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Mitral Regurgitation After Percutaneous Mitral Valvuloplasty:

Insights Into Mechanisms and Impact on Clinical Outcomes

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Abstract

OBJECTIVES—The aim of this study was to assess the incidence, mechanisms, and outcomes of mitral regurgitation (MR) after percutaneous mitral valvuloplasty (PMV).

BACKGROUND—Significant MR continues to be a major complication of PMV, with a wide range in clinical presentation and prognosis.

METHODS—Consecutive patients with mitral stenosis undergoing PMV were prospectively enrolled. MR severity was evaluated by using quantitative echocardiographic criteria, and its mechanism was characterized by 3-dimensional transesophageal echocardiography, divided

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broadly into 4 categories based on the features contributing to the valve damage. B-type natriuretic peptide levels were obtained before and 24 h after the procedure. Endpoints estimated cardiovascular death or mitral valve (MV) replacement due to predominant MR.

RESULTS—A total of 344 patients, ages 45.1 ± 12.1 years, of whom 293 (85%) were women, were enrolled. Significant MR after PMV was found in 64 patients (18.6%). The most frequent mechanism of MR was commissural, which occurred in 22 (34.4%) patients, followed by commissural with posterior leaflet in 16 (25.0%), leaflets at central scallop or subvalvular damage in 15 (23.4%), and central MR in 11 (17.2%). During the mean follow-up period of 3 years (range 1 day to 10.6 years), 60 patients reached the endpoint. The event-free survival rates were similar among patients with mild or commissural MR, whereas patients with damaged central leaflet scallop or subvalvular apparatus had the worst outcome, with an event-free survival rate at 1 year of only 7%. Long-term outcome was predicted by net atrioventricular compliance (C_n) at baseline and post-procedural variables, including valve area, mean gradient, and magnitude of decrease in B-type natriuretic peptide levels, adjusted for the mechanism of MR.

CONCLUSIONS—Significant MR following PMV is a frequent event, mainly related to commissural splitting, with favorable clinical outcome. Parameters that express the relief of valve obstruction and the mechanism by which MR develops were predictors of long-term outcomes.

Keywords

mitral regurgitation; mitral stenosis; outcomes; percutaneous mitral valvuloplasty

Percutaneous mitral valvuloplasty (PMV) has become the therapy of choice for intervention in rheumatic mitral stenosis (MS) (1). The procedure has evolved with significant improvements in the technique and patient selection, which led to an expansion of the indications (2–4). However, despite high technical expertise that has reduced procedural risks, mitral regurgitation (MR) continues to be a major procedure-related complication (5–9). The incidence of severe MR has remained unchanged over the last decades, and it can occur in up to 15% of patients after PMV, depending on criteria used to define MR severity (2,7–13).

Previous attempts to identify predictive factors for the development of post-procedural MR have had inconsistent results, which may be related to heterogeneity in study populations and MR severity quantification (5,14–16). In particular, previous studies used different methods to assess MR, including angiographic and echocardiographic qualitative criteria, rather than the more accurate quantitative indices, which frequently resulted in the overestimation of the degree of MR (3,5,9,10). Significant MR has been shown to occur more frequently in patients with an asymmetrical commissural thickening and severe subvalvular and valvular disease (6,17–19). However, controversy over valve morphology as a predictor of MR remains (20), and severe MR continues to be an unpredictable complication, with a wide range of clinical presentations (5,7,10).

Several different mechanisms by which MR develops or is exacerbated following PMV have been reported (5,7,8,21). Splitting of fused commissures is the most frequent mechanism that usually causes a mild increase in MR. In some cases, it appears to result from excessive

splitting of the less calcified commissure, thereby resulting in eccentric but more significant MR. Severe MR is also associated with the disruption of the valvular apparatus integrity, including leaflet tearing and subvalvular rupture, which cannot be predicted by any echocardiographic or procedure-related factor. Attempts at characterizing the anatomic features of surgically excised mitral valves (MVs) have revealed that leaflet lacerations were often related to uneven leaflet thickening, but these findings are mostly qualitative in nature (6). In this context, real-time 3-dimensional (3D) echocardiography provides a unique noninvasive method with which to accurately assess MV morphology and elucidate the mechanisms by which severe MR develops after PMV (22,23).

Therefore, the aims of this study were to: 1) evaluate the incidence and predictors of MR after PMV; 2) assess the mechanisms of post-procedural MR using real-time 3D transesophageal echocardiography (TEE); and 3) determine the impact of the mechanism of MR on long-term outcomes following PMV.

METHODS

STUDY POPULATION.

Of the 610 patients who were referred to a tertiary care referral center for management of rheumatic MS, 344 patients who underwent PMV for significant MS between 2011 and 2019 were prospectively enrolled in the study. The study protocol was approved by the Ethical Committee of the Universidade Federal de Minas Gerais (Certificado de Apresentação de Apreciação Ética–32715214.9.0000.5149). Written informed consent was obtained from all patients.

ECHOCARDIOGRAPHIC STUDY.

Comprehensive 2-dimensional (2D) transthoracic and 3D TEE images were performed prospectively in all patients with commercially available equipment (iE33 and EPIQ 7 with an X7–2t TEE probe, Philips Medical Systems, Andover, Massachusetts). In patients who developed MR, a 3D TEE was also performed immediately post-procedure to explore the mechanism of MR.

The morphological features of the MV were categorized by the Wilkins score (24) and also by the echo score revisited, as previously described (11). Briefly, the score includes quantitative parameters to assess leaflet displacement and asymmetry in commissural remodeling in addition to valve area and subvalvular thickening. Apical displacement of the leaflets was measured to assess leaflet mobility in the apical 4-chamber view as the distance from the mitral annulus to the mid portion of the leaflets at their point of maximal displacement from the annulus in diastole. Assessment of commissural morphology was based on the ratio of the commissural areas and defined as symmetrical or asymmetrical commissural thickening (11). The pattern of commissural remodeling was also qualitatively assessed by 3D-TEE (Figure 1). Three risk groups were defined: low (score: 0 to 3), intermediate (score: 5), and high (score: 6 to 11).

The MV area was measured by direct planimetry at the parasternal short axis view, and the continuous wave Doppler used to assess the transmitral pressure gradients. Net

atrioventricular compliance (C_n) was also determined noninvasively by using Doppler echocardiography (25,26). All results were based on the average of 3 measurements for patients in sinus rhythm and 5 measurements for patients in atrial fibrillation.

A comprehensive evaluation of the MV and quantification of MR involved an integration of multiple measures, including a combination of valve morphology, color, and continuous wave Doppler of the regurgitant jet, vena contracta width, regurgitant volume, and effective orifice area, according to guidelines (27). Changes in MR severity were assessed between the baseline echocardiographic study and immediately post-procedure. Mitral regurgitation after PMV was considered significant when it graded as moderate or severe. As for quantification of primary MR, it was graded as moderate or severe, based mainly on an effective regurgitant orifice (ERO) area of 0.20 to 0.39 cm^2 and ≥0.4 cm^2, respectively (27).

THREE-DIMENSIONAL TEE.

TEE images were acquired from the midesophageal view using the full volume and the live 3D zoom mode in the long-axis view to include the MV, aorta, and left atrial appendage, providing a live en face surgical view of the MV from the left atrial perspective (28).

