Pulmonary Hypertension and Elevated Transpulmonary Gradient in Patients with Mitral Stenosis

Stephen A. Hart[1,2], Richard A. Krasuski[2], Andrew Wang[3], Katherine Kisslo[3], J. Kevin Harrison[3], Thomas M. Bashore[3]

[1]*Cleveland Clinic Lerner College of Medicine of Case Western Reserve University, Cleveland, Ohio,* [2]*Division of Clinical Cardiology, Heart and Vascular Institute, Cleveland Clinic, Cleveland, Ohio,* [3]*Duke University Medical Center, Durham, North Carolina, USA*

Background and aim of the study: **Pulmonary hypertension frequently complicates mitral stenosis, with a subset of these patients exhibiting pressures well in excess of their mitral valve hemodynamics. The prevalence of this condition and its impact on clinical outcome following percutaneous balloon mitral commissurotomy (PBMC) is unknown.**

Methods: **The transpulmonary gradient (TPG) was measured in 317 patients undergoing PBMC; patients were subsequently defined as having either an appropriate or excessive TPG (≤15 mmHg or >15 mmHg, respectively). Twenty-two patients were excluded due to valvuloplasty-related significant mitral regurgitation. The remaining 295 patients (250 females, 45 males; mean age 52 ± 13 years) were prospectively followed up, with each patient underwent serial echocardiography.**

Results: **Among the patients, 214 (73%) had pulmonary hypertension (pulmonary artery pressure >25 mmHg) and 55 (19%) also had an elevated TPG. Females were almost fivefold more likely than males to have an elevated TPG (p = 0.003). Patients with an elevated TPG had a worse mean NYHA functional class than those with a normal TPG (3.0 ± 0.5 versus 2.7 ± 0.6, p = 0.01), while the mitral valve area (MVA) was slightly smaller in patients with an elevated TPG (1.0 ± 0.2 versus 1.1 ± 0.2 cm^2, p = 0.003). All patients demonstrated a significant increase in MVA after commissurotomy (final MVA 1.7 ± 0.6 cm^2, p <0.001 for elevated TPG; 1.8 ± 0.4 cm^2, p <0.001 for normal TPG), and the NYHA class at six months was improved for all patients (2.8 ± 0.6 versus 1.6 ± 0.7, p <0.001). The improvements in NYHA class, TPG and MVA were sustained at 36 months.**

Conclusion: **Pulmonary hypertension with elevated TPG occurs in patients with mitral stenosis, and is significantly more common in females. Despite worse symptoms and higher right-sided pressures, PBMC is equally successful in patients with a normal TPG, and provides sustained benefit for up to 36 months after the procedure.**

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Mitral stenosis is closely coupled with pulmonary hypertension, and it is well known that some patients exhibit a pulmonary artery pressure (PAP) in excess of their mitral valve hemodynamics (1,2). Pulmonary venous hypertension appears when an increased left atrial pressure is transmitted passively to the lungs. It has also been theorized that the pulmonary artery endothelium promotes vasoconstriction and remodeling in response to elevated blood pressure (3). These phenomena may lead to pulmonary arterial hypertension and an abnormally elevated transpulmonary gradient (TPG) (4,5). An elevated pulmonary pressure in the setting of mitral stenosis can lead to right-sided heart disease and complications following surgical commissurotomy (6-8).

Percutaneous balloon mitral commissurotomy (PBMC) has been shown to be an effective alternative to surgical commissurotomy, and is preferred in patients with severe pulmonary hypertension (9,10). Numerous studies have demonstrated that PBMC reverses severe pulmonary hypertension; however, no study has yet been conducted to investigate the effect of PBMC on patients with an elevated TPG. In light of this, the study aim was to examine the prevalence of an elevated TPG in patients with mitral stenosis, and to investigate the effect of PBMC in this unique population.

