Persistent pulmonary artery hypertension in patients undergoing balloon mitral valvotomy

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ABSTRACT

Pulmonary artery pressure (PAP) is known to regress after successful balloon mitral valvotomy (BMV). Data of persistent pulmonary artery hypertension (PPAH) following BMV is scarce. We analyzed the clinical, echocardiographic, and hemodynamic data of 701 consecutive patients who have undergone successful BMV in our institute from 1997 to 2003. Data of 287 patients who had PPAH (defined by pulmonary artery systolic pressure [PASP] of ≥ 40 mmHg at one year following BMV) were compared to the data of 414 patients who did not have PPAH. Patients who had PPAH were older (39.9 ± 9.9 years vs. 29.4 ± 10.1; \( P < 0.001 \)). They had higher prevalence of atrial fibrillation (AF; 21.9 vs. 12.1%, \( P < 0.05 \)), moderate or severe pulmonary artery hypertension (PAH) defined as PASP more than 50 mmHg (43.5 vs. 33.8%, \( P = 0.00 \)), anatomically advanced mitral valve disease as assessed by Wilkin’s echocardiographic score > 8 (33.7 vs. 23.2%, \( P < 0.001 \)), and coexistent aortic valve disease (45.6 vs. 37.9%, \( P < 0.001 \)) at the baseline. Those patients with PPAH had comparatively lower immediate postprocedural mitral valve area (MVA). On follow-up of more than five years, the occurrence of restenosis (39.3 vs. 10.1%, \( P = 0.000 \)), new onset heart failure (14% vs. 4%, \( P < 0.05 \)) and need for reinterventions (9.5% vs. 2.8%, \( P < 0.05 \)) were higher in the PPAH group. Patients with PPAH were older, sicker, and had advanced rheumatic mitral valve disease. They had higher incidence of restenosis, new onset heart failure, and need for reinterventions on long term follow-up. PPAH represents an advanced stage of rheumatic valve disease and indicates chronicity of the disease, which may be the reason for the poorer prognosis of these patients. Patients with PPAH requires intense and more frequent follow-up.

Key Words: rheumatic heart disease, balloon mitral valvotomy, pulmonary artery hypertension, regression

BMV has become the treatment of choice in patients with hemodynamically significant mitral stenosis (MS) and pliable mitral valve. Even though BMV is reported to be technically difficult\(^1\) in patients with PAH, the PAP usually regresses once the transmitral obstruction is relieved.\(^2,3\) Studies have reported excellent and comparable short-term results following BMV in patients with all grades of PAH.\(^6\)

Even though there have been studies showing excellent results following BMV in all grades of PAH, nonregression of PAH following BMV is not uncommon.\(^4\) Fawzy\(^4\) and others\(2,3,5-7\) have shown that in patients with mild PH, the PASP and the pulmonary vascular resistance (PVR) decreased to normal or near normal levels immediately after a successful BMV. On the contrary, in patients with moderate or severe PH,\(8\) despite greater absolute and relative reductions, PASP and PVR remained significantly elevated.

The component of PAP contributed by the passive transmission of the elevated left atrial (LA) pressure regresses immediately after a successful BMV proportional to the reduction in transmitral gradient (TMG).\(9\) The PAH contributed by pulmonary arteriolar constriction slowly comes down over weeks or a few months.\(4,9\) But the “fixed” component due to pulmonary vascular disease usually persists.\(10\)

PPAH (defined in the study as PASP of ≥ 40 mmHg at one year after BMV), in the absence of mitral valve restenosis, may reflect either the slowly reversible or fixed component, or both. The study was conducted to identify the baseline clinical, echocardiographic, and hemodynamic parameters

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which can predict PPAH and also to determine the long-term outcome of these patients.

