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Research Article

Effect of Percutaneous Balloon Mitral Valvuloplasty on Left Atrial Appendage Function: Immediate and 6 months follow-up: A Trans-esophageal Echocardiographic Study

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Abstract

Introduction: Mitral stenosis (MS) causes structural and functional abnormalities of the left atrium (LA) and left atrial appendage (LAA), and studies show that LAA performance improves within a short time after (PBMV).

Material and Methods: 25 patients with symptomatic severe MS (MVA ≤ 1.0 cm^2) with NYHA class II and above who underwent successful PBMV were enrolled in this prospective observational study. All underwent standard TTE, TEE before, 3days and 6-months after PBMV. LA dimensions were measured. Trans mitral diastolic pressure gradient and MVA by both planimetry and pressure half-time were measured by using TTE. LAA function was evaluated by TEE. LAA flow velocities, including peak systolic (S wave), peak early diastolic (E wave), and peak late diastolic (A wave), were measured at the outer third of LAA by pulsed-wave Doppler, LAA tissue Doppler velocities 'e' LAA, 'a' LAA, and 's' LAA respectively, were obtained.

Conclusion: The present study showed contractile dysfunction of the LAA in patients with critical MS, which significantly improved after PBMV and at a 6-month follow-up.

Keywords: CRHD (chronic rheumatic heart disease), Percutaneous mitral balloon mitral valvuloplasty (PBMV), Left atrial appendage (LAA

Introduction

Rheumatic fever is the leading cause of acquired heart disease in children and young adults worldwide. The burden of rheumatic fever and RHD has been characterized by at least four changing patterns over the past 150 years [1]. CRHD, being the dominant form of valvular heart disease in developing nations like India, constitute a major cause of cardiovascular morbidity and mortality. Although data on incidence and prevalence on a nationally represented sample are lacking, there is an indication of declining trends especially after 2000 mirroring with improving the economic growth of the country [2]. These changes led to multicentric survey studies across the country over a period of 40 years. The mitral valve is the most commonly involved valve in CRHD. The aetiology of valvular involvement in patients with mitral stenosis is almost exclusively of rheumatic aetiology (84.67%) [3]. This is also shown in a study by Manjunath, et al. [4]. Left atrial appendage (LAA) normally prevents stasis of blood due to its high compliance and contractility. Patients with critical, rheumatic MS have Left atrial (LA) and Left atrial appendage (LAA) dysfunction because of pressure and volume overload [5]. The LAA being a compliant chamber, plays an important role as a reservoir in this situation [6]. It is also a highly dynamic and contractile structure, which helps prevent local blood stagnation in healthy individuals (7). Patients with MS have a propensity for local thrombus formation in the LA and LAA because of blood stasis, impaired contractile function and atrial fibrillation (AF) [8]. The LAA is a common site of thrombus formation and a source of systemic embolism in these patients [9,10]. Risk of cerebrovascular accident (CVA) is increased approximately five-fold in non-rheumatic AF and 17-fold in patients with MS with AF [11]. Even patients of MS in sinus rhythm with depressed LA and LAA function are at high risk of CVA [12]. Assessment of LAA function helps predict the risk of thromboembolism.

Since it's introduction in 1984 by Inoue et.al. [13] PBMV has become established as a safe and effective treatment for rheumatic mitral stenosis with results equivalent to surgical valvuloplasty [14]. Mitral valve area (MVA) is increased during balloon dilatation by commissural splitting [15]. Transesophageal echocardiography (TEE) allows semi-invasive, highly accurate imaging of the functional efficiency of LAA by Doppler and Doppler tissue imaging (DTI) flow profile. MS causes decreased LAA Doppler and DTI velocities in patients even with sinus rhythm [16]. LAA functional status can be assessed by Doppler flow velocities and ejection fraction, measured by two-dimensional tranesophageal echocardiography (TEE). Although there have been many studies of LAA functional assessment in patients with MS who undergo percutaneous balloon mitral valvuloplasty (PBMV) [17-19] very few studies have studied the short and long-term improvement of LAA function after PBMV. Mitral stenosis (MS) causes structural and functional abnormalities of the left atrium (LA) and left atrial appendage (LAA), and studies show that LAA performance improves within a short time after percutaneous PBMV. Importantly, the left atrial appendage (LAA) has an important pathophysiological function because it is more compliant than the LA and its contractile capacity prevents blood stasis due to its high compliance and contractility [20,21]. The aim of the present study was to compare left atrial appendage (LAA) function by transesophageal echocardiography before and after percutaneous balloon mitral valvuloplasty (PBMV). LAA velocities were obtained by TEE in all the patients before, 3 days and 6 months after successful PBMV therefore, assessed pulse wave Doppler velocities, tissue Doppler velocities, and LAA ejection fraction before PBMV, 3 days and at 6-month follow-up in patients with sinus rhythm.