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Address for correspondence:
Richard A. Krasuski MD, Director of Adult Congenital Heart Disease Services, Cleveland Clinic Foundation, J2-4, 9500 Euclid Avenue, Cleveland, OH 44195, USA
e-mail: krasusr@ccf.org

Table I: Demographics and clinical characteristics of the patients.

Parameter	All patients (n = 295)	Normal TPG (n = 240)	Elevated TPG (n = 55)	p-value
Age (years)*	51.7 ± 13.1	51.5 ± 12.7	52.7 ± 15.1	0.53
Female gender	250 (84.7)	197 (82.1)	53 (96.4)	0.003
NYHA functional class*	2.8 ± 0.6	2.7 ± 0.6	3.0 ± 0.5	0.01
History of:				
Coronary artery disease	16 (5.5)	13 (5.5)	3 (5.5)	0.99
Atrial fibrillation	100 (34.0)	83 (34.7)	17 (30.9)	0.59
Surgical MV commissurotomy	43 (14.6)	37 (15.4)	6 (10.9)	0.38
Percutaneous MV commissurotomy	7 (2.4)	6 (2.5)	1 (1.8)	0.76
MV commissurotomy score*	8.7 ± 2.3	8.7 ± 2.3	8.7 ± 2.4	0.83

*Values are mean ± SD.
Values in parentheses are percentages.
MV: Mitral valve; TPG: Transpulmonary gradient.

Clinical material and methods

Patients

A total of 317 patients underwent Inoue PBMC at the Duke University Medical Center between 1990 and 1999. The enrollment criteria included a suitable valve morphology for PBMC, and the absence of significant mitral regurgitation (MR) after PBMC. Consent was obtained from each patient to conduct serial follow up examinations and transthoracic echocardiography (TTE); these were performed at six months and one year postoperatively, and annually thereafter.

The study was approved by the institutional review board at the Duke University Medical Center.

Echocardiography

Pre-procedural echocardiography

All patients underwent TTE and transesophageal echocardiography prior to PBMC, in order to determine the valve morphology and to rule out left atrial thrombus, respectively (11). The mitral valve morphology was evaluated using a semi-quantitative score assessing leaflet mobility, leaflet thickness, calcification, and subvalvar stenosis (12); MR was also evaluated, using a semi-quantitative scale from grade 0 to 4+ (13). Baseline hemodynamic measurements were obtained during left- and right-heart catheterization, and repeated following Inoue PBMC (14,15). Sequential balloon dilation was stopped if the intraprocedural TTE demonstrated open commissures, a worsening MR, or if the mitral transvalvular gradient fell by more than 50%. Procedural success was defined as a ≥50% increase in the mitral valve area (MVA), or a final MVA >1.5cm^2 combined with MR grade ≤2+. Twenty-two patients were excluded from the study after valvuloplasty because of hemodynamically significant (grade >2+), valvuloplasty-related MR; thus, the final study group comprised 295 patients (250 females; 45 males; mean age 52 ± 13.1 years).

Post-procedural echocardiography

Post-procedural TTE was performed blinded to the patient's history. Standard views were obtained, and the mitral inflow was measured using continuous-wave Doppler echocardiography from the apical view. The mean mitral transvalvular gradient was calculated by integrating the instantaneous pressure gradients during diastole, and averaging over three cardiac cycles. The MVA was calculated using the Gorlin equation and the pressure half-time method (16). The TPG was calculated as: [mean PAP - mean PCWP] (where PCWP = pulmonary capillary wedge pressure) at the time of catheterization. Patients were defined as having either an appropriate (≤15 mmHg) or elevated (>15 mmHg) TPG, based on previously established criteria (17,18). Cardiac output was measured using the Fick method. Restenosis was defined as a ≥50% loss of the gained MVA following PBMC, or a MVA <1.5cm^2 (19).