The 3D datasets were digitally stored, and measurements were performed off-line on a dedicated workstation (Philips Q-Lab, version 12.1 software). After properly orienting the 3D dataset, the software automatically displays different views that enabled optimization of the position of each of the 3 planes to improve the identification of valve abnormalities. All 3 scallops of both leaflets were visualized by using different omniplane angles in the midesophageal position to provide a more precise anatomic assessment of MV lesions. Careful attention was paid when adapting the width and elevation of the zoom function over the region of interest with minimized sector width to improve temporal resolution.

MECHANISMS OF MR FOLLOWING PMV.

Significant MR after PMV was divided broadly into 4 categories, based on the features contributing to the valve damage, as follows (23):

1. Central MR: wide valve opening with no recognizable structural abnormalities (Figures 2A to 2C);
2. Isolated commissural MR: jet originated at the site of split commissure, either from the anterolateral or posteromedial or both commissures (Figures 2D to 2F);
3. Commissural with posterior leaflet: jet originated either at the anterolateral commissural scallop, P1, in contiguity with the anterolateral commissure, or at the posteromedial commissural scallop, P3, in contiguity with the posteromedial commissure (Figures 2G to 2I);
4. Anterior or posterior leaflets at the central scallop location (A2/P2), or subvalvular damage that resulted in chordae rupture and flail motion of the leaflets, or a combination of lesions including both leaflet laceration without commissural involvement (Figures 3A to 3F).

The mechanism of MR was determined by 2 independent observers and the discrepancies were resolved by repeated analysis until consensus on a final mechanism of the MR was obtained.

PMV.

PMV was performed by using an anterograde trans-septal approach using the Inoue technique as previously described (4). After each dilatation, a periprocedural transthoracic echocardiogram was performed to assess MV orifice area by planimetry and the degree of MR to determine if further dilatation was required. Conventional hemodynamic measurements of the left ventricular, left atrial, right ventricular, and pulmonary artery pressures were recorded before and immediately after the procedure. After the procedure, patients were subdivided into groups depending on the presence of significant MR at echocardiographic examination.

Additionally, samples of blood from the femoral vein were obtained from all patients during the procedure and repeated after 24 h using peripheral venous puncture to measure B-type natriuretic peptide (BNP) by using standard radioimmunoassay.

ENDPOINT DEFINITIONS.

The long-term outcome was determined as a composite endpoint of cardiovascular death or MVR, especially due to predominant MR or mixed MV disease. Repeated PMV or MVR because of predominant stenosis was not included as an endpoint. Outcome data were obtained from clinic follow-up appointments every 4 months or more often according to the patients' clinical status on an outpatient basis. Additional information was also obtained by reviewing medical records, contacting family members, or telephone interview of the patients. Patients who underwent MV intervention were censored at the time of the procedure, and the echocardiogram was performed at the last follow-up only in those under medical treatment.

STATISTICAL ANALYSIS.

Categorical variables, expressed as numbers and percentages, were compared using chi-squared testing, whereas continuous data, expressed as mean ± SD or median and interquartile range, were compared using Student's unpaired Student's *t*-test or the Mann-Whitney *U* test, as appropriate.

The relationship of baseline echocardiographic variables with significant MR was assessed by using logistic regression analysis. Risk scores that have been shown to predict outcome after PMV were tested. Calibration was based on the Hosmer and Lemeshow test, and discrimination was based on the C-statistic.

Cox proportional hazards regression analyses were performed to identify predictors of adverse outcome, including baseline and post-procedural variables. Patients who died of noncardiac causes or died after surgery were censored as nonevents at the time of death or the surgical procedure, respectively. The proportional hazards assumption was confirmed by using statistics and graphs based on the Schoenfeld residuals.

The variables were checked for collinearity, and obviously interdependent covariates were not used simultaneously in any of the analyses. For outcome prediction, we selected variables that were significantly associated with events and also were clinically relevant, with prognostic value well established. The selected variables for the multivariable model were age, New York Heart Association functional class, C_n, and pulmonary artery pressure at baseline. After the procedure, variables included in the model were MR severity, mechanism of MR, MV area, pulmonary artery pressure, mean transvalvular gradient, and changes in BNP levels.

Kaplan-Meier analysis was used to determine the clinical event-free survival rate according to the mechanisms of MR, and between-group differences in survival rates were assessed with the log-rank test. Statistical analysis was performed by using SPSS for Windows, version 22.0 (SPSS Inc., Chicago, Illinois) and R for Statistical Computing, version 2.15.1 (R Foundation, Vienna, Austria).

RESULTS

CHARACTERISTICS OF THE STUDY POPULATION.

Clinical characteristics of the study population, overall and those with significant MR post-procedure, are presented in Table 1. The mean age was 45.1 ± 12.1 years, and 293 (85%) patients were women. There were 129 patients who had limiting symptoms with NYHA functional class III or IV, despite diuretic agents and beta-blockers at the time of enrollment into the study. Permanent atrial fibrillation was present in 100 (29%) patients at enrollment.

All patients had severe MS, with an area of 0.99 ± 0.3 cm^2, mean gradient of 11.2 ± 4.9 mm Hg, and systolic pulmonary artery pressure of 48.1 ± 18.4 mm Hg before PMV. Baseline echocardiographic features according to significant MR are summarized in Table 2. The MV morphology was suitable for PMV, and 81% of the patients were in the low-risk category of revisited score. The median of the Wilkins score was 7 (range 4 to 10).

Sixty-four patients developed significant MR after PMV: 23 (6.7%) patients had severe MR, and 41 (11.9%) had moderate MR. Logistic regression analysis showed that the echo score revisited was a predictor of significant MR after PMV (odds ratio [OR]: 1.181; 95% confidence interval [CI]: 1.0047 to 1.331; p = 0.007). However, the discrimination of the model was poor (C-statistic: 0.60; 95% CI: 0.51 to 0.68). The Wilkins score was not associated with an increase in MR after PMV in this population.

The echocardiographic and hemodynamic data after PMV according to significant MR are summarized in Table 3. Patients with MR had significantly higher pressure gradients than those who did not develop MR. Similarly, PMV resulted in a greater reduction of left atrial and pulmonary artery pressures as well as in BNP levels in the patients without compared to those with significant MR.

MECHANISMS OF MR AFTER PMV AND IMPACT ON CLINICAL OUTCOME.

The most frequent mechanism of MR was commissural MR, which occurred in 22 patients (34.4%), with an ERO of 0.26 ± 0.1 cm^2 and regurgitant volume of 39 ± 9.3 ml.

Posteromedial commissural MR occurred more frequently (n = 14) than anterolateral commissural MR (n = 6); in 2 patients, MR originated from both commissures. During a mean follow-up of 31 months, only 3 patients (14%) underwent MVR.

Posterior leaflet tear with commissural MR was the second most frequent mechanism, detected in 16 patients (25%), with an ERO of 0.43 ± 0.2 cm^2 and regurgitant volume of 63 ± 20 ml. MR jet origin at the posteromedial scallop (P3) in continuity with the posteromedial commissure occurred in 12 patients and at the anterolateral scallop (P1) in 4 patients. During a mean follow-up of 24 months, 5 patients (31%) underwent MVR.

