ORIGINAL ARTICLE

Percutaneous mitral balloon valvuloplasty: beyond classic indications

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A b s t r a c t

Background and aim: In patients with mitral stenosis (MS) percutaneous mitral balloon valvuloplasty (PMBV) is used to improve symptoms and prognosis. Although there is some evidence for potential long-term benefits from PMBV in asymptomatic patients with mitral valve area (MVA) between 1.0 and 1.5 cm^2, there are no follow-up data on patients with symptomatic MS with MVA > 1.5 cm^2, who underwent PMBV.

Methods: We retrospectively analysed periprocedural results of 113 symptomatic patients who underwent PMBV for MS with MVA > 1.5 cm^2 (group 1) and compared them with a control group of patients with MVA ≤ 1.5 cm^2 (group 2). Clinical and procedural variables were compared between groups.

Results: In group 1, PMBV resulted in a significant increase of MVA as well as a decrease of mean and maximal mitral gradients and mean left atrial pressure (LAP), and a subsequent decrease of mean and systolic pulmonary artery pressures (PAPs). Moreover, 6.3% of patients developed moderate to severe (3+) or severe (4+) post-procedural mitral regurgitation (MR). Post-procedural increase in MVA and decrease of LAP were more pronounced in group 2 than group 1 (ΔMVA 0.74 cm^2 vs. 0.41 cm^2, $p < 0.05$, and ΔLAP 8.2 mmHg vs. 6.0 mmHg, $p < 0.05$). Nonetheless, no significant differences were observed for Δ of mean and systolic PAPs. The grade of post-procedural MR was comparable between groups.

Conclusions: PMBV is a feasible procedure in highly selected patients without classic echocardiographic indications. Nonetheless, it is associated with a small but non-negligible periprocedural risk of developing severe MR.

Key words: mitral stenosis, percutaneous mitral balloon valvuloplasty

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INTRODUCTION

In patients with mitral stenosis (MS) interventional treatment is used to improve both the symptoms and prognosis. Indications for interventional treatment in patients with significant MS are well-established and proven by extensive evidence.

The current heart valve disease guidelines of the European Society of Cardiology (ESC), the American Heart Association and American College of Cardiology (AHA/ACC) recommend percutaneous mitral balloon valvuloplasty (PMBV) as the first-line therapy in rheumatic patients with isolated significant MS and feasible valve morphology.

The long-term outcome after PMBV is multifactorial [1] but mainly determined by the immediate post-procedural results. Post-procedural parameters associated with poorer late outcome include smaller mitral valve area (MVA), more severe mitral regurgitation (MR), higher mean mitral gradient (MG), and higher systolic pulmonary artery pressure (PAP) [2]. Most common patient-related factors predicting worse outcome at follow-up included female sex, age, and New York Heart Association (NYHA) functional class [3]. Because these two types of factors interplay, appropriate pre-interventional assessment of valve- and patient-related factors is crucial.

The treatment strategy is dependent on the stage of MS, but no randomised trial has been performed to ascertain the best timing of PMBV [2]. This intervention is performed increasingly often for indications from both sides, namely in

aged patients with more comorbidities and less favourable valve morphology and in patients who do not necessarily yet meet classic echocardiographic indications.

A MVA < 2.5 cm^2 is usually considered a criterion for any MS [4], and the significance of MS is determined by MVA < 1.0 cm^2, mean MG > 10 mmHg, and systolic PAP > 50 mmHg.

In detail, the 2012 ESC guidelines recommend PMBV only in symptomatic or asymptomatic patients with MVA ≤ 1.5 cm^2 [5]. Such a criterion, however, is not based on sufficient evidence, but is rather conventionally admitted. Thus, the 2014 AHA/ACC guidelines add a subgroup of MS patients who do not meet the above basic criterion (MVA ≤ 1.5 cm^2) but in whom PMBV may still be considered under additional conditions. This subtype of MS is referred to as progressive MS, defined as MVA > 1.5 cm^2 with evidence of haemodynamically significant MS based on pulmonary artery wedge pressure > 25 mmHg or mean MG > 15 mmHg during exercise (2006 AHA/ACC guidelines mention also systolic PAP > 60 mmHg). Such an entity leads to haemodynamic consequences expressed by mild to moderate left atrial enlargement, and these patients may benefit from early PMBV (class of recommendation IIb) [6].