Material and Methods

Study location

This observational prospective study was conducted in the department of cardiology in our institution, over a period from June 2018 to May 2019. The institutional ethical committee has approved and informed consent from each patient was obtained.

Sample Size Calculation

As it was an observational study, no power analysis for sample size was performed. All patients with chronic rheumatic heart disease with severe mitral stenosis and in normal sinus rhythm were enrolled in the study. We enrolled fifty patients in our study with symptomatic severe MS (MVA ≤ 1.0 cm^2) with NYHA functional

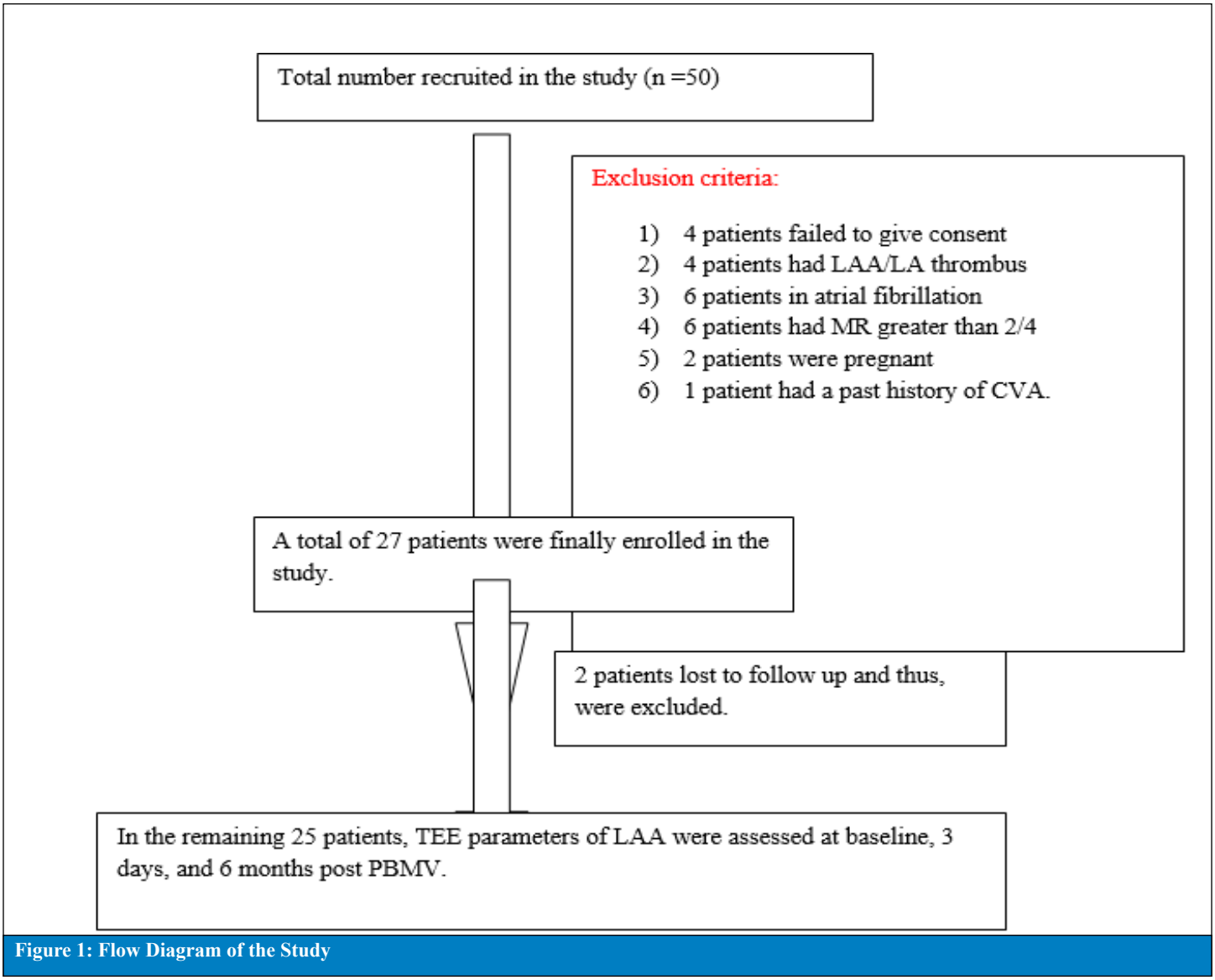


Figure 1: Flow Diagram of the Study

class II and above who underwent successful PBMV. Inclusion criteria and exclusion criteria were shown in the figure 1. Inclusion criteria are 1) Those who were fulfilling the PBMV intervention criteria.2) Those who had a successful intervention only were included.(Successful PBMV was defined as patients who had MVA >1.5 cm2 without MR ≥ grade 2/4). 23 patients were excluded and 2 patients lost follow up.

A detailed history was taken from the patient regarding presenting complaints, past history of PBMV, or CVA.ECG and basic blood investigations were done in all the patients. All enrolled patients underwent standard transthoracic echocardiography (3.5-MHz transducer) and multiplane TEE (PHILIPS) (3.5-MHz multiphase-array probe) before, 3days after, and 6-months after PBMV. LA dimensions were measured in the parasternal long-axis view. Trans mitral diastolic