

Effects of Percutaneous Balloon Mitral Valvuloplasty on Plasma B-type Natriuretic Peptide in Rheumatic Mitral Stenosis With and Without Atrial Fibrillation

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Background and aim of the study: The study aim was to evaluate the effect of percutaneous balloon mitral valvuloplasty (PBMV) on plasma B-type natriuretic peptide (BNP) levels in patients in sinus rhythm (SR) and with atrial fibrillation (AF).

Methods: Thirty patients with rheumatic mitral stenosis who underwent successful PBMV were included in the study. Of these patients, 21 were in SR (SR group) and nine had AF (AF group). Plasma BNP levels were measured using the Triage BNP Test in all patients before, and at 20 min and 24 h after, PBMV. Control levels were measured in eight healthy volunteers.

Results: Basal plasma BNP levels in patients were significantly higher than those in controls (123.5 ± 69.5 versus 16.4 ± 7.6 pg/ml, $p < 0.01$), and correlated with mean left atrial pressure (mLAP; $r = 0.441$, $p < 0.05$) and pulmonary artery pressure (PAP; $r = 0.488$, $p < 0.01$). No significant difference was observed in BNP levels between the SR and AF groups. In the SR group, BNP levels decreased after PBMV (pre-PBMV 128.7 ± 75.9 pg/ml; at 20 min, 88.6 ± 62.0 pg/ml; at 24 h, 43.4 ± 26.7 pg/ml; respectively, $p < 0.05$). Changes in

plasma BNP (Δ BNP) correlated positively with those in mLAP (Δ mLAP) ($r = 0.696$, $p < 0.01$) and PAP (Δ PAP) ($r = 0.456$, $p < 0.05$). Left ventricular end-diastolic volume (LVEDV) (96.1 ± 21.6 versus 111.5 ± 25.2 ml, $p < 0.01$) and stroke volume (SV) (59.2 ± 15.8 versus 69.0 ± 17.9 ml, $p < 0.05$) augmented accordingly without any changes in left ventricular end-diastolic pressure (LVEDP) ($p = \text{NS}$). In contrast, in group AF, BNP levels remained unchanged (pre-PBMV 111.6 ± 53.4 pg/ml; at 20 min, 122.0 ± 68.7 pg/ml; at 24 h, 106.1 ± 56.2 pg/ml; respectively, $p = \text{NS}$), while LVEDP increased (6.4 ± 3.6 versus 8.6 ± 3.2 mmHg, $p < 0.01$), without any changes in LVEDV and SV ($p = \text{NS}$).

Conclusion: The study results indicate that, in mitral stenosis patients, a high BNP level is associated with high mLAP and PAP. Cardiac rhythm may play an important role in changes of BNP level after PBMV. BNP may be a valid marker to reflect changes in mLAP and PAP after PBMV in patients with SR, but not in those with AF.

B-type natriuretic peptide (BNP) is a newly discovered peptide which can promote natriuresis and diuresis, act as vasodilator, and also antagonize the vasoconstrictor effects of the renin-angiotensin-aldosterone system. Plasma BNP levels increase in patients with heart conditions such as myocardial infarction, dilated cardiomyopathy, hypertrophic cardiomyopathy and hypertensive heart disease. Although several reports have been made showing that the plasma BNP level is a valid diagnostic and prognostic marker in heart failure (1-4), most of these studies have focused

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on the relationship between BNP levels and left ventricular function. To date, little is known about the relationship between BNP levels and right ventricular function.

It is well known that mitral stenosis significantly increases left atrial pressure, and this results in right heart dysfunction. Percutaneous balloon mitral valvuloplasty (PBMV), which has become a worldwide non-surgical treatment for symptomatic mitral stenosis, can extend the mitral orifice with a rapid fall in left atrial pressure and an improvement in right ventricular function. To the present authors' knowledge, few clinical investigations have been undertaken to determine the response of plasma BNP levels to short-term changes in hemodynamics after PBMV, and few reports have demonstrated whether the rapid changes in hemodynamics make the same contribution to the