Interestingly, no criterion of systolic PAP is included in the current American indications for PMBV of progressive MS, whereas it is already included in European indications for PMBV in patients with asymptomatic MS.

In 1999 Pan et al. [7] addressed the concept of percutaneous treatment of mild MS for the first time. All 21 patients remained in functional NYHA class II and flexible mitral valve was observed in 86% of cases. Mean MVA increased from 1.7 cm^2 to as much as 3.1 cm^2 after PMBV, and no significant post-procedural MR was observed. Although those results in a small study were encouraging, this concept has not gained wide acceptance.

Although there is some evidence of potential long-term benefits of PMBV in asymptomatic patients with MVA measuring between 1.0 cm^2 and 1.5 cm^2 [8], there is a lack of follow-up data of symptomatic MS patients with MVA > 1.5 cm^2, who underwent PMBV.

In summary, at present there are no data supporting more liberal indications for PMBV (level of evidence C in the American guidelines) [6].

We retrospectively analysed the immediate periprocedural outcomes in patients who underwent PMBV for MS with MVA > 1.5 cm^2 (group 1) and compared them with a propensity score-matched control group of patients treated with PMBV for MVA ≤ 1.5 cm^2 (group 2).

METHODS
Patient population
From September 1988 through November 2016, 1794 consecutive patients underwent PMBV for rheumatic MS at the

Institute of Cardiology in Warsaw, Poland. All pre-interventional and interventional data were entered prospectively into a database, beginning in 1988. In 85 patients, a repeated PMBV was done due to mitral restenosis, and among this subgroup seven patients underwent third PMBV for recurrent mitral restenosis. The results of this subgroup were published previously [9]. Thus, a total of 1886 PMBV procedures were performed, of which 116 were done for de novo MS with MVA > 1.5 cm^2 (group 1). Due to the lack of critical matching data (see below), three patients were excluded, and 113 patients (group 1) were included in further analysis. This group was subsequently divided into the following subgroups, according to additional echocardiographic and haemodynamic parameters: group 1a (mean MG ≤ 10 mmHg) and group 1b (mean MG > 10 mmHg).

The whole cohort of patients with MVA > 1.5 cm^2 (group 1) was then matched by demographics (sex and age), clinical characteristics (presence of atrial fibrillation [AF]), and echocardiographic findings (Wilkins score and MR grade) to the equal number of patients with MVA ≤ 1.5 cm^2 (group 2) by propensity score, and subsequently compared. By analogy, these patients were divided according to initial systolic PAP: group 2a (mean MG ≤ 10 mmHg) and group 2b (mean MG > 10 mmHg).

Indications for PMBV included functional NYHA class II or higher, MR ≤ 2+, suitable mitral valve morphology, and the absence of concomitant cardiovascular disease requiring surgical correction or serious contraindication to necessary corrective surgery.

The requirement for informed consent was waived because of the retrospective nature of this study.

Echocardiographic evaluation
Each patient underwent transthoracic echocardiographic examination on the day preceding PMBV and between 24 and 48 h after the procedure. The most widely used Wilkins scoring was applied to assess the severity of pathological lesions in the mitral valve and subvalvular apparatus [10]. MG was measured with continuous-wave Doppler, and the MVA was determined by planimetry and/or by pressure half-time calculation. MR severity was assessed semi-quantitatively or by using quantitative methods, and classified as absent (0), mild (1+), moderate (2+), moderate to severe (3+), or severe (4+). Systolic PAP was measured invasively during periprocedural assessment. The size of the left atrium was assessed from the leading edge of the anterior wall to the leading edge of the posterior wall [11]. Pre-interventional transoesophageal echocardiography was done to exclude the presence of thrombi in the left atrium.