pressure gradient and mitral valve area by both planimetry and pressure half-time were measured using transthoracic echocardiography. There were no significant abnormalities of other valves except functional TR.LAA function was evaluated in the transverse plane using TEE. LAA flow velocities, including peak systolic (S wave), peak early diastolic (E wave), and peak late diastolic (A wave), were measured at the outer third of LAA using electrocardiographically gated pulsed-wave Doppler. Corresponding LAA tissue Doppler velocities 'e' LAA, 'a' LAA, and 's' LAA respectively, were obtained. LAA tissue Doppler

velocities were measured using the spectral mode of myocardial Doppler imaging (5 MHz) in the transverse plane, with the positioning of the sample volume in the free wall midway between the tip and the outlet of the LAA. The cursor was placed as parallel as possible to the LAA lateral wall during the entire recorded cardiac cycle. Gain setting filter and Nyquist limit were adjusted to optimize the Doppler signal. After the electrocardiographic P wave, LAA contraction by tissue Doppler is reflected as a positive wave ('a'LAA), which is followed by a negative wave ('s'LAA) coinciding with left ventricular contraction and then a positive wave ('e' LAA) is coinciding with the isometric relaxation phase of left ventricular diastole. LAA end-diastolic and peak systolic volumes were measured using the modified Simpson's method, and the ejection fraction was calculated.

Table 1: Showing the baseline clinical and echocardiographic characteristics of the population.

