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Original Article

Acute Impact of Balloon Mitral Valvotomy on Left Atrial Functions in Mitral Stenosis

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ABSTRACT

Background: Rheumatic mitral stenosis (MS) is associated with progressive impairment of left atrial (LA) mechanical functions. This study was conducted to assess the acute impact of Balloon Mitral Valvotomy (BMV) on these functions. **Methods:** This single centre observational study included 25 patients with severe MS (aged 34.1 ± 7.1 years, with mean mitral valve area of 0.74 ± 0.13 cm²), in sinus rhythm, who underwent successful BMV at our hospital. Phasic LA volumes (V_{max}: maximal LA volume, V_{min}: minimal LA volume, and V_p: LA volume at the onset of P-wave) were measured by modified Simpson's method. Parameters of LA reservoir function i.e. LA total emptying fraction (LATEF) and LA expansion index (LAEI); conduit function i.e. LA passive emptying fraction (LAPEF); and pump function i.e. LA active emptying fraction (LAAEF) were calculated from these volumes. All these parameters were evaluated before and 24-48 hours after BMV. **Results:** Successful BMV led to significant reduction in V_{max} ($p < 0.001$), V_{min} ($p < 0.001$), and V_p ($p < 0.001$). There was a significant increase in LATEF ($p= 0.001$) and LAEI ($p= 0.002$). LAPEF increased insignificantly ($p= 0.057$), while there was no significant change in LAAEF ($p =0.127$) after BMV. **Conclusion:** Successful BMV leads to early improvement in left atrial reservoir and conduit functions, without significantly affecting left atrial pump function. Whether these acute changes translate into long term left atrial reverse remodelling and clinical benefits thereof needs to be established by further studies.

Key words: Rheumatic Heart Disease, Mitral Stenosis, Left Atrial Volume, Left Atrial Functions, Balloon Mitral Valvotomy.

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INTRODUCTION

Atrial function, in a close interdependence with left ventricular (LV) function, plays a pivotal role in maintaining optimal cardiac output. The left atrium (LA) modulates LV filling through its reservoir, conduit, and booster pump function.[1] LA acts as a reservoir, receiving pulmonary venous return during LV systole; as a conduit, passively transferring blood to the LV during early diastole and diastasis; and as a pump, actively priming the LV in late diastole. Rheumatic mitral stenosis is associated with LA structural remodeling and increased LA afterload, which lead to significant impairment of left atrial mechanical functions.[2,3] Balloon Mitral Valvotomy (BMV) is presently the preferred treatment for patients with severe mitral stenosis and suitable valve morphology. The hemodynamic and clinical benefits of BMV have been firmly established by many short term and long term studies.[4-7] However, there are very few studies reported in literature which have assessed the impact of BMV on left atrial mechanical functions.[8,9] The present study was conducted to evaluate the acute impact of successful BMV on phasic left atrial volumes and left atrial mechanical functions in patients with severe mitral stenosis and normal sinus rhythm.

Patients and Methods

This hospital based prospective, non-randomized, observational study included 25 patients of symptomatic severe mitral stenosis [defined as NYHA functional class II-IV, mitral valve area (MVA) of ≤ 1 cm² by planimetry, pressure half time (PHT) ≥ 220 msec and/or mean diastolic gradient (MDG) of ≥ 10mm Hg],[10-12] in normal sinus rhythm, with suitable valve morphology (defined as Wilkins's score ≤ 8, no or mild mitral regurgitation, and no commissural calcification or LA thrombus)[13,14] who underwent a successful BMV (defined as post-procedural MVA of ≥ 1.5cm² or ≥ 50% increase from pre-procedural MVA, and no more than moderate mitral regurgitation after the procedure) at our hospital.[15,16] Exclusion criteria included: *i.*Documented history or peri-procedural` occurrence of AF or any other sustained arrhythmia. *ii.* Significant involvement of other valves (aortic valve, pulmonary valve, tricuspid valve) on echocardiography. *iii.* Known history or clinical evidence of coronary artery disease, primary cardiomyopathy, left ventricular (LV) dysfunction, conduction abnormalities, pericarditis, thyroid dysfunction, anemia, renalfailure (serum creatinine of > 1.5mg/dl), pulmonary disease, hypertensive cardiovascular disease, or systemic inflammatory disease. *iv.* Past history of any mitral valve intervention (BMV, closed mitral valvotomy, open mitral valvotomy) or other cardiac surgeries.

