitral valve is done frequently, closed surgical mitral valve commissurotomy remains the treatment of choice for mitral stenosis in patients whose preoperative evaluation has revealed no heavy mitral valve calcification, no significant fusion and shortening of chordae, no atrial thrombus, and no significant mitral regurgitation.¹²⁻¹⁴ This study demonstrates that PMV is an attractive alternative to surgical mitral commissurotomy. Although there are risks associated with both surgical commissurotomy and PMV, this series indicates that the risks of PMV are minor. The procedure is performed with sedation and local anesthesia and avoids a thoracotomy. The hospital cost is low, and hospital stay and convalescent periods are short. When restenosis occurs after PMV, the procedure can be repeated or, if needed, cardiac surgery can still be performed without the scarring of a previous thoracotomy. Finally, PMV may be preferred or may represent the only therapeutic alternative for patients with limit-

ing symptoms due to calcific mitral stenosis who cannot undergo cardiac surgery because of other major medical problems.⁶

For most patients mitral commissurotomy is a palliative procedure. In general 10% of patients require reoperation within 5 years and up to 60% within 10 years after surgical commissurotomy.¹⁴ If parallels can be drawn to surgical commissurotomy, PMV should also provide long-lasting results.

Even though the long-term results of PMV are unknown, the encouraging short-term results of this study suggest that PMV may become the treatment of choice for patients with mitral stenosis.

We are grateful to Brenda White for her assistance in typing the manuscript.

References

1. Gordis L: The virtual disappearance of rheumatic fever in the United States: lessons in the rise and fall of disease. T. Duckett Jones Memorial Lecture. *Circulation* **72**: 1155, 1985
2. Markowitz M: Observations on the epidemiology and preventability of rheumatic fever in developing countries. *Clin Ther* **4**: 240, 1981
3. Community control of rheumatic heart disease in developing countries. 1. A major public health problem. *WHO Chron* **34**: 336, 1980
4. Inoue K, Owani T, Nakamura T, Kitamura F, Miyamoto N: Clinical application of transvenous mitral commissurotomy by a new balloon catheter. *J Thorac Cardiovasc Surg* **87**: 394, 1984
5. Lock JE, Khalilullah M, Shrivasta S, Bahl V, Keane JF: Percutaneous catheter commissurotomy in rheumatic mitral stenosis. *N Engl J Med* **313**: 1515, 1985
6. Palacios I, Lock JE, Keane JF, Block PC: Percutaneous transvenous balloon valvotomy in a patient with severe calcific mitral stenosis. *J Am Coll Cardiol* **7**: 1416, 1986
7. McKay RG, Lock KE, Keane JF, Safian RD, Aroesty JM, Grossman W: Percutaneous mitral valvotomy in an adult patient with calcific rheumatic mitral stenosis. *J Am Coll Cardiol* **7**: 1410, 1986
8. Zaibag MA, Kasab SA, Ribeiro PA, Fagih MR: Percutaneous double balloon mitral valvotomy for rheumatic mitral valve stenosis. *Lancet* **1**: 757, 1986
9. Sellar RD, Levy MJ, Amplatz K, Lillehei CW: Retrograde cardioangiography in acquired cardiac disease: technique, indications and interpretation of 100 cases. *Am J Cardiol* **14**: 437, 1964
10. Lewis BM, Gorlin R, Houssay HEJ, Haynes FW, Dexter L: Clinical and physiological correlations in patients with mitral stenosis. *Am Heart J* **43**: 2, 1952
11. Block PC, Palacios IF, Jacobs M, Fallon J: The mechanism of successful mitral valvotomy in humans. *Am J Cardiol* **59**: 178, 1987
12. Nathaniels EK, Moncure AC, Scannell JG: A fifteen year follow up study of closed mitral valvuloplasty. *Ann Thorac Surg* **10**: 27, 1970
13. Grantham RN, Daggett WM, Cosimi AB, Buckley MJ, Mundth ED, McEnany MT, Scannell JG, Austen WG: Transventricular mitral valvotomy: analysis of factors influencing operative and late results. *Circulation* **50**(suppl II): II-200, 1974
14. John S, Bashi VV, Jairaj PS, Muralidharan S, Ravikumar E, Rajarajeswari T, Krishnaswami S, Sukumar IP, Sundar Rao PSS: Closed mitral valvotomy: early results and long-term follow-up of 3724 consecutive patients. *Circulation* **68**: 891, 1983

Percutaneous balloon valvotomy for patients with severe mitral stenosis.

I Palacios, P C Block, S Brandi, P Blanco, H Casal, J I Pulido, S Munoz, G D'Empaire, M A Ortega and M Jacobs

Circulation. 1987;75:778-784

doi: 10.1161/01.CIR.75.4.778

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231

Copyright © 1987 American Heart Association, Inc. All rights reserved.

Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:

<http://circ.ahajournals.org/content/75/4/778>

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in *Circulation* can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the [Permissions and Rights Question and Answer](#) document.

Reprints: Information about reprints can be found online at:
<http://www.lww.com/reprints>

Subscriptions: Information about subscribing to *Circulation* is online at:
<http://circ.ahajournals.org/subscriptions/>