Characteristics	Value
Age (years)	31.48 ± 7.6
Sex Female (%) Male (%)	 23 (92%) 2 (8%)
Functional class (NYHA) II(%) III-1V(%)	 16 (64%) 9 (36%)
Previous/past CVA Yes No	 0 25
LA size (mm)	4.7 ± 0.4
LV Ejection fraction (%)	58.04 ± 3.5
LV diastolic diameter (mm)	3.9± 0.2
LV systolic diameter (mm)	2.57 ± 0.05
Wilkins score	7.6 ± 1.03

* p < 0.05: ** P < 0.01, Value are given n (%) or mean ± Standard Deviation

LAA Ejection Fraction =

$$\frac{\text{End diastolic volume} - \text{End systolic volume}}{\text{End-diastolic volume}} \times 100$$

PBMV was performed using a standard trans septal approach with an Inoue balloon. Pre-PBMV and post-PBMV cardiac catheterization were performed. Data regarding all the above mentioned parameters were collected before, 3 days, and at 6 months follow up in all the patients and were subjected to statistical analysis.

Statistical Analysis

Data was tabulated using Excel software (Microsoft Corp. Redmond, U.S.A). Statistical analysis was done with SPSS version 26.0. Results are presented as tables and charts. Continuous variables are expressed as mean ± SD if normally distributed or as medians if their distributions were skewed. Categorical variables are presented as proportions. A comparison of pre-treatment and post-treatment observations was performed using paired-sample Student's t-test for continuous variables and McNamara's test for categorical variables. One-way analysis of variance (ANOVA) was done to compare between 3 groups. A p-value < 0.05 was considered to indicate statistical significance.