The third mechanism, characterized by severe valve damage, including anterior or posterior leaflets at the central scallop location (A2/P2) and/or subvalvular damage, occurred in 15 patients (23.4%), resulting in severe MR, with an ERO of 0.60 ± 0.3 cm^2 and regurgitant volume of 70 ± 21 ml. Of these patients, 14 underwent surgery for MVR, of whom 9 required surgery during their hospital stay. Of note, 5 (1.5%) patients who had tearing of the anterior leaflet at the A2 scallop underwent emergency surgery because of immediate onset of dyspnea with hemodynamic instability immediately after the procedure.

Central MR associated with excessive valve opening without structural abnormalities was the least common mechanism and occurred in 11 (17.2%) patients, with an ERO of 0.31 ± 0.1 cm^2 and regurgitant volume of 43 ± 14 ml. The patients were in a good functional class 4.4 years after the procedure, and 4 patients (36%) underwent MVR mainly as a result of associated restenosis.

In the overall population, during a mean follow-up period of 3 years (range 1 day to 10.6 years), 60 patients reached the endpoints, including 9 deaths from cardiovascular causes and 51 MVRs. The event-free survival rates at 1, 3 and 5 years of follow-up in patients without significant MR were 95%, 86%, and 75%, respectively, whereas in patients who developed only commissural MR, they were 89%, 81%, and 67% respectively, with no differences in event-free survival rates among these patients (p = 0.200). Although similar in MR extent, the event-free survival rate at 1 year in patients with commissural MR with posterior leaflet tear was 60%, in contrast to those who developed MR due to leaflet damage involving the central scallop, for whom the event-free survival rate was only 7%. Among all types of MR, the last mechanism was associated with the worst event-free survival rate (Figure 4).

Univariable Cox proportional hazards analyses identified several clinical pre- and post-procedural variables as predictors of adverse outcomes (Table 4). Baseline variables that reflect the consequences of MS were associated with events. The immediate procedural results including commissural splitting, valve area, transmitral pressure gradients, and left atrial and pulmonary artery pressures were associated with events. Similarly, the mechanism by which MR worsened and its severity were predictors of adverse outcome. BNP after PMV, especially the magnitude of decrease in BNP levels, was also associated with events. In the multivariable model, among the baseline variables, C_n was an important determinant of outcomes. Low C_n contributed to an unfavorable course of post-procedural MR with subsequent increased left atrial pressure, resulting in pulmonary congestion and the need for surgery.

The post-procedural variables that were independently associated with events were MV area, mean pressure gradient, delta of BNP, and the mechanisms of MR worsening (Table 5). In particular, MR severity post-PMV did not emerge as an independent predictor of cardiac death or valve intervention in a model that included MR mechanisms.

DISCUSSION

The present study systematically addresses the frequency, severity, mechanisms, and impact on outcomes of MR following PMV in a large cohort of patients with rheumatic MS undergoing the procedure in the last decade (Central Illustration). The majority of patients were middle-age women (approximately 45 years of age) with favorable valve morphology and in a low-risk score category.

The major findings of this study are as follows: 1) significant MR was found in 18.6% of patients following PMV based on quantitative echocardiographic parameters, with severe MR in 6.7% of patients; 2) 4 mechanisms for the development of MR were identified, with major differences in outcomes; 3) MR resulting from tearing along nonanatomic planes of the valve, especially at the central scallop of the anterior leaflet, was mostly associated with severe hemodynamic impairment requiring emergency surgery; and 4) long-term outcome was predicted by C_n at baseline and post-procedural variables that may express hemodynamic improvement provided by the relief of MS, adjusted for the mechanism of MR.

IMPACT OF MR ON OUTCOMES.

As a whole, significant MR is a determinant factor of adverse outcomes following PMV (5,7,9,11,29,30). However, the mechanism by which MR develops plays a major role in predicting prognosis (5,7). MR that originated at the site of the commissural split or at the central orifice of the valve remains stable over time (5,7,31), similar to our results. The hemodynamic improvement because of successful commissural splitting with gain in MV area and reduction in pressure gradient determines a favorable prognosis, despite the increased MR (7). The decrease in valve area usually is progressive over time, whereas commissural MR tends to be stable or decrease during follow-up (7,10,32).

Although various mechanisms may account for the development of MR after PMV, MR resulting from a tear in the anterior leaflet involving the central segment is one of the most severe types (21). This may occur due to sudden pressure delivered by the balloon, which would then cause the splitting of the valve along the path of least resistance, which usually occurs at the points of commissural fusion. Commissural calcification may represent sites of greater resistance than the valve tissue itself, leading to delivery of the balloon pressure to the relatively thin anterior leaflet and causing it to tear (21). Additionally, uneven thickness of the valve with thick areas coexisting with thin or almost normal zones may also lead to leaflet tearing, because the normal tissue may tear with the pressure imposed by the balloon (17). An examination of surgically excised MVs showed 3 distinct anatomic derangements in the mitral apparatus that were associated with significant MR after PMV: uneven leaflet thickening, severe and extensive subvalvular deformation, and commissural calcification (17,21,33).

The clinical course of patients with significant MR after PMV has been reported to be variable (7,16). However, studies addressing the impact of MR after PMV on outcomes assessed regurgitation severity by semiquantitative angiographic or echocardiographic criteria, which have several limitations (7–9,14,32). Although color flow Doppler provides visualization of the origin of the regurgitant jet and its size, overestimation of regurgitant severity may occur in high Doppler gain and smaller left atrium size (27). In contrast, structural valve damage after PMV including perforation of the leaflet at the commissural site can be misleading, because the eccentric jets appear significantly smaller than centrally directed jets of similar hemodynamic severity. Additionally, 2D echocardiography may underestimate the valve abnormalities compared with the operative findings (21); in particular, anterolateral or posteromedial scallop tear in association with commissural MR may have not been identified by the earlier studies, and hence, leaflet tear was under-reported as the mechanism.

RISK FACTORS FOR MVR.

The evolution of MR after PMV depends mainly on the severity of the regurgitant lesion and the cardiovascular response to the regurgitant volume. Usually, acute MR in patients undergoing PMV with pre-existing chronic pulmonary venous hypertension with a larger left atrium is better tolerated than in those without the underlying condition (16). Additionally, the hemodynamic improvement provided by the relief of valve obstruction is the key predictor of the need for MVR. Kim et al (7) found that atrial fibrillation, non-commissural MR, and higher mean mitral gradient immediately after PMV were predictors of surgery for MVR. In the present study, we also found that the mean mitral gradient and valve area were independent determinants of surgery. In particular, low C_n at baseline was associated with worse tolerance of MR and high risk for surgery. Of note, even in patients who developed severe MR, those who had normal left atrial compliance may tolerate well the acute volume overload imposed by MR. Additionally, BNP level reduction, reflecting decreased left atrium pressure, was also a predictor of outcome.