Consent process, patient evaluation and data collection

After explaining the study in detail, an informed consent was taken from each patient. The study protocol was cleared by the Institutional Ethics Committee.

Baseline evaluation including clinical history, physical examination, complete blood count, serum biochemistry, coagulation profile, serum electrolytes, electrocardiogram (ECG), chest X-ray was performed before the procedure. A comprehensive echocardiographic examination (as mentioned in detail below) was done before, immediately after, and 24-48 hours after the procedure. BMV was performed using a standard trans-septal approach with an Inoue balloon.

Echocardiography

Pre-procedural echocardiographic examination of each patient was carried out on the morning of the day of procedure, using a commercially available echocardiography machine equipped with 2.5 and 3.5 MHz transducers (Aloka, Prosound, SSD α-110, South Korea), by an experienced cardiologist who was blinded to the clinical details of the patient. Examination was performed in the left lateral position, and included precordial two dimensional, M-mode and Doppler imaging according to the American Society of Echocardiography guidelines.[17,18] During the examination, one-lead ECG was recorded continuously. For the measurement of each parameter, an average of three consecutive cycles was analyzed. Left ventricular end-systolic and end-diastolic diameters

(LVIDS and LVIDD), left atrial (LA) end-systolic diameter were measured by M-mode imaging in the parasternal long axis view. LV end-systolic volume (LVESV), LV end-diastolic volume (LVEDV) and ejection fraction (LVEF) were estimated by Simpson's rule in the apical 4-chamber view. The severity of mitral stenosis was quantified by estimation of mitral valve area by 2D planimetry (MVA-2D) in parasternal short axis view and by the pressure half time method (MVA-PHT) in the apical 4-chamber view using continuous wave (CW) Doppler.[11,12] Peak and mean transmitral diastolic pressure gradients (PDG and MDG) were measured by continuous wave Doppler in the apical four chamber view. Mitral valve morphology and the sub-valvular apparatus were assessed by 2D imaging, and Wilkins's score was calculated.[13,14] Pulmonary artery systolic pressure (PASP) was calculated by adding the estimated right atrial pressure to {(tricuspid regurgitation velocity)^2 × 4},measured by continuous wave Doppler in the apical four chamber view.[19] Color flow Doppler imaging was used to detect and quantify the severity of mitral regurgitation.[20]

The left atrial phasic volumes were calculated by the modified Simpson's method from the apical four chamber view at the onset of P-wave on the ECG [pre-atrial contraction volume, V_p (Figure 1)], just before the mitral valve opening [maximal volume, V_{max} (Figure 2)] and at the mitral valve closure [minimal volume, V_{min} (Figure 3)].[21-23] These values were corrected for the body surface area (BSA). For the assessment of LA mechanical functions, the following indices calculated from the volumes were used.[24-27]

- LA total emptying volume (LATEV) = V_{max} - V_{min}
- LA total emptying fraction (LATEF) = LATEV / V_{max} x 100
- LA expansion index (LAEI) = (V_{max}-V_{min})/V_{min} x 100
- LA active emptying fraction (LAAEF) = (V_p-V_{min})/V_p x 100
- LA passive emptying fraction (LAPEF) = (V_{max}-V_p)/V_{max} x 100

LATEF and LAEI were used to assess *LA reservoir function*; LAPEF was used to evaluate *LA conduit function*; and LAAEF was used to assess *LA pump function*.[2,28]

Immediately after the BMV procedure a repeat echocardiogram was performed to define the success of procedure as mentioned previously.[15,16-29] All patients, in whom BMV was successful, underwent a repeat echocardiographic evaluation 24-48 hours after the procedure for the measurement of post-procedural parameters.