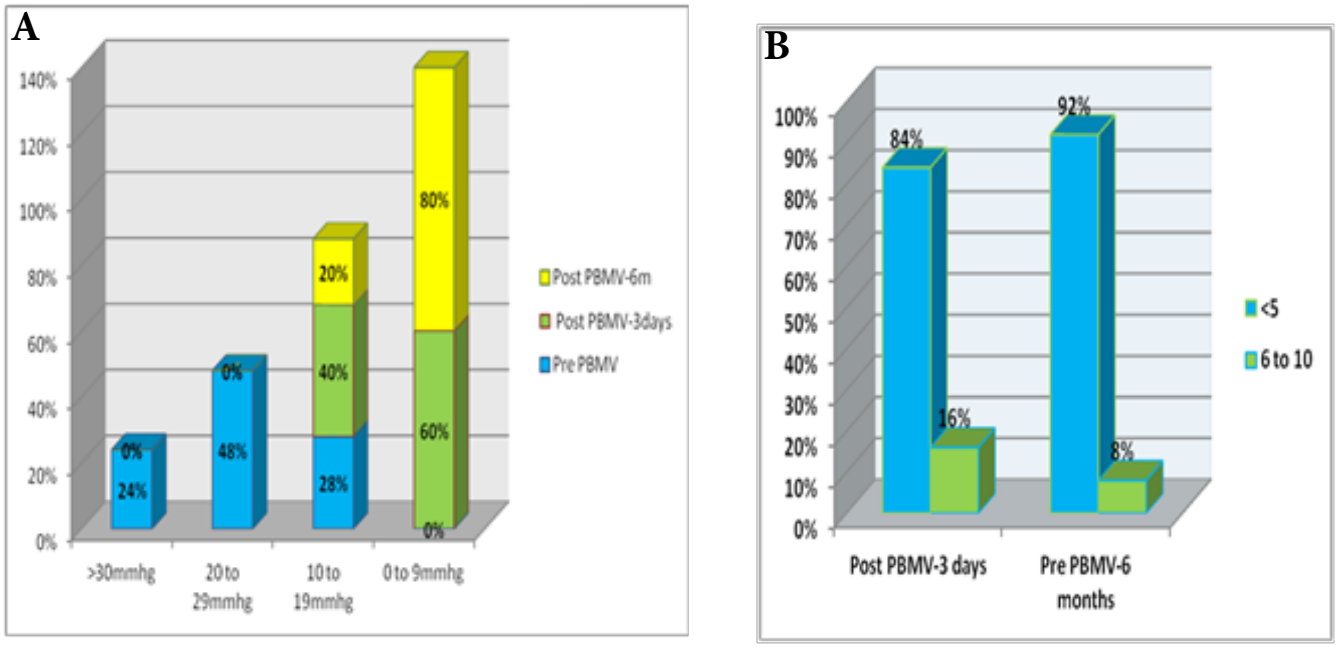
Results

A total number of 25 patients who fulfilled the inclusion criteria were enrolled. The baseline clinical and transthoracic echocardiographic parameters were analysed, as shown in (Table 1). The mean left atrial size in the population was 4.7 ± 0.4. Pre PBMV Left ventricular ejection fraction in most of the cases (n=23) is between 51-60%, and only 2 cases had LV dysfunction. The mean Wilkins score in the study population was 7.6 ± 1.03. (Table 2), Showing a comparison of ECHO parameters pre and post PBMV. There was a significant decrease in mean MVG from 13.92 ± 4.1mmHg pre-PBMV to 4.6 ± 1.04mmHg at 3 days and 4.3 ± 0.75mmHg at 6 months post-PBMV, and the p-value < <0.001 which was statistically significant. There was a significant increase in LAA Peak early diastolic (E wave) (cm/s) from 15.1 ± 1.2 pre-PBMV to 17.5 ± 1.5at 3 days and 19.0 ± 1.6 at 6 months post-PBMV, and the p-value is <0.001 statistically significant. Fig 2A Showing the dis-

Table 2: Showing a comparison of ECHO parameters pre and post PBMV.

Variable	Pre PBMV (mean±SD)	Post PBMV 3 days (mean±SD)	Post PBMV -6momths (mean±SD)	p-value
Peak MVG	23.88 ± 6.3	9.7 ± 2.2	8.4 ± 1.44	<0.001
Mean MVG	13.92 ± 4.1	4.6 ± 1.04	4.3 ± 0.75	<0.001
MVA(PHT)	0.9 ± 0.09	1.6 ± 0.12	1.72 ± 0.13	<0.001
MVA(PL)	0.9 ± 0.11	1.65 ± 0.1	1.65 ± 0.01	<0.001
PCWP	17.6 ± 4.33	6.8 ± 3.27	-	<0.001
LAA Peak early diastolic (E wave) (cm/s)	15.1 ± 1.2	17.5 ± 1.5	19.0 ± 1.6	<0.001
LAA Peak late diastolic (A wave) (cm/s)	24.2 ± 2.5	26.54 ± 2.4	28.3 ± 2.4	<0.001
Peak systolic (S wave)(cm/s)	27.4 ± 1.6	29.7 ± 1.8	31.5 ± 3.2	<0.001
"e" LAA(cm/s)	4.27 ± 0.5	5.02 ± 0.4	5.3 ± 0.3	<0.001
"a" LAA(cm/s)	6 ± 0.3	6.8 ± 0.3	6.93 ± 0.31	<0.001
"s" LAA (cm/s)	4.58 ± 0.75	5.76 ± 0.5	5.86 ± 0.5	<0.001
LAA EF(%)	52.6 ± 5.4	52.68 ± 6.4	52.8 ± 5.2	0.202

* p < 0.05: ** P < 0.01,Value are given n (%) or mean ± Standard Deviation LAA Doppler velocities, including pulse wave analysis of flow, tissue Doppler velocities, and ejection fraction, were collected pre-PBMV, 3 days post-PBMV, and 6 months post-PBMV.



* p < 0.05: ** P < 0.01,Value are given n (%) or mean ± Standard Deviation

Figure 2: Showing the distribution of distribution of peak mitral gradient in the study population. (Peak and mean gradients)

tribution of LAA Peak late diastolic (A wave) (cm/s) pre-PBMV, post-PBMV 3days, and 6 months in the study population. There was a significant increase in LAA Peak late diastolic (A wave) (cm/s) from 24.2 ± 2.5 pre-PBMV to 26.54 ± 2.4 at 3 days and 28.3 ± 2.4 at 6 months post-PBMV and the p-value <<0.001.