Statistical analysis

All data were compiled and analyzed using JMP 8.0 (SAS Institute, Inc., Cary, NC, USA). Continuous variables were tabulated as mean ± SD, and dichotomous variables as numbers and percentages. Comparisons across time points were made using paired *t*-tests, while comparisons between groups at the same time point were made using unpaired *t*-tests. Dichotomous variables were compared using chi-square likelihood ratios and Fisher's exact test, when appropriate. A p-value <0.05 was considered to be statistically significant, and all comparisons were two-tailed.

Table II: Acute changes following percutaneous balloon mitral commissurotomy.

Parameter	Timing	Normal TPG (n = 240)	Elevated TPG (n = 55)	p-value
Mitral valve area (cm^2)	Pre	1.1 ± 0.2	1.0 ± 0.2	0.003
	Post	1.8 ± 0.4*	1.7 ± 0.6*	0.10
Mitral valve gradient (mmHg)	Pre	11.7 ± 4.4	14.5 ± 5.3	<0.001
	Post	6.3 ± 2.8*	7.3 ± 3.4*	0.02
Mean RA pressure (mmHg)	Pre	7.6 ± 3.4	9.5 ± 4.6	<0.001
	Post	7.3 ± 3.7	8.9 ± 4.7	0.007
Mean PAP (mmHg)	Pre	29.1 ± 7.0	48.4 ± 12.1	<0.001
	Post	27.4 ± 8.0*	41.4 ± 11.4*	<0.001
Mean PCWP (mmHg)	Pre	20.7 ± 5.8	24.1 ± 7.0	<0.001
	Post	16.8 ± 6.1*	18.5 ± 6.3*	0.07
Mean LA pressure (mmHg)	Pre	23.0 ± 5.8	26.0 ± 6.5	<0.001
	Post	16.5 ± 5.8*	17.5 ± 6.1*	0.27
TPG (mmHg)	Pre	8.3 ± 3.4	24.3 ± 8.4	<0.001
	Post	10.7 ± 5.2*	23.0 ± 10.6	<0.001
PVR (Wood units)	Pre	1.5 ± 1.3	5.0 ± 2.4	<0.001
	Post	2.4 ± 1.3*	5.2 ± 3.0	<0.001

Values are mean ± SD.
Matched pairs analysis: *, p <0.001.
LA: Left atrial; PAP: Pulmonary artery pressure; PCWP: Pulmonary capillary wedge pressure;
PVR: Pulmonary vascular resistance; RA: Right atrial; TPG: Transpulmonary gradient.

Results

Study population

An elevated TPG was found in 55 patients (19%). The demographic and clinical characteristics of the patient cohort are listed in Table I. No differences in mean age were seen between those with and without an elevated TPG (52.7 ± 15.1 versus 51.5 ± 12.7 years, p = 0.53), although 21% of females had an elevated TPG compared to only 4% of males (p = 0.003). The NYHA functional class of the entire cohort was 2.8 ± 0.6; those patients with an elevated TPG had a worse NYHA class than those with a normal TPG (3.0 ± 0.5 versus 2.7 ± 0.6, p = 0.01). Forty-three patients (14.6%) had undergone prior surgical mitral valve commissurotomy, and seven (2.4%) prior percutaneous mitral valve commissurotomy. No differences in prior commissurotomy rates between those with and without an elevated TPG were observed (10.9% versus 15.4%, p = 0.38 and 1.8% versus 2.5%, p = 0.76 for surgical and percutaneous commissurotomy, respectively). The echocardiographic mitral valve commissurotomy score was 8.7 ± 2.3 for the entire cohort, and almost identical among those with and without elevated TPG (8.7 ± 2.4 versus 8.7 ± 2.3, p = 0.83) (Table I). Coronary artery disease was present in 16 patients (5.5%), and atrial fibrillation in 100 (34.0%); again, no differences were detected between those with and without an elevated TPG (5.5% versus 5.5%, p = 0.99 and 30.9% versus 34.7%, p = 0.59, respectively). Pulmonary hypertension (PAP >25 mmHg) was evident in 214 patients (73%); the distribution of pressures between patients with and without an elevated TPG is shown in Figure 1 (20).