Technique of PMBV
Considering the complexity of PMBV and the learning curve [12], the procedure was performed by two of only

four experienced cardiologists over the whole study period. The technical aspects were described in detail before [5]. In short, a transseptal approach was used in all cases under local anaesthesia and transoesophageal echocardiographic monitoring. Haemodynamic measurements were done during the procedure and the Inoue balloon system (Toray Industries Inc, Tokyo, Japan) was used to perform the PMBV in all our patients. The diameter of the balloon was at the operator's discretion and based on the previously proposed formula [13]. Stepwise or single balloon inflation was done at the discretion of the operator.

Definitions of immediate procedural outcome

Success of PMBV was defined as a $\geq 50\%$ increase in baseline MVA with an absence of $> 2+$ increase in the severity of MR.

Failure of PMBV was defined as post-procedural MR $> 2+$.

Statistical analysis

The statistical evaluation was performed using IBM SPSS Statistics 20 (Armonk, NY, USA). Continuous variables were presented as mean $\pm$ standard deviation and were compared using the Student's t-test (unpaired and paired) or the Mann-Whitney U test, as appropriate. Categorical variables were expressed as numbers and percentages and were compared by the χ^2 test and Fisher's exact test.

To reduce the effect of treatment selection bias, analyses were performed on the appropriate matched variables. This was done on the basis of the propensity score method with the nearest neighbour matching on the covariates involving sex, age, Wilkins Score, pre-interventional MR grade, and the presence of AF. After propensity score matching [14, 15], the underlying covariates were compared between matched groups with the paired t-test or the Wilcoxon signed-rank test for continuous variables, and the χ^2 test and Fisher's exact test for categorical variables.

Multivariable logistic regression analysis was carried out to identify the predictors of procedural success. A p-value < 0.05 was assumed as a cut-off point to select eligible variables for the multiple logistic regression models.

A value of $p < 0.05$ was considered significant.

RESULTS

The baseline clinical and demographic data of both groups are presented in Table 1.

Baseline characteristics

Group 1 consisted of 113 patients (mean age 54.0 ± 10.0 years, women; 89.4%). Sinus rhythm was observed in 60.2% of patients. Among this group most patients (83.2%) had mean MG ≤ 10 mmHg (group 1a).

Table 1. Demographic and clinical variables of the study groups

	Group 1	Group 2	p
Number of patients	113	113	–
Age [years]	54.0 ± 10.0	53.4 ± 10.2	0.7
Female sex	89.4%	93.8%	0.3
Body mass index [kg/m²]	26.7 ± 4.4	26.7 ± 4.4	0.9
Atrial fibrillation	39.8%	31.8%	0.3
HF NYHA class:			
II	80.6%	18.9%	< 0.05
III	19.4%	78.4%	< 0.05
IV	0%	2.7%	0.2

Data are shown as mean and standard deviation or percentage.
HF — heart failure; NYHA — New York Heart Association

Procedural characteristics

Comparison of pre- and post-interventional variables within group 1 is presented in Table 2. PMBV resulted in improvement of almost all MS-related parameters as expressed by increased MVA (from 1.7 ± 0.1 cm² to 2.0 ± 0.3 cm², $p < 0.05$), decreased MGs, PAP, and left atrial pressure (LAP), respectively. No change in cardiac output was observed. Significant post-procedural MR ($> 2+$) was observed in 6.3% of patients; among them, severe MR ($4+$) was present in 1.8% of patients. There was no in-hospital death.

Control group

Propensity score matching for the whole cohort yielded 113 matched pairs of patients. A comparison between group 1 and matched control group 2 is presented in Table 2.

Patients in group 1 presented with significantly less severe heart failure compared to group 2, as expressed by functional NYHA class.

All pre-interventional echocardiographic and invasive measurements assessing MS, like MVA (as per definition), MGs, LAP, and PAPs, indicated significant differences between groups. A trend toward a higher number of patients with systolic PAP > 50 mmHg was observed in the control group. Wilkins score was similar in both groups. No differences between the groups were observed in terms of MR severity or balloon sizes.