The mechanism of MR plays a major role in the natural history of MR after PMV and the need for MVR. A previous study (21) with 1,388 patients who underwent PMV from 1990 to 2003 showed that 27 patients (1.7%) required emergency surgery, which is similar to our study 1 decade later (n = 5; 1.5%). In this study, only the leaflet tearing warranted emergency surgery, and anterior leaflet tearing occurred in its central areas in all the cases studied. Another study including 3,650 patients showed that 1.8% of the patients required urgent surgery for severe MR, mainly due to leaflet tearing (34). Similarly, our patients who required emergency surgery were noted to have tears at the central scallop of the anterior leaflet (A2). Indeed, the anterior leaflet has a greater surface area compared to the posterior leaflet, and it accounts for the majority of the closing surface area of the MV. The anterior leaflet tearing led to a sharp increase in left atrial pressure, which, in association with unrelieved valve obstruction, may cause pulmonary edema and eventually death. In contrast, a tear of the posterior mitral leaflet is more frequent than the anterior leaflet and usually is better tolerated, especially small tears along the natural planes of the commissures (5). Therefore, early clarification of MR mechanisms helps identify patients who are at high risk of clinical instability to provide timely lifesaving heart surgery.

STUDY LIMITATIONS.

This is a single-center study that was restricted to relatively young patients who had good valve morphology. Therefore, our results cannot be directly extrapolated to other subgroups of MS patients. Although surgical findings are helpful in determining the mechanism of MR in cases of emergency surgery, reliable insights on this mechanism cannot be provided by surgical inspection of the excised valves. Additionally, we used a quantitative evaluation of MR severity based on ERO area, which may be inaccurate in cases of eccentric jets associated with leaflet tear or perforation. However, the essential echocardiographic parameters were integrated for the overall accuracy of assessment of MR severity, including 3D-TEE analysis of the valve apparatus (27). Event-free survival rates in patients who develop MR may be associated with restenosis due to disease progression and not directly attributed to MR worsening. However, the prediction model was adjusted for post-procedural variables, especially valve area, which is the main predictor of restenosis (32). Finally, variable selection was not based on statistical power, thereby increasing the risk of models overfitting.

CLINICAL IMPLICATIONS.

In a contemporary series of selected patients with rheumatic MS who undergo PMV, significant MR may occur by different mechanisms. Although some of them can be predicted by echocardiographic features, the most severe type of MR remains unpredictable. On the other hand, clinical tolerance and progression of post-procedural MR can be well predicted, which provides a strong basis for decision making about emergency surgery. The present study addresses the main gap in the current state of knowledge by providing additional evidence on the management of post-procedural MR. More specifically, our study highlights which patients must be referred for emergency surgery as well as which patients can be discharged from the hospital with the need for surgery assessed during follow-up on an outpatient basis. Therefore, it is important to underline that PMV should be performed in an experienced center with a team having high level of surgical expertise available to intervene in selected cases of MR.

CONCLUSIONS

An increase in the severity of MR following PMV is relatively frequent, mainly related to commissural splitting and with favorable clinical outcome. MR due to tearing of the leaflets at the central scallop location or subvalvular damage results in severe adverse hemodynamics requiring immediate surgery. The hemodynamic improvement after the relief of MS expressed by gain in the valve area, reduction in the pressure gradient, and BNP levels is associated with better event-free survival in addition to the mechanism of MR.

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AUTHOR DISCLOSURES

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ABBREVIAT IONS AND ACRONYMS

2D	2-dimensional
3D	3-dimensional
BNP	B-type natriuretic peptide
C_n	net atrioventricular compliance
MR	mitral regurgitation
MS	mitral stenosis
MV	mitral valve
MVR	mitral valve replacement
PMV	percutaneous mitral valvuloplasty
TEE	transesophageal echocardiography

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PERSPECTIVES

COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS:

The clinical significance and prognosis of MR following PMV is not well defined. The adaptive hemodynamic response of MR relies basically on the relief of valve obstruction and the mechanism by which MR develops. Leaflet tearing along nonanatomic planes of the valve translates to more severe hemodynamic impairment and induction of clinical instability, which requires timely lifesaving heart surgery.

TRANSLATIONAL OUTLOOK:

The underlying mechanism related to disruption of the valve integrity after the procedure is a critical issue in the management of patients with acute MR. Further studies are needed to better determine the predictors of MR after PMV and improve patient selection for the procedure.

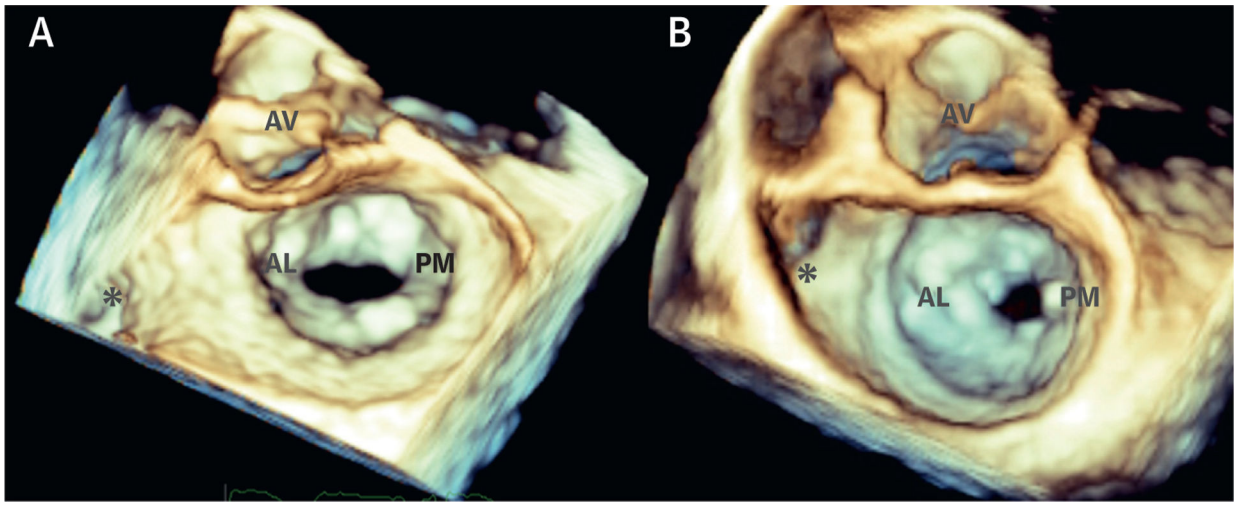


FIGURE 1. Pattern of Commissural Thickening in Rheumatic Mitral Stenosis Using 3-Dimensional Transesophageal Echocardiography

(A) Symmetrical thickening of both the anterolateral and posteromedial commissures. **(B)** The anterolateral commissure is more thickened compared to the posteromedial commissure, with an asymmetric pattern of commissural involvement by the rheumatic process. *Left atrial appendage. AL = anterolateral commissure; AV = aortic valve; PM = posteromedial commissure.