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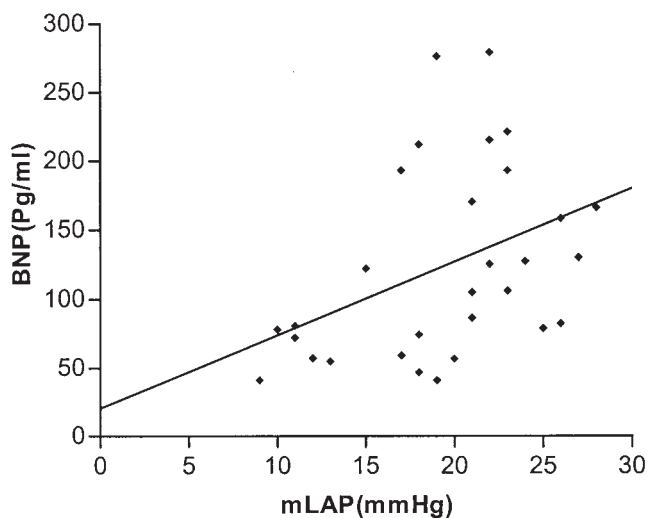


Figure 1: Correlation of plasma B-type natriuretic peptide (BNP) level with mean left atrial pressure (mLAP) in all patients ($n = 30$) with mitral stenosis. $r = 0.441$; $y = 5.81x + 11.10$; $p < 0.05$

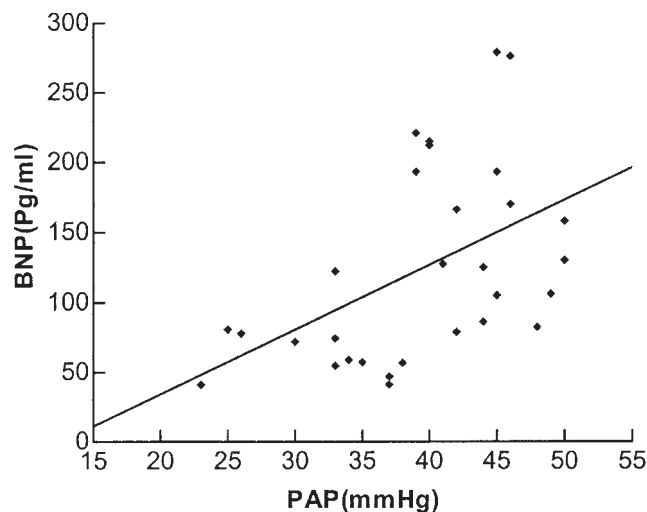


Figure 2: Correlation between plasma B-type natriuretic peptide (BNP) level and pulmonary artery pressure (PAP) in all 30 patients ($n = 30$) with mitral stenosis. $r = 0.488$; $y = 4.62x - 58.02$; $p < 0.01$.

synthesis and secretion of BNP in patients in sinus rhythm and with atrial fibrillation. In the present study, plasma BNP levels were measured before and after PBMV in symptomatic mitral stenosis patients in sinus rhythm and with atrial fibrillation. In addition, the relationship was studied between BNP levels and hemodynamic parameters and atrial fibrillation.

Clinical material and methods

Study patients

Between June 2003 and April 2004, 32 consecutive patients with symptomatically severe rheumatic mitral stenosis underwent PBMV. Two patients were excluded from the study; one patient showed grade 2+ mitral regurgitation after valvuloplasty, while the other had atrial fibrillation. The remaining 30 patients (25 women, five men; mean age 48.9 ± 11.2 years; range: 31 to 75 years) who successfully underwent PBMV without complication were included in the study. Among the patients, 21 were in normal sinus rhythm with no history of atrial fibrillation, whilst nine had been in permanent atrial fibrillation for at least six months, without a rapid ventricular rate (resting ventricular rate < 100 /min, proven by at least two electrocardiograms during the previous month). Ten patients showed mild mitral or aortic regurgitation. Two patients were in NYHA class I, 22 in class II, and seven in class III. None of the patients had received angiotensin-converting enzyme inhibitors or beta-blockers during the previous month, and diuretics and digitalis were withdrawn 48 h before blood sampling. No other cardiovascular diseases such as dilated car-

diomyopathy, hypertrophic cardiomyopathy, hypertension and coronary heart disease were identified in the subjects, and no patient showed any evidence of renal impairment.

The plasma BNP levels of eight healthy volunteers (six females, two males) were monitored as controls. These subjects were age-matched (mean 49.2 ± 5.2 years; range: 38 to 55 years) with the study patients. Informed consent was obtained from all patients and volunteers, and the study was approved by the local ethics committee before its commencement.