MATERIALS AND METHODS

Study population
Clinical, echocardiographic, and hemodynamic data of 701 consecutive patients who underwent BMV in our institute from 1997 to 2003 were analyzed retrospectively. Data of 287 patients who had PPAH (defined by PASP of ≥ 40 mmHg at one year after BMV) were compared to the data of 414 patients who did not have PPAH. BMV performed as emergency procedure under mechanical ventilation and pregnant patients were excluded. Those patients who developed mitral valve restenosis within one year were excluded (defined as a valve area < 1.5 cm$^2$ or a > 50% loss of the initial gain in valve area on follow-up after a successful valvotomy).

Methods
All patients had a detailed clinical and echocardiographic (2 dimensional [2D]-echo, Doppler, and color flow imaging) evaluation to assess the severity of MS, valve morphology, and mitral regurgitation (MR). The Wilkin's echocardiographic scoring system was used to assess the severity of mitral valve thickness, leaflet mobility, valvular calcification, and subvalvular disease, each being graded from 1 to 4, to a maximum score of 16.

The MVA was determined by 2D-echocardiography with planimetry in the parasternal short axis view utilizing standard technique. Transesophageal echocardiography (TEE) was routinely performed prior to BMV in all patients. Transthoracic echocardiogram was performed during BMV, 24 hours after the procedure, and at follow-up visits. The contraindications to the procedure were MR of Seller’s grade more than 2, LA thrombus on TEE performed prior to BMV, and extensive commissural calcification.

BMV was performed using the antgrade trans-septal technique as already described. The entry site was right femoral vein in all patients. All procedures were performed with standby facility for closed- and open-heart surgery. All patients were given antibiotic cover and all were heparinized after septal dilatation. Septal puncture was performed using the Brockenbrough technique. Immediately before and after BMV, the left and right heart pressures and the mean TMG were measured. Left ventricular (LV) angiogram in the 30° right anterior oblique view was completed prior to the procedure in all patients suspected to have more than mild MR. MR was graded 1-4 as per increasing severity. Procedure success was defined as increase in MVA of at least 50% from the basal, or a final valve area of at least 1.5 cm$^2$ in the absence of more than grade 2 MR.

Statistical analysis
Statistical analysis was completed using the software SPSS version 10.0. Continuous variables are expressed as mean ± standard deviation (SD). Procedural results were compared using an unpaired Student’s t-test. For comparison of group means, a t-test was used. Proportions were compared by use of the $c^2$-test and the Fisher’s exact test. P-value < 0.05 was considered significant.

RESULTS

Preprocedure clinical and demographic variables
Baseline demographic and clinical characteristics of the two groups of patients are shown in Table 1. Patients who had PPAH were older, presented more frequently with AF, and were more likely to be in NYHA (New York Heart Association) Functional Class III-IV. They had higher prevalence of aortic valve disease, a higher Wilkin’s echocardiographic score (33.7% with a score > 8 in PPAH group vs. 23.2% in the no PPAH group), and moderate or severe PAH.

| Table 1: Clinical and demographic data |
|--------------------------------------|
| **Total** | **Patients with no PPAH** | **Patients with PPAH** | **P value** |
| Number | 701 | 414 (59) | 287 (41) | >0.05 |
| Male | 150 | 93 (22.4) | 57 (19.8) | >0.05 |
| Juvenile (<20) | 130 | 68 (16) | 62 (21.6) | >0.05 |
| Prior surgical commissurotomy | 100 | 51 (12) | 49 (17) | >0.05 |
| Prior BMV | 34 | 15 (3.6) | 19 (6.6) | >0.05 |
| Age (years) | 29.4±10.1 | 39.9±9.9 | 0.000 |
| Height (cm) | 153.6±10.4 | 153.6±10.4 | 0.52 |
| Weight (kg) | 47.4±9.5 | 46.1±9.7 | 0.07 |
| Class III/IV | 251 | 115 (28) | 136 (47) | 0.00 |
| AF | 113 | 50 (12.1) | 63 (21.9) | >0.05 |
| Wilkins score of >8 | 193 | 96 (23.3) | 97 (33.7) | <0.001 |
| Aortic valve disease | 288 | 157 (37.9) | 131 (45.6) | <0.05 |
| Organic TVD | 22 | 10 (2.4) | 12 (4.2) | >0.05 |
| PAH (moderate to severe) | 265 | 140 (33.8) | 125 (43.5) | 0.000 |
| LA size (mm) | 42.7±6 | 49.5±6.4 | 0.000 |