Acute changes following PBMC

Successful commissurotomy was achieved in 213 patients (72%), and those with a normal TPG were no more likely to have a successful outcome than patients with an elevated TPG (75% versus 62%, p = 0.06). The valvar and hemodynamic changes before and immediately after commissurotomy are listed in Table II. The initial MVA was smaller in patients with an elevated TPG than in those with a normal TPG (1.0 ± 0.2 versus 1.1 ± 0.2 cm^2, p = 0.003), although the absolute difference was quite small. Both groups demonstrated a significant increase in MVA following commissurotomy (final MVA 1.7 ± 0.6 cm^2, p <0.001 for elevated TPG, and 1.8 ± 0.4 cm^2, p <0.001 for normal TPG). A similar response was observed with the gradient across the mitral valve. Prior to commissurotomy, those patients with an elevated TPG demonstrated a significantly higher mitral valve gradient (MVG) compared to those with a normal TPG (14.5 ± 5.3 versus 11.7 ± 4.4 mmHg, p <0.001), but both groups demonstrated significant improvements following commissurotomy (final gradient 7.3 ± 3.4 mmHg, p <0.001 for elevated TPG and 6.3 ± 2.8 mmHg, p <0.001 for normal TPG).

The mean right atrial pressure was 9.5 ± 4.6 mmHg in the elevated TPG group, compared to 7.6 ± 3.4 mmHg in the normal TPG group (p <0.001). With

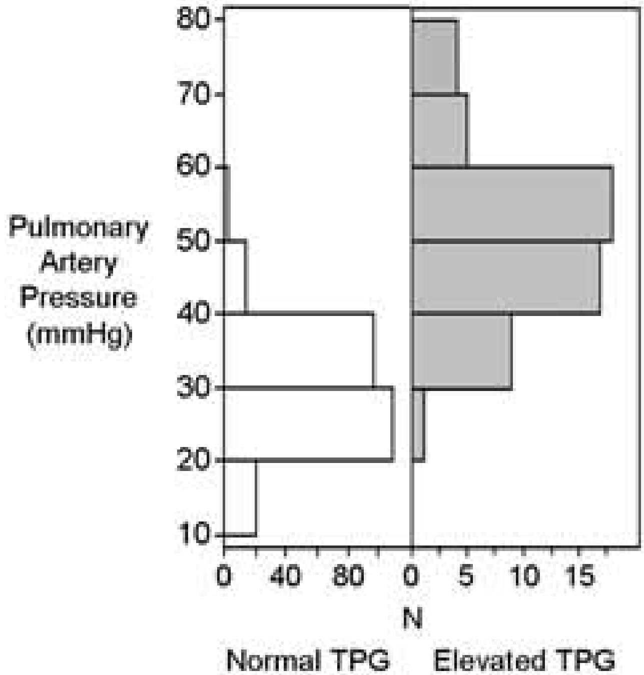
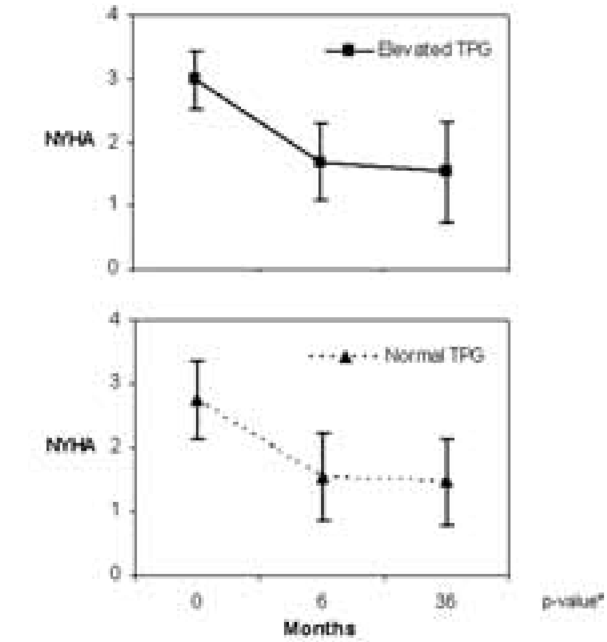


Figure 1: Frequency of mean pulmonary artery pressure among patients with normal and elevated (>15 mmHg) transpulmonary gradient (TPG).