PBMV and hemodynamic determinations

PBMV was performed with an Inoue balloon catheter, using the trans-septal Brockenbrough method. The mean right atrial pressure and pulmonary artery systolic pressure were measured with a Swan-Ganz catheter, the mean left atrial pressure with a trans-septal sheath, and the left ventricular end-diastolic pressure with an end-hole balloon catheter placed into the left ventricle by way of the trans-septal sheath. Measurements were made before the first balloon inflation, and at 20 min after the final balloon inflation. Echocardiographic examinations (using a Toshiba 8000 instrument) were performed before and at 24 h after PBMV in order to measure the mitral valve area, left atrial diameter, left ventricular end-diastolic volume and stroke volume. The mitral valve area was calculated by planimetry, while the left ventricular end-diastolic volume and stroke volume were estimated using a two-dimensional Simpson's biplane analysis. All measurements represented an average of five consecutive cardiac cycles. In all cases, two independent expert

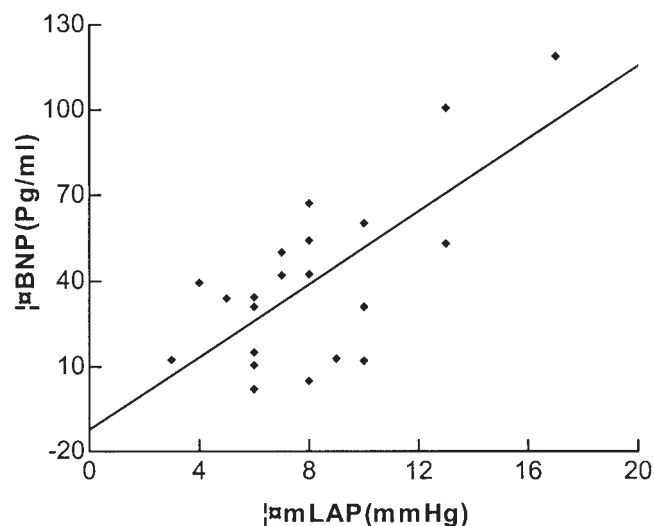


Figure 3: Correlation between changes in plasma B-type natriuretic peptide level (Δ BNP) and in mean left atrial pressure (Δ mLAP) at 20 min after PBMV in sinus rhythm patients ($n = 21$). $r = 0.696$; $y = 6.38x - 12.28$; $p < 0.01$.

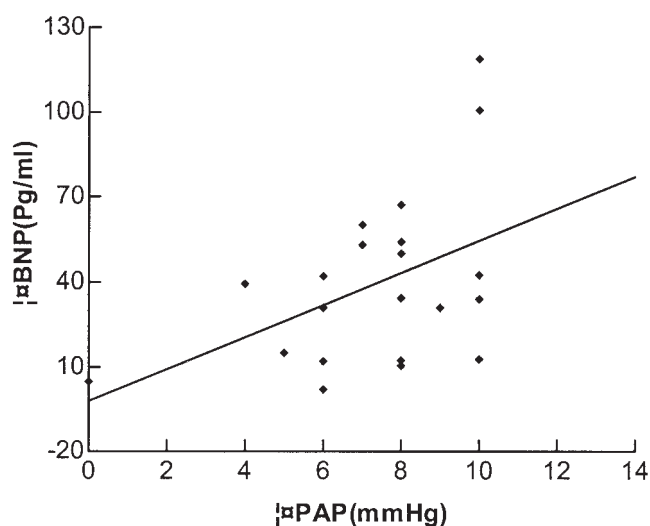


Figure 4: Correlation between changes in plasma B-type natriuretic peptide level (Δ BNP) and in pulmonary artery pressure (Δ PAP) at 20 min after PBMV in sinus rhythm patients ($n = 21$). $r = 0.456$; $y = 5.64x - 1.79$; $p < 0.05$.

observers analyzed the echocardiograms, with values being reported as the mean.

Blood sampling and assays

Blood samples (1 ml) were collected from a peripheral vein before valvuloplasty, and at 20 min and 24 h after the last balloon inflation. Control blood samples were obtained from a peripheral vein during the early morning. All patients and volunteers were asked to remain in a supine position for at least 30 min before blood samples were taken. The samples were immediately placed into test tubes containing aprotinin and ethylenediamine tetra-acetic acid, and centrifuged at 900 g for 3 min. Plasma BNP concentrations were measured using the Triage BNP Test, which is a rapid, objective point-of-case diagnostic tool (Biosite Inc., San Diego, CA, USA). The limit of detection for plasma BNP with this assay was 5 pg/ml.