Figures in parenthesis are in percentage; PPAH: persistent pulmonary artery hypertension; BMV: balloon mitral valvotomy; LA: left atrium; PPAH: persistent pulmonary artery hypertension; AF: atrial fibrillation; TVD: tricuspid valve disease
severe PAH at the time of BMV. LA was larger in patients with PPAH (49.5 ± 6.4 mm vs. 42.7 ± 6 mm). There was no difference in the number of patients with history of prior BMV/surgical commissurotomy or in the number of juvenile patients (patients with MS less than 18 years) between the two groups.

Hemodynamic variables prior to BMV
Hemodynamic findings before BMV are shown in Table 2. Patients who had PPAH had higher LA pressure, PA pressure (pulmonary artery systolic, diastolic, and mean), and TMG prior to BMV. The preprocedural valve area was slightly less in the PPAH group (0.8 ± 1 cm² vs. 0.9 ± 1 cm²), but not statistically significant.

Hemodynamic variables after BMV
Hemodynamic findings after BMV are shown in Table 3. PA pressure (systolic, mean, and diastolic), LA mean pressure, and TMG decreased in both groups. Patients who had PPAH had higher LA and PA pressures after BMV. The TMG was also higher in the PPAH group (6.9 ± 3.9 mmHg vs. 6.1 ± 5.5 mmHg, P = 0.049). Patients in the PPAH group had significantly less postprocedural MVA (1.7 cm² vs. 1.5 cm², P < 0.05) derived from the invasive hemodynamic measurements.

In-hospital events
In-hospital events are shown in Table 4. There was no difference between the two groups regarding acute complications (e.g., thromboembolism, major bleeding, and stroke/transient ischemic attack [TIA]).

Mitral regurgitation
The incidence of hemodynamically significant MR (moderate or more and not requiring emergent MVR) was more in the PPAH group (13.2 vs. 3.38%, P < 0.05).

Follow-up at one year after BMV
In the PPAH group, 64 (22.3%) patients were in AF at one year after BMV versus 51 (12.4%) in the no PPAH group (P = 0.001). TMG was significantly higher in the PPAH group. The PPAH group had comparatively lower mean MVA (Table 5).

Last follow-up after BMV
Data regarding the last follow-up (at mean 5.5 ± 1.3 years) is given in Table 6. Data of 629 patients was available at the time of last follow-up of five years, 242 in the PPAH group and 387 in the no PPAH group. A total of 72 patients were lost to follow-up, 27 patients in the PPAH group, and 45 patients in the no PPAH group. In the PPAH group, 63 (26.2%) patients were in AF versus 56 (14.6%) in the no PPAH group (P < 0.05). TMG was significantly higher in the PPAH group. The incidence of restenosis was more in PPAH group with comparatively lower mean MVA five years after the BMV (Table 6).

In the PPAH group, events included 13 strokes, 34 MVR, 23 redo BMV, 34 new onset heart failures, and five deaths

| Event | PPAH | No PPAH | P value |
|-------|------|---------|---------|
| Stroke/TIA | 4 (0.96) | 3 (1.04) | <0.05 |
| Moderate MR (3+ and 3-4+) | 14 (3.38) | 38 (13.2) | <0.05 |

PPAH: persistent pulmonary artery hypertension; TIA: transient ischemic attack; MR: mitral regurgitation

| Total | Patients with no PPAH | Patients with PPAH | P value |
|-------|---------------------|-------------------|---------|
| Number | 701 | 414 (59) | 287 (41) | >0.05 |
| Male | 150 | 93 (22.4) | 57 (19.8) | >0.05 |
| Asymptomatic | 688 | 408 (98.5) | 280 (97.5) | >0.05 |
| AF | 109 | 48 (11.5) | 61 (21.2) | 0.001 |
| MVA | 1.63±0.25 | 1.50±0.23 | <0.05 |
| TMG | 5.5±3 | 6.2±3.6 | <0.05 |
| PASP | 34.4±4.9 | 53.4±10.9 | 0.000 |