	0	6	36	p-value*
Elevated TPG	3.0 ± 0.5	1.7 ± 0.6	1.5 ± 0.8	<0.001
Normal TPG	2.7 ± 0.6	1.5 ± 0.7	1.5 ± 0.7	<0.001
p-value	0.01	0.21	0.71	

* Matched pairs comparison between 0 and 36 months

Figure 2: Long-term follow up of NYHA functional class at baseline, immediately after percutaneous balloon mitral commissurotomy (PBMC), and at six and 36 months post-procedure in patients with an elevated or normal transpulmonary gradient (TPG).

PBMC, the mean right atrial pressure did not drop acutely in either group (8.9 ± 4.7 mmHg, p = 0.23 for elevated TPG and 7.3 ± 3.7 mmHg, p = 0.11 for normal TPG). The mean PAP was 48.4 ± 12.1 mmHg in the elevated TPG group, and 29.1 ± 7.0 mmHg in the normal TPG group (p <0.001). Both groups demonstrated a significant fall in pressure after PBMC (final mean PAP 41.4 ± 11.4 mmHg, p <0.001 for elevated TPG and 27.4 ± 8.0 mmHg, p <0.001 for normal TPG). The mean PCWP was higher in the elevated TPG group compared to the normal TPG group (24.1 ± 7.0 versus 20.7 ± 5.8 mmHg, p <0.001) and significant reductions with PBMC were observed across the cohort (final PCWP 18.5 ± 6.3 mmHg, p <0.001 for the elevated TPG group and 16.8 ± 6.1 mmHg, p <0.001 for the normal TPG group). The mean left atrial pressure displayed a similar pattern (26.0 ± 6.5 mmHg in the elevated TPG group and 23.0 ± 5.8 mmHg, p <0.001 in the normal TPG group at baseline and 17.5 ± 6.1 mmHg, p <0.001 for elevated TPG and 16.5 ± 5.8 mmHg, p <0.001 for normal TPG after PBMC).

At baseline, the mean TPG was 24.3 ± 8.4 mmHg in the elevated TPG group and 8.3 ± 3.4 mmHg in the normal TPG group (p <0.001). Following PBMC, the TPG rose in the normal TPG group to 10.7 ± 5.2 mmHg (p <0.001) but remained essentially unchanged in the elevated TPG group (23.0 ± 10.6 mmHg, p = 0.19). As expected, the pulmonary vascular resistance (PVR) mirrored the changes in TPG; prior to PBMC, this was 5.0 ± 2.4 Wood units in the elevated TPG group and 1.5 ± 1.3 Wood units (p <0.001) in the normal TPG group. Immediately after commissurotomy, the PVR was increased to 2.4 ± 1.3 Wood units (p <0.001) in the normal TPG group, but remained essentially unchanged in the elevated TPG group (5.2 ± 3.0 Wood units, p = 0.38).

No deaths, left ventricular perforations or embolic events occurred as a result of the PBMC. The rate of severe MR (grade >2+) was 7% (22 of 317). The incidence of large iatrogenic atrial septal defect (ASD; Qp:Qs >1.5:1) was 5% (n = 14), and that of any iatrogenic ASD 31% (n = 89), detected immediately after PBMC. No differences in ASD rates were seen between those with or without an elevated TPG (p = 0.85 for any ASD, p = 0.99 for large ASD). Among patients with normal baseline TPG, those with residual atrial level shunting had a lower post-procedure TPG than those with no shunting (10 ± 4 versus 11 ± 6 mmHg, p = 0.04), but no difference was observed among patients with an elevated baseline TPG. No differences were seen in post-procedural TPG between patients with and without large ASDs (Qp:Qs >1.5:1).