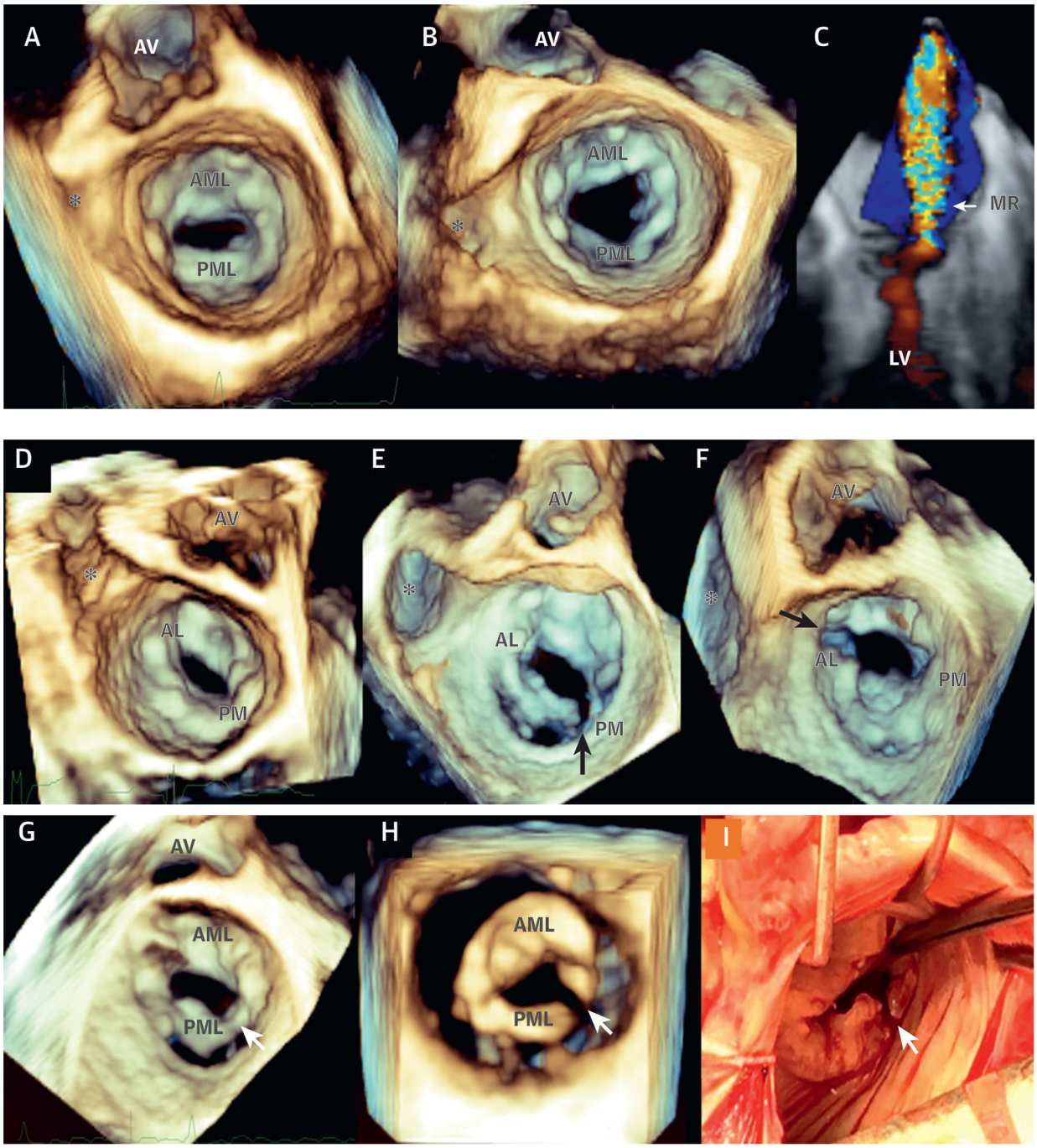


FIGURE 2. Central Mitral Regurgitation, Isolated Commissural Mitral Regurgitation, and Commissural With Posterior Leaflet

(A) Three-dimensional TEE of a patient with mitral stenosis before percutaneous mitral valvuloplasty. **(B)** Image of the mitral valve post-procedure showing an increased mitral valve orifice at the central location, with no recognizable structural abnormalities. **(C)** Central mitral regurgitation is shown by color Doppler flow mapping. **(D)** Three-dimensional TEE of a patient with mitral stenosis before percutaneous mitral valvuloplasty showing the fusion of both commissures. **(E)** Mitral valve after the procedure with

posteromedial commissure opening **(arrow)**. (**F)** Post-procedural mitral valve image with anterolateral commissure opening **(arrow)**. **(G)** Three-dimensional TEE before percutaneous mitral valvuloplasty **(arrow)**. **(H)** Three-dimensional TEE showing a tear of P2 after the procedure **(arrow)**. **(I)** Intraoperative view through the opened left atrium and aortotomy shows perforation between P2 and P3 **(arrow)**. *Left atrial appendage. AML = anterior mitral leaflet; MR = mitral regurgitation; PML = posterior mitral leaflet; TEE = transesophageal echocardiography; other abbreviations as in Figure 1.