Statistical analysis

Data were expressed as mean \pm SD. The paired or unpaired Student's *t*-test was used for comparison between the two means. A one-way analysis of variance was used for the comparison of more than two means. Linear regression analysis was used to determine correlations between BNP levels and hemodynamic data. A *p*-value < 0.05 was considered to be statistically significant.

Results

Hemodynamic parameters

Balloon valvuloplasty resulted in an increase in mitral valve area, which caused significant reductions in mean left atrial pressure, left atrial diameter and pulmonary artery pressure. The mean right atrial pressure remained unchanged (Table I). No differences were observed in these hemodynamic parameters between sinus rhythm patients and atrial fibrillation

Table I: Hemodynamic parameters before and after PBMV ($n = 30$).

Parameter	Before PBMV	20 min after PBMV	24 h after PBMV	p-value
mRAP (mmHg)	2.7 \pm 2.6	2.9 \pm 2.9	-	NS
mLAP (mmHg)	19.4 \pm 5.3	11.9 \pm 3.2	-	<0.01
PAP (mmHg)	39.3 \pm 7.3	31.4 \pm 6.2	-	<0.01
MVA (cm ²)	1.0 \pm 0.7	-	1.8 \pm 0.3	<0.01
LAD (mm)	49.5 \pm 9.4	-	44.8 \pm 6.4	<0.01

Values are mean \pm SD.

LAD: Left atrial diameter; mLAP: Mean left atrial pressure; mRAP: Mean right atrial pressure; MVA: Mitral valve area; NS: Not significant; PAP: Pulmonary artery systolic pressure; PBMV: Percutaneous balloon mitral valvuloplasty.

patients, both before and after PBMV (Table II). Among sinus rhythm patients, the left ventricular end-diastolic volume and stroke volume were each augmented after PBMV, but without any significant change in left ventricular end-diastolic pressure. However, among atrial fibrillation patients, the left ventricular end-diastolic volume and stroke volume both remained unchanged, while the left ventricular end-diastolic pressure increased (Table II).

Plasma BNP levels

Plasma BNP levels in all patients were significantly higher than those in the control group (123.5 ± 69.5 versus 16.4 ± 7.6 pg/ml, $p < 0.01$). No differences were observed in BNP levels between patients in sinus rhythm and with atrial fibrillation (111.6 ± 53.4 versus 128.7 ± 76.0 pg/ml, $p = \text{NS}$). BNP levels remained unchanged in patients with atrial fibrillation after

valvuloplasty (pre-PBMV, 111.6 ± 53.4 pg/ml; at 20 min, 122.0 ± 68.7 pg/ml; at 24 h, 106.1 ± 56.2 pg/ml; $p = \text{NS}$, respectively), but decreased rapidly in patients with sinus rhythm (pre-PBMV, 128.7 ± 76.0 pg/ml; at 20 min, 88.6 ± 62.0 pg/ml; at 24 h, 43.4 ± 26.7 pg/ml; $p < 0.05$, respectively). At 24 h after PBMV, BNP levels in sinus rhythm patients were significantly lower than those in atrial fibrillation patients ($p < 0.01$), but still higher than those in healthy controls ($p < 0.05$).

Relationship between BNP level and hemodynamic parameters

Basal plasma BNP levels in all patients were significantly correlated with basal mean left atrial pressure ($r = 0.441$, $p < 0.05$) and pulmonary artery pressure ($r = 0.488$, $p < 0.01$) (Figs. 1 and 2). However, no relationship was observed between basal BNP levels and left atrial diameter or mitral valve area (Table III). In

Table II: Hemodynamic parameters in patients in sinus rhythm (SR) and with atrial fibrillation (AF).