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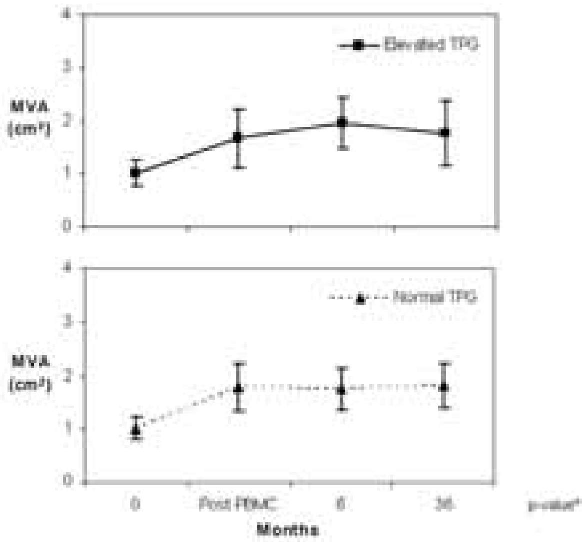
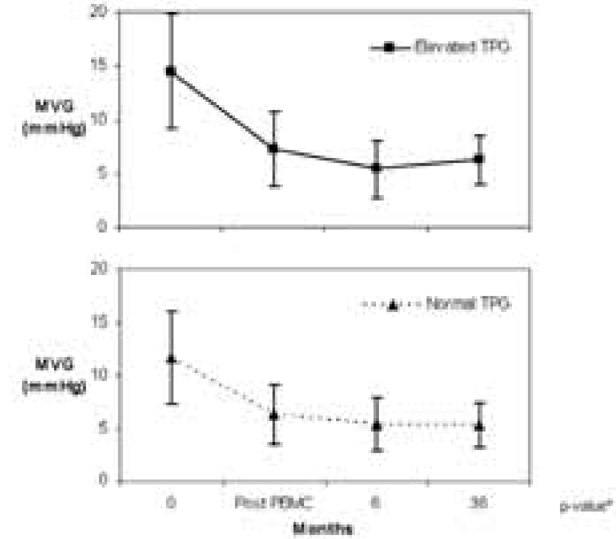


	0	Post PBMC	6	36	p-value*
Elevated TPG	1.0 ± 0.2	1.7 ± 0.6	2.0 ± 0.5	1.8 ± 0.6	<0.001
Normal TPG	1.1 ± 0.2	1.8 ± 0.4	1.8 ± 0.4	1.8 ± 0.6	<0.001
p-value	0.003	0.10	0.02	0.74	

* Matched pairs comparison between 0 and 36 months

Figure 3: Long-term follow up of mitral valve area (MVA) at baseline, immediately after percutaneous balloon mitral commissurotomy (PBMC), and at six and 36 months post-procedure in patients with an elevated or normal transpulmonary gradient (TPG).



	0	Post PBMC	6	36	p-value*
Elevated TPG	14.5 ± 5.3	7.3 ± 3.4	5.5 ± 2.7	6.3 ± 2.3	0.008
Normal TPG	11.7 ± 4.4	6.3 ± 2.8	5.4 ± 2.5	5.4 ± 2.1	<0.001
p-value	<0.001	0.02	0.79	0.16	

* Matched pairs comparison between 0 and 36 months

Figure 4: Long-term follow up of mitral valve gradient (MVG) at baseline, immediately after percutaneous balloon mitral commissurotomy (PBMC), and at six and 36 months post-procedure in patients with an elevated or normal transpulmonary gradient (TPG).