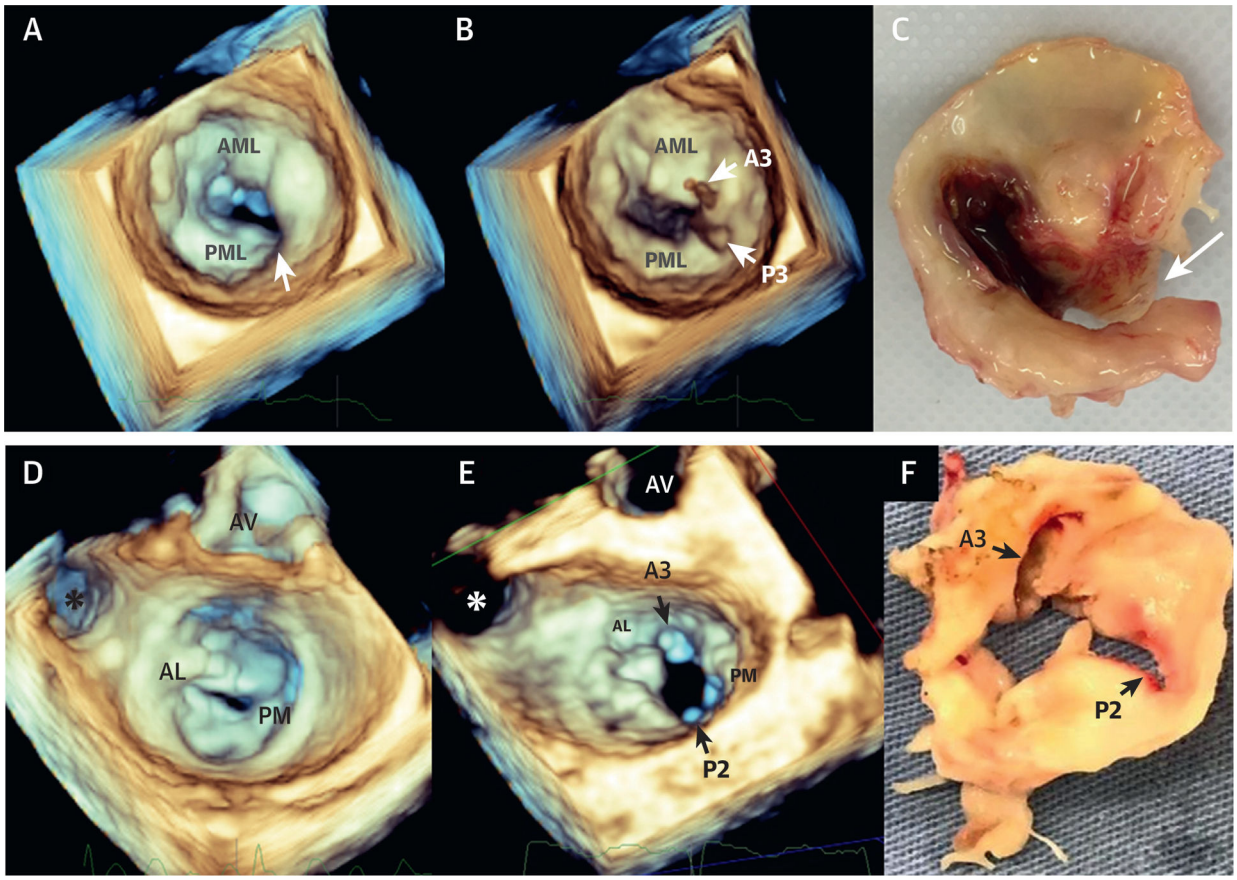


FIGURE 3. Posteromedial Commissure With the Posterior (P3) and the Anterior (A3) Leaflet Laceration and Mitral Regurgitation due to a Combination of Lesions

(A) Three-dimensional transesophageal image before percutaneous mitral valvuloplasty. **(B)** Three-dimensional transesophageal image post-procedure showing lacerations of P3 and A3 in continuity with posteromedial commissure. **(C)** Mitral valve removed during surgery. Note that the lesions are present throughout and most prominent in the posteromedial commissure **(arrow)**. (**D)** Three-dimensional TEE before percutaneous mitral valvuloplasty from a young patient with severe mitral stenosis and marked valve deformity. **(E)** Three-dimensional TEE post-procedure showing lacerations of P2 and A3 without opening of the commissures. **(F)** Mitral valve removed during surgery showing a combination of lesions **(arrows)**. *Left atrial appendage. Abbreviations as in Figures 1 and 2.

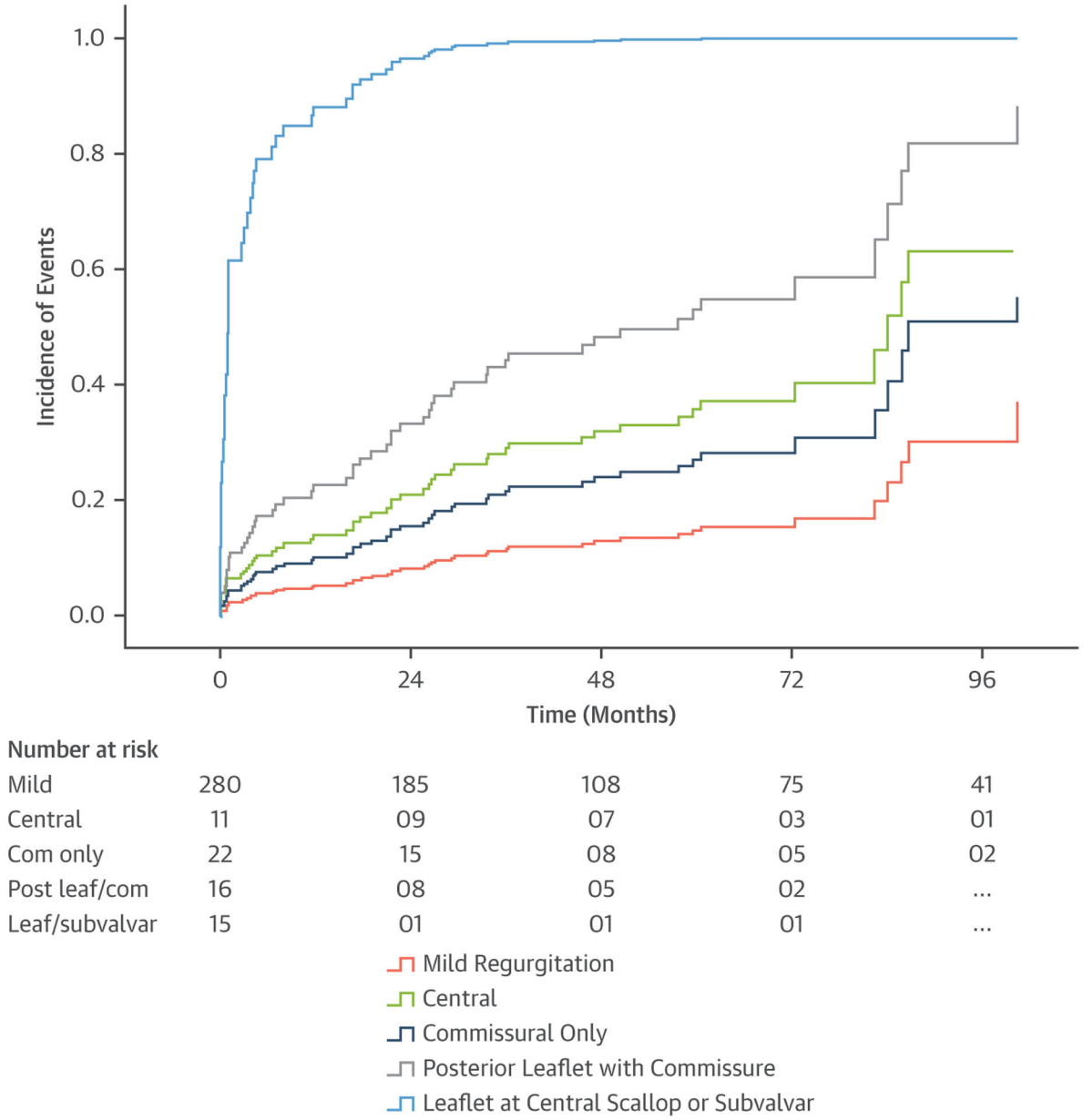
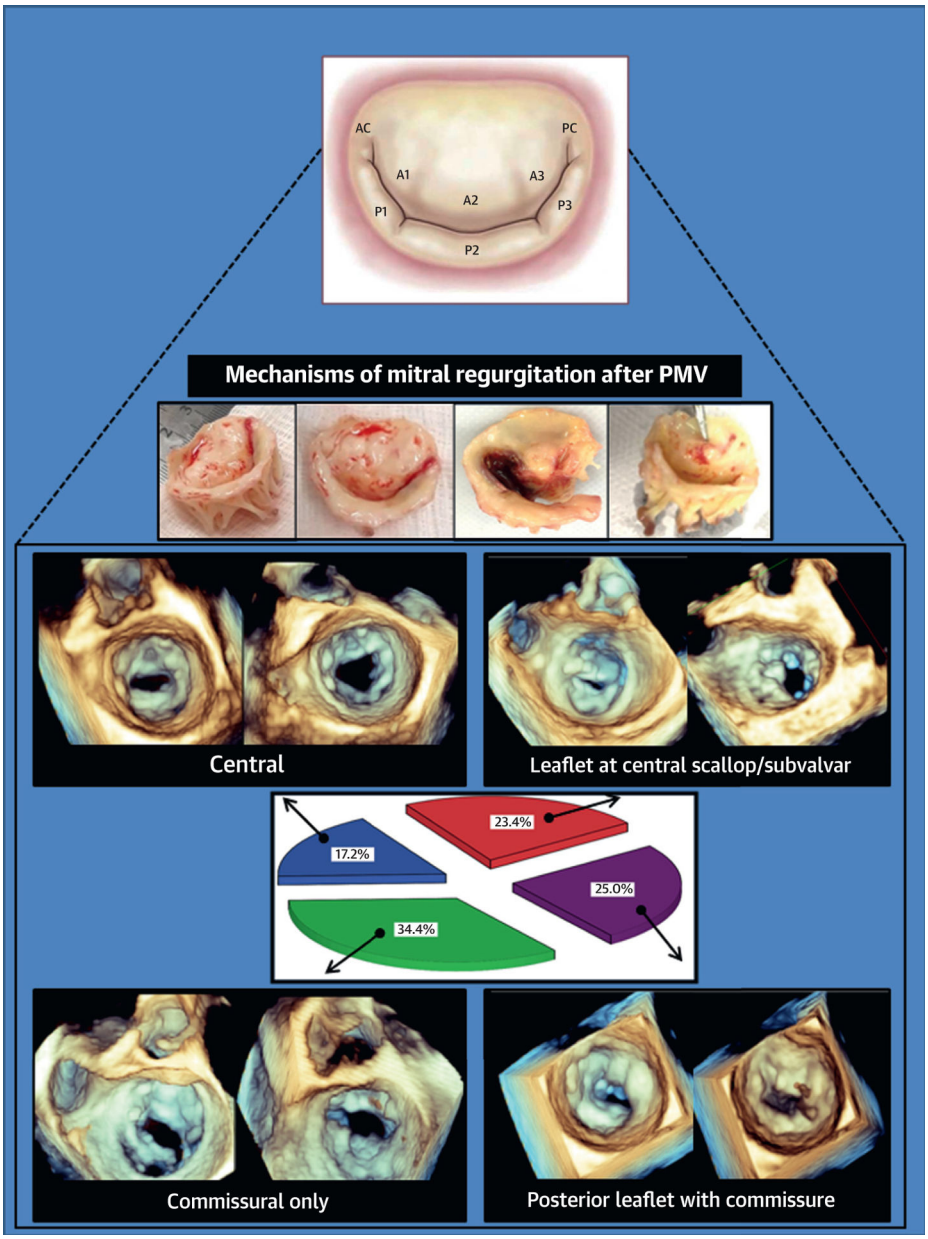