By analogy, the same parameters were used to assess the mitral valve after PMBV. Although post-interventional MS severity expressed by MVA, mean (echocardiographic but not haemodynamic) MG, mean PAP, and mean LAP was significantly more pronounced in group 2, the rate of PMBV success (see definition above) and associated parameters were higher in this group. There was no periprocedural mortality. The procedural complication rate expressed by MR $> 2+$ was similar in both groups.

Table 2. Echocardiographic and haemodynamic variables before and after percutaneous mitral balloon valvuloplasty. Intra- and inter-group comparison

	Before PMBV		p	After PMBV		p	p
	Group 1	Group 2		Group 1	Group 2	(intra-group 1)	(inter-groups)
Number of PMBV procedures	113	113	–	–	–	–	–
Wilkins score	6.1 ± 1.4	6.1 ± 1.5	0.9	–	–	–	–
MVA (planimetry)							
cm²	1.7 ± 0.1	1.1 ± 0.2	< 0.05	2.0 ± 0.3	1.8 ± 0.3	< 0.05	< 0.05
Δ	–	–		0.4 ± 0.3	0.7 ± 0.3	–	< 0.05
Mean MG (Doppler)							
mmHg	7.3 ± 3.5	9.4 ± 5.3	< 0.05	4.1 ± 1.5	4.6 ± 2.3	< 0.05	0.06
	Group 1a	Group 2a					
≤ 10 mmHg	83.2%	71.7%	0.05	100%	97.1%	< 0.05	0.1
> 10 mmHg	Group 1b	Group 2b					
	16.8%	28.3%		0%	2.9%		
Δ	–	–	–	3.1 ± 3.4	4.7 ± 5.1	–	< 0.05
Maximal MG (Doppler)							
mmHg	14.7 ± 5.5	17.4 ± 6.7	< 0.05	9.2 ± 3.3	10.2 ± 4.0	< 0.05	0.05
Δ	–	–	–	5.3 ± 5.1	7.1 ± 6.0	–	< 0.05
MG haemodynamics				4.9 ± 3.2	5.5 ± 3.5	< 0.05	0.2
mmHg	11.3 ± 5.3	14.5 ± 6.1	< 0.05	6.3 ± 3.9	9.0 ± 5.0	–	< 0.05
Δ	–	–	–				
Systolic PAP				33.6 ± 11.7	38.3 ± 10.3	< 0.05	< 0.05
mmHg	41.9 ± 13.1	48.3 ± 14.6	< 0.05	–	–		
>50 mmHg	22.6%	33.3%	0.09	8.4 ± 8.0	9.9 ± 9.1	–	0.2
Δ	–	–	–				
Mean PAP							
mmHg	27.1 ± 10.2	31.0 ± 10.5	< 0.05	21.8 ± 8.6	25.5 ± 8.5	< 0.05	< 0.05
Δ	–	–	–	5.3 ± 6.9	5.6 ± 6.7	–	0.8
Cardiac output							
L/min	5.1 ± 1.5	4.8 ± 1.3	0.1	5.2 ± 1.4	4.8 ± 1.3	0.4	0.06
Δ	–	–	–	0.0 ± 1.0	0.0 ± 1.0	–	0.7
Mean LAP							
mmHg	20.1 ± 6.7	24.1 ± 7.0	< 0.05	13.9 ± 6.4	15.7 ± 6.2	< 0.05	< 0.05
Δ	–	–	–	6.2 ± 6.5	8.4 ± 6.5	–	< 0.05
Size of the left atrium [mm]	47.4 ± 0.7	48.4 ± 0.7	0.3	–	–	–	–
Balloon size [mm]	27.8 ± 1.3	27.9 ± 1.5	0.4	–	–	–	–
Mitral regurgitation:							
0	61.1%	69.6%	0.2	45.9%	52.2%	< 0.05	0.3
1	31.9%	22.1%	0.1	30.6%	28.3%	1	0.7
2	7.1%	8%	0.8	17.1%	13.3%	< 0.05	0.4
3	0%	0%	1	4.5%	4.4%	–	1
4	0%	0%	1	1.8%	1.8%	–	1
ΔMVA ≥ 50%	–	–	–	11.0%	68.9%	–	< 0.05
Success (ΔMVA ≥ 50% and no post-MR > 2)	–	–	–	11.1%	68.9%	–	< 0.05
Failure (post-MR > 2)	–	–	–	6.3%	6.2%	–	1