Fig 2B Showing the distribution of LAA Peak early diastolic (S wave) (cm/s) pre-PBMV, post-PBMV 3days, and 6 months in the study population. There was a significant decrease in peak systolic (S wave) (cm/s) from 27.4 ± 1.6 pre-PBMV to 29.7 ± 1.8 at 3 days and 31.5 ± 3.2 at 6 months post-PBMV and the p-value <0.001 Showing the distribution of distribution of LAA Peak early diastolic "e" LAA (cm/s) pre- PBMV in the study population. There was a significant increase in "e" LAA (cm/s) from 4.27 ± 0.5 pre-PBMV to 5.02 ± 0.4 at 3 days and 5.3 ± 0.3 at 6 months post-PBMV, and the p-value < <0.001 which is statistically significant. There was a significant increase in "a" LAA(cm/s) from 6 ± 0.3 pre-PBMV to 6.8 ± 0.3 at 3 days and 6.93 ± 0.31 at 6 months post-PBMV and the p<0.001(Table 3) Fig 3a Showing the distribution of LAA Peak early diastolic "s" LAA (cm/s) pre-PBMV in the study population. There was a significant decrease in "s" LAA (cm/s) from 4.58 ± 0.75 pre-PBMV to 5.76 ± 0.5 at 3 days and 5.86 ± 0.5 at 6 months post-PBMV and the P-value is <0.001. There was a significant decrease in LAA ejection fraction (%)from 52.6 ± 5.4 pre-PBMV to 61.68 ± 6.4 at 3 days and 62.8 ± 5.2 at 6 months post-PBMV, and the p-value is <0.001 as shown in Fig.3b. There was a significant difference in LAA parameters like E LAA(cm/s) A LAA(cm/s), S LAA (cm/s) with a p-value of <0.05 (Table3).

Table 3: Comparison of LAA parameters post PBMV 3 days and 6 months.

Variable	POST PBMV-3days	POST PBMV-6m	P value
Peak MVG(mmHg)	9.7 ± 2.2	8.4 ± 1.44	0.018
Mean MVG(mmHg)	4.6 ± 1.04	4.3 ± 0.75	0.249
MVA (PHT cm2)	1.6 ± 0.12	1.72 ± 0.13	0.001
MVA(PL- PHT cm2)	1.65 ± 0.1	1.65 ± 0.01	1.000
PCWP(mmHg)	6.8 ± 3.27	-	-
LAA Peak early diastolic (E wave)(cm/s)	17.5 ± 1.5	19.0 ± 1.6	<0.001
LAA Peak late diastolic (A wave)(cm/s)	26.54 ± 2.4	28.3 ± 2.4	0.013
Peak systolic (S wave) (cm/s)	29.7 ± 1.8	31.5 ± 3.2	0.019
ELAA(cm/s)	5.02 ± 0.4	5.3 ± 0.3	0.008
ALAA(cm/s)	6.8 ± 0.3	6.93 ± 0.31	0.139
SLAA (cm/s)	5.76 ± 0.5	5.86 ± 0.5	0.483
LAA ejection fraction (%)	61.68 ± 6.4	62.8 ± 5.2	0.500

* p < 0.05: ** P < 0.01,Value are given n (%) or mean ± Standard Deviation LAA Doppler velocities, including pulse wave analysis of flow, tissue Doppler velocities, and ejection fraction, were collected pre-PBMV, 3 days post-PBMV, and 6 months post-PBMV.

Discussion

In patients with Mitral stenosis, chronic stretch in LA/LAA due to pressure and volume overload causes atrial electro physiologic and electro anatomic abnormalities (22). PBMV reverses these changes in LA and LAA by an acute decrease in LA after load as evidenced by increased LAA blood flow velocities. This study demonstrates improvement in LAA function as evidenced by LAA velocities and LAA ejection fraction immediately i.e., at 3 days and after at 6-month follow-up in patients with critical mitral stenosis undergoing PBMV. Our study showed that there was a significant decrease in the LAA velocities in terms of both pulse wave Doppler velocities (E wave, A wave and S wave) and tissue Doppler velocities ("e" wave, "a" wave and "s" wave).