FIGURE 4. Incidence of Adverse Events at Long-Term Follow-Up

The cumulative incidence of events (cardiac death or mitral valve replacement) during the follow-up period stratified according to post-procedural MR mechanisms. Results of the Cox proportional analysis. Com = commissure.



CENTRAL ILLUSTRATION. Mechanisms of Mitral Regurgitation Following Percutaneous Mitral Valvuloplasty

(A) Schematic of the mitral valve from left atrial view showing the 3 scallops of the anterior (A1, A2, A3) and posterior (P1, P2, P3) leaflets. **(B)** gross morphological aspects of the mitral valves from patients with mitral stenosis who underwent cardiac surgery after percutaneous mitral valvuloplasty. **(C)** Examples of the 4 mechanisms of mitral regurgitation by 3D transesophageal image pre- and post-percutaneous mitral valvuloplasty. The pie chart indicates the frequency of each mechanism of mitral regurgitation.

TABLE 1

Demographic and Clinical Characteristics of the Study Population Stratified According to MR Severity After Percutaneous Mitral Valvuloplasty

Clinical Data	Overall Study Group (n = 344)	Without Significant MR (n = 280)	Significant MR (n = 64)	p Value
Age, yrs	45.1 ± 12.1	44.9 ± 11.8	45.9 ± 13.4	0.499
Female, %	293 (85)	238 (85)	55 (86)	0.678
Body surface area, m^2	1.68 ± 0.2	1.69 ± 0.2	1.66 ± 0.2	0.317
NYHA functional class III-IV	129 (38)	100 (36)	29 (45)	0.192
Chest pain	155 (45)	120 (43)	35 (55)	0.046
Right-sided heart failure	99 (29)	84 (30)	15 (23)	0.324
Atrial fibrillation	100 (29)	83 (29)	17 (27)	0.938
Previous valvuloplasty *	104 (30)	91 (32)	13 (20)	0.107
Ischemic cerebrovascular events †	54 (16)	45 (16)	9 (14)	0.710
Penicillin benzathine use	100 (29)	90 (32)	10 (16)	0.018
Anticoagulation therapy	113 (33)	90 (32)	23 (36)	0.535
Heart rate, beats/min	70.8 ± 13.9	70.3 ± 13.5	72.8 ± 15.2	0.228
Systolic blood pressure, mm Hg	115.4 ± 17.0	115.5 ± 17.0	114.9 ± 17.1	0.797
Diastolic blood pressure, mm Hg	74.6 ± 10.6	74.9 ± 9.9	73.3 ± 13.1	0.305
Natriuretic peptide BNP, pg/ml	166 (101–300)	158 (98–279)	233(132–350)	0.023

Values are mean ± SD, n (%), or median (interquartile range).

*Surgical commissurotomy or percutaneous valvuloplasty. Nine patients underwent both procedures.

†Stroke or transient ischemic attack at baseline. BNP = B-type natriuretic peptide; MR = mitral regurgitation; NYHA = New York Heart Association.

TABLE 2

Baseline Echocardiographic and Hemodynamic Characteristics of the Study Population Stratified by MR Severity After Percutaneous Mitral Valvuloplasty

	Overall Study Group (N = 344)	Without Significant MR (n = 280)	Significant MR (n = 64)	p Value
Echocardiographic data				
LVDd, mm	47.9 ± 6.1	47.9 ± 6.6	46.9 ± 6.4	0.287
LVSd, mm	31.2 ± 5.2	31.3 ± 5.4	30.6 ± 5.4	0.337
LVEF, %	58.2 ± 6.7	58.4 ± 6.8	57.1 ± 6.1	0.791
LA dimension, mm	50.8 ± 6.8	50.8 ± 7.6	49.8 ± 5.1	0.262
LAV index, ml/m^2	61.2 ± 23.5	61.7 ± 24.8	59.1 ± 16.2	0.270
RA area, cm^2	17.2 ± 6.9	17.6 ± 7.3	15.8 ± 4.8	0.039
Peak gradient, mm Hg	19.4 ± 6.9	19.2 ± 6.8	20.7 ± 7.3	0.109
Mean gradient, mm Hg	11.2 ± 4.9	11.0 ± 4.7	12.1 ± 5.8	0.069
Mitral valve area, cm^{2*}	0.99 ± 0.26	1.01 ± 0.25	0.94 ± 0.24	0.072
Leaflet displacement, mm	14.7 ± 2.5	14.9 ± 2.5	14.2 ± 2.4	0.059
Asymmetrical commissures	72 (21)	50 (18)	22 (34)	0.024
Wilkins score	7 (6–8)	7 (6–8)	7 (7–8)	0.834
Revisited echo score	2 (0–3)	2 (0–3)	2 (1–5)	0.017
SPAP, mm Hg	47.7 ± 1.5	46.7 ± 17.6	51.7 ± 21.1	0.060
Systolic annular velocity, cm/s†	10.4 ± 2.1	10.5 ± 2.2	10.3 ± 2.0	0.639
RVFAC, %	46.3 ± 10.7	46.8 ± 10.5	44.7 ± 11.1	0.189
Moderate or severe TR	59 (17)	50 (18)	9 (14)	0.543
C_n, ml/mm Hg	4.9 ± 1.6	4.9 ± 1.7	4.5 ± 1.6	0.115
Pre-procedural hemodynamic data				
LA pressure, mm Hg	23.6 ± 8.3	23.5 ± 8.2	24.4 ± 8.9	0.556
Systolic PAP, mm Hg	52.3 ± 20.0	51.1 ± 18.6	57.5 ± 24.9	0.076
Diastolic PAP, mm Hg	21.0 ± 9.8	22.7 ± 9.1	25.8 ± 12.4	0.082
Mean PAP, mm Hg	33.4 ± 12.9	32.6 ± 11.7	37.2 ± 16.7	0.048
Cardiac index, l/min/m^2	2.5 ± 0.8	2.5 ± 0.8	2.4 ± 0.9	0.533
PVR index, Wood units	2.3 (0.9–4.8)	2.1 (0.8–4.4)	3.0 (1.4–5.3)	0.195