Data are shown as mean and standard deviation or number or percentage. LAP — left atrial pressure; MG — mitral gradient; MR — mitral regurgitation; MVA — mitral valve area; PAP — pulmonary artery pressure; PMBV — percutaneous mitral balloon valvuloplasty

Prediction of procedural success

Among variables entered in the bivariate analysis, more frequent NYHA class III, lower Wilkins score, smaller pre-interventional MVA, higher LAP and mean and systolic PAP, and higher haemodynamic MG were significantly associated with procedural success (see definition above). Apart from Wilkins score, all remaining parameters were more frequently associated with the control group.

In multivariable logistic regression analysis, lower Wilkins score, smaller pre-interventional MVA, and more frequent NYHA class III were independent predictors of the procedural success (see definition above).

DISCUSSION

The aim of our study was to focus on symptomatic patients with mild MS (MVA > 1.5 cm^2), who underwent PMBV. It extends the pioneering observations of Pan et al. [7] in a similar cohort. Two direct outcome findings are critical.

First, PMBV was effective in this cohort of patients. An increase in MVA resulted in a significant decrease of mean and maximal MGs as well as PAPs and mean LAP. Although the final MVA was larger than in the control group, the relative increase in MVA was smaller than in the control group. Because the balloon sizes were comparable, this only means that the dilatation process of stenotic valve was more delicate in the studied group than in the control group.

Second, the rate of post-procedural severe MR in the studied group was not negligible, and it was similar in our control group as well as in the Korean cohort of patients with moderate MS (1.0–1.5 cm^2) who underwent PMBV [8]. MR was observed despite the fact that post-procedural increase in MVA was significantly smaller in our group than in the historical group of Pan et al [7] (1.7 cm^2 to 2.0 cm^2 vs. 1.7 cm^2 to 3.1 cm^2, respectively). Intuitive interpretation of such results is that less aggressive PMBV (as expressed by lower increase of post-procedural MVA) does not necessarily protect against this complication.

Impact of MS on left atrial diameter and pressures

Percutaneous mitral balloon valvulopasty does not seem to reduce the incidence of AF in patients with significant MS, and its influence on the decrease in the incidence of AF in patients with mild MS is not clear. This may be explained by advanced enlargement of the left atrium secondary to MS, which is a well-known and independent predictor of AF in MS patients [16]. Patients from both our groups presented with at least moderate left atrial enlargement and comparable dimensions. This might suggest that even mild MS may lead to a change of left atrial geometry, despite lower pre-interventional LAP compared with significant MS. Successful PMBV without severe MR immediately decreases LAP and is one of the independent predictors of systolic PAP decrease [17]. This was also observed in both our groups. Although the LAP in group 1 was significantly lower than in the control group, PMBV still resulted in significant reduction of LAP in both groups. Of note, factors other than MS, such as left ventricular diastolic dysfunction, may also contribute to elevated LAP, and their presence is associated with a greater risk of failure of PMBV to improve symptoms [18].

Impact of PMBV on systolic PAP

Post-capillary pulmonary hypertension is the effect of elevated LAP and loss of left atrial compliance. Pulmonary hypertension frequently complicates MS, and elevated systolic PAP reflects the consequences of MS rather than its severity. Thus, systolic PAP is only an additional sign and not a surrogate marker of MS severity [19]. Nonetheless, there is a direct correlation between successful PMBV and immediate decrease in systolic PAP [20], which was also observed in our analysis. The latter is one of the post-procedural parameters associated with long-term outcome [21]. PMBV may even be, to some extent, effective in patients with severe pulmonary hypertension (systolic PAP > 75 mmHg) [22]. Still, preventive intervention before development of pulmonary hypertension is of utmost importance because the positive effect of PMBV on right ventricular function in the acute period may disappear in the mid-term [23].