Parameter	AF	SR	p-value
No. of patients	9	21	-
Age (years)	50.4 ± 11.2	48.2 ± 14.2	NS
NYHA class (I/II/III)	0/5/4	2/17/2	-
PAP (mmHg)			
Before	40.4 ± 7.2	538.8 ± 7.5	NS
20 min after	31.1 ± 5.9	31.5 ± 6.4	NS
p-value	< 0.01	< 0.01	
mLAP (mmHg)			
Before	17.7 ± 3.8	20.1 ± 5.7	NS
20 min after	11.7 ± 2.1	12.0 ± 3.6	NS
p-value	< 0.01	< 0.01	
MVA (cm ²)			
Before	1.0 ± 0.2	1.0 ± 0.3	NS
24 h after	1.8 ± 0.4	1.9 ± 0.3	NS
p-value	< 0.01	< 0.01	
LAD (mm)			
Before	53.4 ± 11.1	47.8 ± 8.3	NS
24 h after	44.7 ± 6.4	44.9 ± 6.6	NS
p-value	< 0.01	< 0.05	
LVEDP (mmHg)			
Before	6.4 ± 3.6	5.9 ± 3.6	NS
20 min after	8.6 ± 3.2	5.1 ± 4.5	NS
p-value	< 0.01	> 0.05	
LVEDV (ml)			
Before	107.4 ± 26.5	96.1 ± 21.6	NS
24 h after	105.5 ± 24.0	111.5 ± 25.2	NS
p-value	NS	< 0.01	
SV (ml)			
Before	62.5 ± 13.5	59.2 ± 15.8	NS
24 h after	62.8 ± 17.3	69.0 ± 17.9	NS
p-value	NS	< 0.05	

LVEDP: Left ventricular end-diastolic pressure; LVEDV: Left ventricular end-diastolic volume; SV: Stroke volume.

Table III: Relationships between plasma B-type natriuretic peptide (BNP) level and hemodynamic parameters before PBMV.

Parameter	No. of patients	r-value	p-value
mRAP	30	0.276	NS
PAP	30	0.488	<0.01
mLAP	30	0.441	<0.05
MVA	30	-0.135	NS
LAD	30	0.200	NS

For abbreviations, see Table I.

patients with normal sinus rhythm, the reduction in plasma BNP level at 20 min correlated with the decrease in mean left atrial pressure and pulmonary artery pressure ($r = 0.696$, $p < 0.01$; $r = 0.456$, $p < 0.05$, respectively) (Figs. 3 and 4). Changes in plasma BNP levels at 24 h after PBMV did not correlate significantly with corresponding differences for both left ventricular end-diastolic volume ($r = -0.387$, $p = \text{NS}$) and stroke volume ($r = -0.342$, $p = \text{NS}$) (Table IV).

Discussion

B-type natriuretic peptide, which was discovered originally in the porcine brain by Sudoh and colleagues (5), is a 32-amino acid hormone. In humans, it is synthesized in, and secreted predominantly from, the heart. Recent studies have demonstrated that plasma BNP concentrations increase significantly in the presence of left atrial pressure overload (6), pulmonary hypertension (7) and right ventricular dysfunction (6-9). The results of the present study showed that patients with mitral stenosis presented with higher plasma BNP levels than did healthy control subjects, and this was in accord with previous reports (6,10,11). Moreover, positive correlations between basal BNP levels and basal mean left atrial pressure (6) as well as

pulmonary artery pressure were also observed in the present study.

In patients with sinus rhythm, BNP levels were found to fall rapidly after PBMV, in agreement with the report by Tharaux et al. (6), whilst the left ventricular end-diastolic pressure remained unchanged. The decrease in right ventricular after-load, but not the left ventricular after-load, might contribute to this change. Percutaneous balloon mitral valvuloplasty increases the mitral valve area and rapidly relieves left atrial pressure overload caused by mechanical obstruction. The pulmonary artery pressure falls reactively, leading to a decrease in right ventricular after-load and an improvement in right ventricular function (12-15). The cardiac synthesis and secretion of BNP in the right ventricle would be reduced accordingly. The positive correlations observed between changes in plasma BNP level and changes in mean left atrial pressure, as well as pulmonary artery pressure, also supported this hypothesis. Moreover, mitral stenosis restricts left ventricular diastolic filling. In the present patients, PBMV resulted in increases in both left ventricular end-diastolic volume and stroke volume, while the left ventricular end-diastolic pressure was unchanged. Despite no significant relationship being evident between these changes in volume and corresponding changes in plas-

Table IV: Correlations between changes in BNP levels and changes in hemodynamic parameters after PBMV.