Values are mean ± SD, n (%), or median (interquartile range).

[*] Mitral valve area by planimetry.

[†] Peak systolic velocity at the tricuspid annulus.

C_n = net atrioventricular compliance; LA = left atrium; LAV = left atrial volume; LVDd = left ventricular end-diastolic diameter; LVEF = left ventricular ejection fraction; LVSd= left ventricular end-systolic diameter; MR = mitral regurgitation; RA = right atrium; PAP = pulmonary artery pressure; PVR = pulmonary vascular resistance; RVFAC = right ventricular fractional area change; SPAP = systolic pulmonary artery pressure; TR = tricuspid regurgitation.

TABLE 3

Post-Procedural Data According to MR Severity After Percutaneous Mitral Valvuloplasty

	Without Significant MR (n = 280)	Significant MR (n = 64)	p Value
Echocardiographic data			
LA dimension, mm	48.2 ± 7.4	48.2 ± 8.5	0.993
LAV index, ml/m^2	57.9 ± 21.2	60.1 ± 15.9	0.493
Peak gradient, mm Hg	11.1 ± 3.7	16.1 ± 5.4	<0.001
Mean gradient, mm Hg	5.2 ± 2.6	7.5 ± 3.2	<0.001
Mitral valve area, cm^2	1.69 ± 0.26	1.61 ± 0.29	0.041
SPAP, mm Hg	36.9 ± 22.1	44.4 ± 15.2	0.020
Tricuspid annular motion, mm	18.3 ± 4.3	17.9 ± 3.8	0.503
Systolic annular velocity, cm/s	10.2 ± 2.2	10.8 ± 2.1	0.127
RVFAC, %	49.9 ± 8.7	45.9 ± 8.5	0.005
Moderate or severe TR	51 (18)	7 (11)	0.141
Hemodynamic data			
LA pressure, mm Hg	16.7 ± 6.1	19.1 ± 6.7	0.045
Systolic PAP, mm Hg	42.4 ± 14.0	50.7 ± 17.0	0.002
Diastolic PAP, mm Hg	18.6 ± 7.1	23.1 ± 9.8	0.001
Mean PAP, mm Hg	26.6 ± 9.1	32.5 ± 12.1	0.001
Cardiac index, l/min/m^2	2.6 ± 0.9	2.4 ± 0.8	0.251
PVR index, Wood units	2.1 (1.3–4.0)	2.7 (1.8–4.0)	0.205
BNP, pg/ml	91 (53–175)	182 (93–283)	<0.001

Values are mean ± SD, n (%), or median (interquartile range).

Abbreviations as in Table 2.

TABLE 4

Predictors of Long-Term Outcomes After Percutaneous Mitral Valvuloplasty (Univariable Analysis)

	Hazard Ratio	95% CI	p Value
Clinical data			
Age, yrs	1.041	1.041–1.064	<0.001
NYHA functional class	1.395	1.028–1.894	0.032
Right-sided heart failure	1.946	1.138–3.327	0.015
Pre-procedural variables			
C_n at baseline, ml/mm Hg	1.667	1.008–2.791	0.047
Leaflet displacement, mm	0.870	0.775–0.977	0.018
Asymmetrical commissures	4.206	1.049–16.872	0.034
RA area, cm^2	1.054	1.025–1.083	<0.001
Echocardiographic score	1.378	1.152–1.648	0.001
BNP, pg/ml	1.001	1.000–1.002	0.012
Post-procedural data			
Mitral valve area, cm^2 *	0.782	0.727–0.841	<0.001
SPAP, mm Hg	1.009	1.002–1.016	0.012
Moderate or severe TR	2.967	1.730–5.086	<0.001
Tricuspid annular motion, mm	0.920	0.857–0.986	0.019
RVFAC, %	0.970	0.941–0.994	0.045
Commissural splitting	0.610	0.454–0.820	0.001
Significant Mitral regurgitation	3.348	2.090–5.362	<0.001
Mean gradient, mm Hg †	1.112	1.069–1.157	<0.001
Mechanism of MR ‡	4.133	2.466–6.927	<0.001
LA pressure, mm Hg	1.084	1.034–1.136	0.001
Mean PAP, mm Hg §	1.032	1.004–1.060	0.021
Cardiac index, $l/min/m^2$	0.500	0.315–0.791	0.003
BNP, pg/ml	1.002	1.001–1.003	<0.001
Change in BNP, pg/ml ‖	0.487	0.400–0.593	<0.001

*Mitral valve area by planimetry, hazard ratio per 0.1-cm^2 increase.

†Gradient measured 24 h after the procedure by echocardiogram.

‡Reference category is commissural MR.

§PAP invasively measured.

‖Change was calculated using this formula: (Pre-procedure value – Post-procedure value)/Pre-procedure value.

CI = confidence interval; RA = right atrial; other abbreviations as in Tables 1 and 2.

TABLE 5

Independent Predictors of Long-Term Outcomes After Percutaneous Mitral Valvuloplasty (Multivariable Cox Regression Analysis)

	Hazard Ratio	95% CI	p Value
C_n at baseline, ml/mm Hg	1.676	1.155–2.432	0.007
Mechanism of MR *	6.826	2.569–18.139	<0.001
Post-procedural mean gradient, mm Hg	1.921	1.408–2.621	<0.001
Post-procedural MV area, cm^2 †	0.781	0.617–0.985	0.039
Changes in BNP, pg/ml‡	0.327	0.161–0.661	0.002

*Reference category is commissural MR.

†Mitral valve area by planimetry, hazard ratio per 0.1-cm^2 increase.

‡Calculated using this formula: (Pre-procedure value – Post-procedure value)/Pre-procedure value.

MV = mitral valve; other abbreviations as in Tables 1 and 4.