Correlation between PAP and functional class

We do not have follow-up observations on functional class. Still, the scale of PAP has been shown to correlate, at least to some extent, with the grade of functional class. It is debatable which one of these two factors is more important for long-term prognosis.

In patients with idiopathic pulmonary artery hypertension, the NYHA/World Health Organisation system based on the mean right atrial pressure and mean PAP allows separation of classes I and II from III and IV [24].

In patients with heart failure and preserved ejection fraction, diastolic PAP was one of the parameters that were independently associated with advanced NYHA class [25].

Thus, some patients with MS with apparently acceptable MVA suffer from effort intolerance. It may be hypothesised that this is caused by mild MS. However, such an interpretation must be taken with caution. Cohen-Solal et al. [26] found no correlation between MVA or MG at rest and maximal upright exercise tolerance in patients with MS. This may be explained by the fact that other patient-related factors, such as restrictive lung function disorders, chronotropic incompetence, limited stroke volume reserve, and peripheral factors, are also suggested to play a significant role [27]. Nevertheless, these factors may be, at least to some extent, a consequence of MS, even if not significant according to strict echocardiographic criteria. Thus, symptomatic patients even with MVA measuring between 1.6 cm^2 and 2.0 cm^2 might benefit from PMBV [28, 29]. Three explanations were proposed before: 1) the

MVA may be smaller than measured due to vagaries of clinical imaging; 2) there is a variable correlation of pulmonary vascular resistance with MVA; 3) for a given MVA, MG will be higher in persons with a large body surface area (BSA) or those with other reasons to have an elevated cardiac output.

Indexing MVA to BSA

Although Singh et al. [30] showed a strong correlation of MVA with BSA, no threshold of indexed MVA to BSA has been validated so far [19]. Thus, indexing to BSA is only recommended in the case of aortic valve stenosis or aortic dilatation [5]; consequently, we did not perform it.

The lack of data from follow-up observations make it impossible to clarify the implication of a very early invasive strategy for mild MS. Nonetheless, two aspects are worth mentioning. The first one is change in functional class. Results from 37 studies indicate that the assessment of functional class in mildly symptomatic patients is subjective [31], and patients from group 1 in our study remained predominantly in NYHA class II. Thus, more reliable measures (like six-minute walk test, treadmill or cardiopulmonary exercise testing, or natriuretic peptides [32, 33]) would be advisable to prospectively assess the change of functional class after PMBV. The other important aspect is impact of PMBV on the development of mitral restenosis. It may, at least theoretically, lead to MS with more pronounced MS-related symptoms, compared with untreated mild MS. In our patients with mild MS (group 1), we did not observe mitral restenosis after PMBV. Because our matching criteria did not exclude patients with mitral restenosis, the control group included five patients with mitral restenosis after previous PMBV, and eight new patients (7.1%) from this group developed mitral restenosis.

Correlation of pre-interventional PAP and MG

Our results indicate that what makes a greater impact on MGs by echocardiography is the pressure (PAP) and not the MVA itself (to some extent).

The retrospective design of this single-centre study and the lack of randomisation of group 1 to the conservative or interventional arm are inherent limitations of this analysis and leave room for unmeasured effects on procedural methods and outcomes.

The existence of "progressive MS" is difficult to prove for group 1 because the patients were not necessarily assessed for increased MG > 15 mmHg during exercise.

Post-procedural complications are only limited to MR. Due to the long time span of this retrospective study, we do not have reliable data regarding other possible post-procedural complications like stroke or access site bleeding.

In conclusion, PMBV may be a relatively safe and feasible procedure in highly selected patients who do not meet the classic indication for interventional treatment according to 2012 ECS guidelines. Although it provides good immediate results, PMBV is associated with a small, but non-negligible periprocedural risk. Thus, indications for PMBV should be very carefully assessed and balanced against the inherent periprocedural complications. Performance of this procedure in patients with larger MVA would require favourable anatomy to reduce the incidence of complications.

Conflict of interest: *none declared*

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