Figures in parenthesis are in percentage; BMV: balloon mitral valvotomy; PPAH: persistent pulmonary artery hypertension; AF: atrial fibrillation; PASP: pulmonary artery systolic pressure; MVA: mitral valve area; TMG: transmitial gradient
accounting for a total (composite endpoints) of 109 (45%). In the no PPAH group, events included 14 strokes, 18 MVR, 11 redo BMV, 17 new onset heart failures, and three deaths accounting for a total (composite end points) of 63 (15.72%). The PPAH group had a significantly higher event rate compared to the other group (Table 7).

DISCUSSION

PH is a frequent complication of rheumatic mitral valve disease.[4,13,14] It is known to be associated with rheumatic MS and MR.[15] It influences the natural history of the disease, including the post intervention prognosis.[16,17] In rheumatic MS, PH is often out of proportion to the degree of LA hypertension.[4]

As already mentioned, PAH in rheumatic MS is contributed by passive transmission of LA pressure, the vasoreactive component, and fixed pulmonary vascular disease. The pulmonary veins of patients with rheumatic MS and significant PH have been shown to develop muscular media. Moderate to marked hypertrophy is reported to occur in medium sized branches of pulmonary arteries. Tandon et al.[18] and Chopra et al.[19] have reported plexiform lesion in 4% of their autopsy studies. PAH usually regresses following a successful BMV, but it has been observed that PAP fails to regress in a significant percentage of patients.[3-6]

Gamra et al.[5] reported that baseline clinical and hemodynamic characters like advanced age, higher Wilkin’s echocardiographic score, smaller MVA, and higher mean PAP at the baseline could predict persistently high pulmonary vascular resistance (PVR) after BMV. Among our study patients, those who had PPAH were older, presented more frequently with AF, and had higher NYHA functional class at the baseline.

Pulmonary vascular disease develops in long standing PH and will depend upon the chronicity of the disease and also the severity of PH.[20] The PPAH group patients in our study were older, suggesting chronicity. They also had higher systolic and mean PAP. Both these factors might have contributed to pulmonary vascular disease and PPAH.

AF indicates the presence of advanced disease with dilated atria and fibrosis of the atrial musculature. The patients in our study had higher prevalence of AF and they also had larger LA indicating severe chronic disease.

The finding that these patients had higher Wilkin’s echocardiographic score, lower MVA with higher TMG, and higher PAP at the time of the procedure indicates that they had advanced rheumatic heart disease. They also had higher prevalence of aortic valve disease. The coexistent aortic valve disease may contribute to an increase in left ventricular end-diastolic pressure (LVEDP) which can further increase the LA pressure and consequently raise the PA pressure. The postprocedure LVEDP was comparatively higher in our patients with PPAH. We also know that rheumatic pathology affects the left ventricle as indicated by left ventricular systolic dysfunction and regional wall motion abnormality in patients with MS.[21] This can also contribute to the raised LVEDP which is usually proportional to the severity of aortic valve disease and left ventricular systolic function.

Fawzy et al.[22] found that on follow-up, the PAP normalized in many patients who had optimal results after BMV. In contrast, no such improvement was noted in patients with suboptimal results (MVA < 1.5cm² or MR grade > 2). It was also observed in our study that patients who had PPAH after BMV had comparatively less MVA after the procedure. This may be indicative of the fact that PPAH developed in those subgroup of patients who had lesser hemodynamic benefit following BMV.

Krishnamoorthy et al.[3] however, found that the gain in MVA was not always predictive of decrease in the PAP. This discrepancy of the lack of association between relief of mitral obstruction and improvement in pulmonary
hemodynamics is reported by others also.[2,23] So other factors might also contribute to the persistence of PH as discussed below.