A study by Rajesh Vijayvergiya, et al. [23] also showed the improvement in LAA function before and after PBMV. In their study, they have enrolled forty-seven consecutive patients with symptomatic critical mitral stenosis who underwent PBMV. Thirty-eight patients were in sinus rhythm, and the remaining nine were in atrial fibrillation. All had undergone transthoracic and transesophageal echocardiography before, 24 hours and 6 months after PBMV. Pulse Doppler velocities, tissue Doppler velocities of the LAA, including peak early diastolic and LAA ejection fraction were measured. After PBMV and at 6-month follow-up, there was a significant improvement in pulse Doppler velocities of LAA (E wave, A wave, S wave) with statistically significant difference. (P

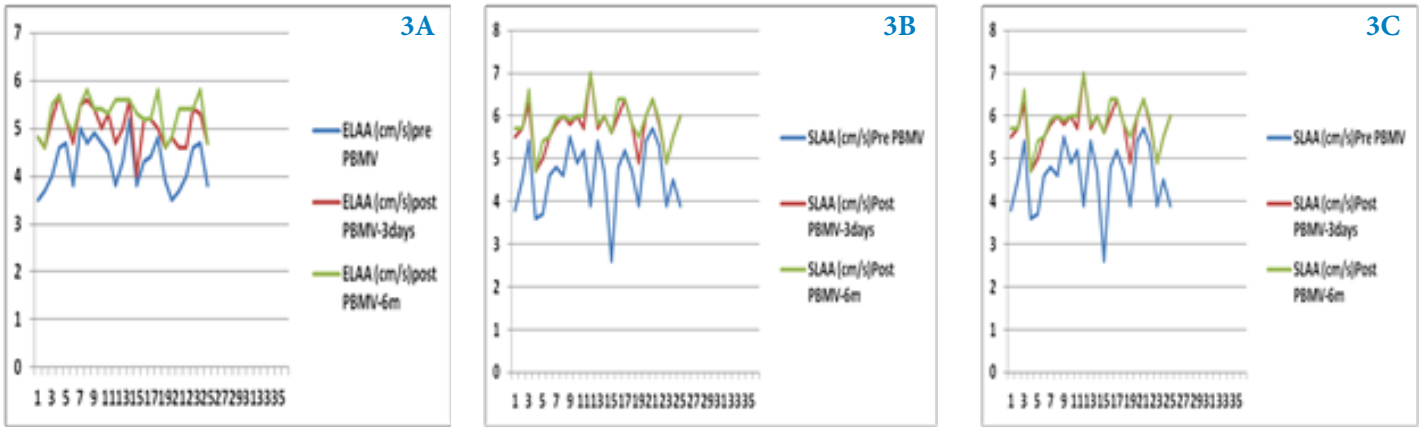


Figure 3: Showing the distribution of distribution of LAA Peak early diastolic "e" LAA (cm/s) "a" LAA(cm/s) "s" LAA (cm/s pre PBMV in the study population.
Figure 3a: Showing the distribution of distribution of LAA Peak early diastolic "e" LAA (cm/s) pre PBMV in the study population.
Figure 3b: Showing the distribution of LAA Peak early diastolic "a" LAA(cm/s) pre-PBMV in the study population.
Figure 3c: Showing the distribution of LAA Peak early diastolic "s" LAA (cm/s) pre-PBMV in the study population.

<.001). The corresponding tissue Doppler velocities of LAA also improved following PBMV. However, there was no significant increase in LAA ejection fraction (P < 0.052), which correlated with our study findings. The findings in our study also are in the same line however LAA ejection fraction also improved significantly in contrast to the above study.

The findings of our study were in correlation with a study by Ganeswara Reddy, et al. [24] who studied fifty-nine patients with symptomatic rheumatic mitral stenosis who underwent PBMV in whom LAA function was measured before and after PBMV. The parameters included in their study were LAA late emptying velocity, LAA late filling velocity and LAA area change percentage, Tissue Doppler velocities of the LAA, including peak early diastolic (eLAA), peak late diastolic (aLAA) and peak systolic (sLAA). There was a significant increase in LAA late emptying velocity, LAA late filling velocity, eLAA, aLAA, sLAA waves measured by Doppler and DTI after PBMV compared with baseline (p < 0.001) but there was no significant change in LAA area change percentage% (p>0.05). According to these findings, they concluded that PBMV improves LAA function and, thereby, may have a favourable influence on future thromboembolic complications. However, in our study post PBMV patients were followed up for 6 months and showed significant improvement in LAA function which helps in predicting the future risk of thromboembolism.