Long-term follow up after PBMC

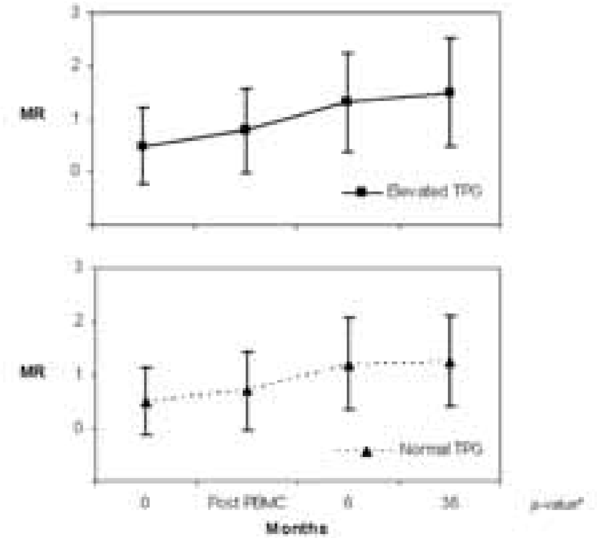
Follow up data were available for 241 patients (82%) after six months, and for 126 patients (43%) at 36 months. The rate of restenosis following successful commissurotomy at six and 36 months was 32% and 36%, respectively.

The NYHA functional class was improved significantly, from 3.0 ± 0.5 in the elevated TPG group and 2.7 ± 0.6 in the normal TPG group at baseline, to 1.7 ± 0.6 ($p < 0.001$) and 1.5 ± 0.7 ($p < 0.001$), respectively, at six months (Fig. 2). This improvement was sustained at 36 months, but the difference between patients with and without an elevated TPG at baseline had disappeared (1.5 ± 0.8 versus 1.5 ± 0.7, $p = 0.71$). The improvement in MVA was also sustained at 36 months, and initial differences in MVA between those with and without an elevated TPG had also disappeared (1.8 ± 0.6 versus 1.8 ± 0.6 cm^2, $p = 0.74$; Fig. 3). The MVG displayed a similar trend, demonstrating significant post-procedural improvements which were sustained at 36 months for both groups. Similarly, a difference at baseline was eliminated at 36 months (6.3 ± 2.3 mmHg for elevated TPG versus 5.4 ± 2.1 mmHg for normal TPG, $p = 0.15$; Fig. 4). MR at each time point was similar between those with and without an elevated TPG, while both groups demonstrated a worsened MR, by about one grade, at 36 months compared to baseline (Fig. 5).

Discussion

Among the present cohort of patients with mitral stenosis, pulmonary hypertension with excessive TPG was common, and females were almost fivefold more likely to have an elevated TPG than were males. The mitral valve morphology was comparable between those patients with and without an elevated TPG, although those with an elevated TPG tended to have a smaller MVA and a higher MVG. Patients with a higher TPG were also significantly more symptomatic. Age, comorbid heart disease and a history of prior valvotomy were similar among those with and without an elevated TPG. The PAP was almost twice as high in the elevated TPG group, despite elevated PAPs occurring in many individuals with an appropriate TPG. This incongruity supported the theory that there is a certain subset of patients with mitral stenosis that demonstrate pulmonary hypertension in excess of the valve derangement (2,21).

Patients with an elevated TPG demonstrated similarities to patients with idiopathic pulmonary arterial hypertension; in addition to an elevated PVR, this cohort demonstrated a female predominance and a poor NYHA class (5,22). It was felt that the female predominance exhibiting an elevated TPG observed in this cohort was not a coincidence, but rather suggested



	0	Post PBMC	6	36	p-value*
Elevated TPG	0.5 ± 0.7	0.8 ± 0.8	1.3 ± 0.9	1.5 ± 1.0	0.01
Normal TPG	0.5 ± 0.6	0.7 ± 0.7	1.2 ± 0.8	1.3 ± 0.8	<0.001
p-value	0.94	0.95	0.63	0.36	

* Matched pairs comparison between 0 and 36 months

Figure 5: Long-term follow up of mitral regurgitation (MR) at baseline, immediately after percutaneous balloon mitral commissurotomy (PBMC), and at six and 36 months post-procedure in patients with an elevated or normal transpulmonary gradient (TPG).

that genetic factors might play a strong role in pulmonary arterial hypertension. While the incidence of elevated TPG in females was much higher than in males, the severity of disease was similar in males and females at presentation, which suggested that the same thresholds for PBMC should be used for both genders.