Parameter/ correlation	AF (n = 9)		SR (n = 21)	
	r-value	p-value	r-value	p-value
ΔBNP and ΔPAP	0.199	NS	0.456	<0.05
ΔBNP and ΔmLAP	-0.039	NS	0.696	<0.01
ΔBNP and ΔLVEDP	0.043	NS	0.245	NS
$\Delta\text{BNP}'$ and ΔMVA	0.241	NS	0.048	NS
$\Delta\text{BNP}'$ and ΔLAD	-0.194	NS	-0.070	NS
$\Delta\text{BNP}'$ and ΔLVEDV	0.155	NS	-0.387	NS
$\Delta\text{BNP}'$ and ΔSV	0.190	NS	-0.342	NS

Changes in parameters after PBMV (for abbreviations, see Tables I-III): ΔBNP : Change in BNP level at 20 min; $\Delta\text{BNP}'$: Change in BNP level at 24 h; ΔLAD : Change in LAD; ΔLVEDP : Change in LVEDP; ΔLVEDV : Change in LVEDV; ΔmLAP : Change in mLAP; ΔMVA : Change in MVA; ΔPAP : Change in PAP; ΔSV : Change in SV.

ma BNP level, the improvement in left ventricular compliance might also be a factor in the decrease in plasma BNP concentrations.

In those patients with atrial fibrillation, despite an immediate fall in the mean left atrial and pulmonary artery pressures, plasma BNP levels were similar before and after the PBMV procedure. Several hypotheses have been outlined to explain the unchanged BNP levels after PBMV in these patients. First, permanent atrial fibrillation may be the main cause of high BNP levels (19,20), as BNP impairs atrial systole and aggravates left atrial dysfunction in mitral stenosis patients. Moreover, atrial fibrillation without a rapid ventricular rate may have a negative impact on left ventricular function, which has been attributed to the loss of atrial transport function (16-18) and to irregularity of the ventricular rhythm (20-24). It has also been reported recently that BNP levels decrease significantly after successful direct current cardioversion in persistent atrial fibrillation patients (25-28). Furthermore, the unchanged left ventricular end-diastolic volume and stroke volume after PBMV in the present study may also suggest that valvuloplasty could not improve impaired cardiac function due to permanent atrial fibrillation, though it clearly removes any mechanical obstruction of the mitral valve. The impairment of left atrial appendage function and subsequent blood stasis caused by persistent atrial fibrillation may be other causes of high BNP levels (29-31). Recent studies have also demonstrated that an elevated BNP level in atrial fibrillation patients is associated with left atrial appendage dysfunction and a prothrombotic state (32,33). In the present study, all nine patients with atrial fibrillation underwent transesophageal echocardiography before PBMV, and none of them demonstrated the presence of thrombi, though prothrombotic states were detected in eight cases. In addition, neither the left ventricular end-diastolic volume nor stroke volume were changed, whilst the left ventricular end-diastolic pressure increased in these patients after PBMV. The reason for the unchanged post-PBMV volumes may be associated with ventricular inter-dependence, as the right ventricular volumes may have decreased to a lesser degree in patients with atrial fibrillation.

In patients with sinus rhythm, the plasma levels of BNP at 24 h after PBMV were significantly lower than those at 20 min after the procedure, but still higher than those in healthy controls. This may be due to the presence of mild mitral stenosis after PBMV and mild dysfunction of other valves, which in turn could affect atrial and ventricular function. In addition, an abnormal synthesis and secretion of BNP was most likely associated with myocardial fibrosis, atrophy and cicatrization from rheumatic inflammation and/or vasculitis in these patients. Moreover, in such patients

the correlations between changes in plasma BNP level and in left ventricular end-diastolic or stroke volumes did not reach statistical significance (respectively, $r = -0.387$, $p = 0.08$; $r = -0.342$, $p = 0.13$), though this may have been due to the small patient numbers involved. Thus, further studies of the relationship between these parameters after PBMV are required.

In conclusion, plasma BNP levels are elevated in patients with mitral stenosis, and are associated with high left atrial and pulmonary artery pressures. The elevated BNP levels were decreased after PBMV in patients with sinus rhythm, but not in those in atrial fibrillation; this implies that cardiac rhythm plays an important role in determining plasma BNP levels after PBMV. Among patients with sinus rhythm, the fall in plasma BNP level at 20 min after PBMV is a direct indication of the fall in left atrial pressure, which implies that BNP might serve as valid indicator to evaluate the success of PBMV in sinus rhythm patients.

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