As found by many authors, we also observed significant decreases in pulmonary capillary wedge pressure (P < 0 .000) and an increase in mitral valve area (P < 0.00) after PBMV. Arora R, et al. [25] in his study on a total of 4,850 patients who underwent PBMV the mean left atrial pressure decreased from 32.1 +/- 9.8 to 13.1 +/- 6.2 mm Hg (P < 0.001). He concluded that PBMV is an effective and safe procedure with gratifying results in a high percentage of patients. The benefits are sustained in a majority of these patients on long-term follow-up. It should be considered as the treatment of choice in patients with rheumatic mitral stenosis of all age groups. Nasir, et al. [26] in his study, enrolled 56 patients with severe mitral stenosis who underwent PBMV. Underlying heart rhythm was sinus rhythm (SR) in 28 patients and atrial fibrillation (AF) in the remainder of 28 cases. LAA ejection fraction and the LAA emptying velocity were improved significantly after PBMV in both groups with SR and AF (P<0.001 for both).

As reported by Goswami, et al. LAA ejection fraction is significantly lower in those with LAA clots compared with those without clots (P < 0.01). Eryol, et al. [27] demonstrated that LAA ejection fraction is significantly lower in patients with MS with

thromboembolism compared with those without it (P = 0.01). In this study, we observed a baseline LAA ejection fraction of 52%. Relatively higher LAA ejection fraction and peak emptying velocity in our study was possibly due to the exclusion of patients with LAA clots at the time of enrolment. No significant improvement of LAA ejection fraction was observed after PBMV in the present study (P = 0.202). The percentage change in mean LAA ejection fraction also did not show significant improvement, because of the wide dispersion of the data, with many negative values and a mean near zero.

Goswami, et al. demonstrated reduced LAA velocities in patients with AF compared with those in sinus rhythm, but we did not include AF patients in our study. The exclusion of patients with LAA clots also affected the results, as most of these patients are likely to have associated paroxysmal AF and significant LAA contractile dysfunction. The additional 6-month follow-up data of significant improvements in LAA pulse and tissue Doppler velocities and LA dimensions and pressure (P < .001) suggest favourable structural remodelling at short-term follow-up after PBMV, which has not been studied to date. We did not observe any new-onset AF, thromboembolism, or LA or LAA thrombus at a 6-month follow-up in any of our patients. The reasons for the absence of local thrombus formation and systemic embolism at follow-up were multifactorial, including the exclusion of patients with LA or LAA thrombus at the time of enrolment, the lack of blood stasis after successful PBMV, relatively preserved LAA ejection fraction, and progressive improvements in LAA ejection fraction and filling and emptying velocities at follow-up.

Conclusions

The present study showed that the contractile dysfunction of the LAA in patients with critical MS, which significantly improved after PTMC and at a 6-month follow-up. Favourable 6-month improvements of LAA parameters also suggest a continuous structural remodelling of the left atrium and LAA after PBMV, which was clinically evident by the absence of thromboembolism. Thus suggesting a need for continuous long-term monitoring using TEE and management for thromboembolism even in patients with sinus rhythm. Although there was an improvement in the LAA function, it was far below the normal range, suggesting a need for continuous long-term monitoring and management of thromboembolism in these patients.

Limitations

Our study was a single centre one with a limited number of patients. We provided no normal control group and failed to provide long-term follow-up. We excluded patients with high Wilkins echocardiographic scores. Correlation between pulmonary venous peak systolic velocity and LA function and LAA ejection fraction was not addressed. Medications can also affect LAA function.

Conflict of interest

Authors declare no conflict of interest.

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