Occurrence or worsening of MR following BMV is a factor which can cause a gradual increase in PVR or nonregression of PAH following BMV and eventually leading to PPAH. In our study, the incidence of hemodynamically significant MR was more in the PPAH group. MR will increase the LA pressure which will in turn increase the pulmonary arterial pressure.

Another factor which can contribute to PPAH is the shunting of blood from left to right atrium through the iatrogenic atrial septal defect (ASD) created during BMV. But the number of patients with recognizable ASD by color Doppler echo on follow-up in both groups of patients in our study was very low.

Studies have shown that development of restenosis could lead to the return of pulmonary pressure even to the premitral valve dilatation values.[24] In our patients, the occurrence of restenosis on last follow-up was significantly higher in the PPAH group. Restenosis indicates advanced disease and may suggest ongoing rheumatic activity with a possible inflammatory component, which can even contribute to and aggravate pulmonary vascular disease.

Gamra et al.[5] reported the predictors of PPAH as older age and pre-BMV characteristics such as higher Wilkin’s echocardiographic score, smaller baseline MVA, and higher mean basal PAP. Siahaan et al.[20] in a study from Indonesia, reported that a PASP of > 95 mmHg predicted PPAH following BMV with 58% sensitivity and 70% specificity.[20]

The presence of a pulmonary bed gradient (mean PAP-mean LA pressure > 12 mmHg) is shown to be a useful predictor of PPAH following BMV.[9] Assessing the response of the PAP to inhalation of nitric oxide during cardiac catheterization may be useful to divorce fixed from reversible PH.[25]

In our study, patients with PPAH had more adverse events on long-term follow-up. They had higher incidence of strokes, need for redo procedures like mitral valve replacement (MVR) and redo BMV, and new onset of heart failure. PPAH is an indicator of advanced disease as we discussed earlier. This is also associated with higher prevalence of AF and dilated atria. This predisposes the patients to thromboembolism and stroke.

The need for redo procedures like MVR and redo BMV was also higher in the PPAH group of patients. Many reasons may contribute to this phenomenon. These patients are older and also have advanced disease which itself is a contributing factor for the development of restenosis.

The lower MVA obtained following BMV in PPAH group of patients may predispose them for earlier development of mitral restenosis.

The incidence of new onset HF was higher in the PPAH group. One of the factors contributing to this may be the presence of tricuspid regurgitation (TR) which we know is associated and is usually proportional to the degree of PH. Another factor is the presence of disease of other valves like aortic valve and tricuspid valve (organic or primary tricuspid valve disease) which might have contributed to right heart failure. The raised LVEDP subsequent to the left ventricular dysfunction which we have already discussed also might have contributed to the development of heart failure.

As discussed, PPAH indicates poor prognosis. PPAH is contributed mainly by the “fixed PVR” which is mostly due to pulmonary vascular disease. To prevent the development of pulmonary vascular disease an early intervention as recommended by Pan et al.[28] and Ribeiro et al.[6] would be justified.

The American College of Cardiology-American Heart Association (ACC-AHA) recommendation for percutaneous mitral valvotomy includes PAP as a criterion for selecting the patients. PAP > 50 mmHg at rest or > 60 mmHg post exercise is an indication to perform BMV even in asymptomatic patients with moderate or severe MS.[27]

In conclusion, PAH fails to regress in a subpopulation of patients who underwent BMV. Advanced age, higher echocardiographic score, smaller MVA, and mean PAP at baseline could predict PPAH. These patients have increased occurrence of restenosis, new onset heart failure, and need for reinterventions. PPAH represents an advanced stage of rheumatic valve disease and indicates chronicity of the disease, which may be the reason for the poor prognosis of these patients. Patients with PPAH require intense and more frequent follow-up.

**Study limitations**

Ideally, evaluation of PPAH should have been supported by PVR. Due to the retrospective nature of the study, it was not feasible and 72 patients were lost to follow-up, which is a major limitation of this study. We tried to contact them through letters or by telephone multiple times, but we could not contact them. Most of these patients were from remote villages and from poor socioeconomic strata and many were illiterate.

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