Patients with and without an elevated TPG had similar success rates with balloon commissurotomy. The trend toward patients with a normal TPG having a more successful outcome was largely driven by a slightly larger initial MVA. Following PBMC, patients with an elevated TPG had a similar clinical course to those with a normal TPG, with significant improvements in MVA and MVG being recognized, regardless of the TPG level. The left atrial pressure, PCWP and PAP all fell significantly following PBMC across the cohort, with patients having an elevated TPG showing more dramatic pressure reductions. Neither the PVR nor TPG appeared to change immediately following PBMC. Similar results after PBMC in patients with pulmonary hypertension have been reported by other groups (10,21,23-28). The effectiveness of valvotomy in elevated TPG patients may also be appreciated in surgically managed cases, although this proposal warrants further study.

Studies describing the long-term outcome after PBMC in patients with severe pulmonary hypertension are rare (26,29-31). While these have shown PBMC to be safe and effective in patients with a severely elevated PAP, none has examined the unique pathophysiologic state of elevated TPG. The elevated TPG group demonstrated a substantial improvement in NYHA class at six months, with a sustained improvement at 36 months similar to those with a normal TPG. Likewise, the MVA and MVG in both groups each demonstrated considerable improvement after PBMC, with both parameters sustained at the six- and 36-month follow up examinations.

Study limitations

Ideally, the long-term follow up would have included repeat measurements of the PAP and TPG, although repeat hemodynamics could not be justified in this patient population. Following the study closure, other groups have demonstrated additional variables such as tricuspid valve regurgitation which are of interest in this population, but which were not uniformly collected in the present population and, therefore, were not analyzable. As the present study was conducted at a single institution, a referral bias may have confounded the generalization of the results but also ensured that each patient was treated and followed in a consistent manner. Patients lost to follow up also represented a source of bias that should be considered when interpreting these results. A procedural success was achieved in the majority of patients, with significant MR (grade >2+) being present in 7%, which was similar to other reports of 2-10% (11). The incidence of large ASDs was also similar to that reported elsewhere, of <5% (11). The lower post-procedural TPG found among patients with atrial level shunting could be attributed to the residual defect, as left-to-right shunting could diminish the pressure gradient across the pulmonary vasculature. However, it was felt that this small difference did not affect the long-term outcome.

There exists a well-described difference between MVA calculated using the Doppler pressure half-time method and the Gorlin equation, most likely due to residual atrial level shunting (32-35). In order to ensure that the present measurements using the Gorlin equation did not overestimate the MVA, the post-procedure MVA measured with the Gorlin equation was compared to that measured with the Doppler pressure half-time method in matched pairs analysis, but showed no statistical difference between the methods. Consequently, both the measured right ventricular systolic pressure and tricuspid regurgitation severity were considered to be accurate, and not significantly confounded by residual atrial level shunting immediately after balloon valvuloplasty.

In conclusion, despite the above-described limitations, the present study was the first to examine the subset of patients with mitral stenosis who develop pulmonary hypertension with excessive TPG, indicating the presence of pulmonary arterial hypertension. The data obtained suggested that this pathology was common, and that only hemodynamic measurements could reliably differentiate among this population. PBMC proved to be effective across the cohort, with improvements in hemodynamics and functional capacity being sustained at 36 months. It would appear that patients should not be refused percutaneous therapy for mitral stenosis based on the presence of pulmonary arterial hypertension.

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