Statistical analysis

Statistical analysis was performed by SPSS software package (version 20.0, SPSS Inc, Chicago, Illinois, USA). All continuous variables were expressed as mean ± SD, and categorical variables were reported as frequency and percentages. Pearson's correlation coefficients were used to assess the strength of relationship between continuous variables. Paired *t*-test was used to study the difference of means of various continuous variables. Statistical significance was defined as a p- value of < 0.05.

RESULTS

The study population consisted of 25 patients who met all the inclusion criteria.

Patient characteristics

Mean age of the patients was 34.1years, ranging from 21 to 45 years. Among the 25 patients included in the study, 7 (28%) were male while 18 (72%) patients were female.

Pre-BMV echocardiographic parameters

Routine parameters

Pre-procedural parameters of the patients were as follows: LA diameter- 4.82 ± 0.51 cm; LVIDD- 4.39 ± 0.34 cm; LVIDS- 2.73 ± 0.36 cm; LVEDV- 60.99 ± 10.79 ml/m^2; LVESV- 19.37 ± 5.77 ml/m^2; LVEF- 68.52 ± 5.48%; Wilkins score- 6.04 ± 1.27; MVA-2D- 0.74 ± 0.13 cm^2; MVA-PHT- 0.79 ± 0.14 cm^2; PDG- 27.76 ± 6.25 mmHg; MDG- 15.60 ± 4.23 mmHg; and PASP- 58.68 ± 13.14 mmHg.

Phasic LA volumes and LA mechanical functions

Baseline phasic LA volumes were: V_{max}- 79.00 ± 12.30 ml/m^2; V_{min}- 53.50 ± 10.37 ml/m^2; and V_p- 65.54 ± 11.45 ml/m^2. LA total emptying volume (LATEV) was 25.50 ± 5.29 ml/m^2; LA total emptying fraction (LATEF) was 32.43 ± 5.69%; LA expansion index (LAEI) was 49.11 ± 13.54%; LA active and passive emptying fractions (LAAEF and LAPEF) were 18.46 ± 4.28%; and 17.16 ± 5.26% respectively.

Correlation between LA volumes and LA mechanical functions

Pearson correlation analysis of LA volumes and functions is described in Tables 1 and 2. V_{max}, V_{min} and V_p showed a positive correlation with age, LA diameter, LVEF, Wilkins score, PDG, MDG and PASP. V_{max} was negatively correlated with LVIDD, LVIDS, LVESV and MVA. V_{min} showed a negative correlation with LVIDS and MVA. V_p was negatively correlated with LVIDS, LVESV and MVA. LATEF, LAEI and LAPEF were negatively correlated with V_{min} and V_p. LAAEF did not show any significant correlation with other parameters.

Impact of BMV on phasic LA volumes and LA mechanical functions

As described in Table 3, in the acute post-BMV phase there were significant reductions in V_{max}, V_{min}, and V_p; while there were significant increments in LATEF and LAEI. There was a statistically insignificant increase in LAPEF, while there was no significant change in LATEV and LAAEF.

DISCUSSION

The present study showed that in patients with severe MS and normal sinus rhythm, successful BMV led to immediate reduction in phasic LA volumes (V_{max}, V_{min}, and V_p). There was significant improvement in indices of LA reservoir function (LATEF and LAEI), while there was a trend towards improvement in LA conduit function (LAPEF). LA pump function (measured by LAAEF) did not improve significantly in the acute phase.

The pathophysiology of LA mechanical dysfunction in rheumatic MS is multifaceted. The combination of mitral valve disease and atrial inflammation, secondary to rheumatic carditis leads to left atrial (LA) dilation, myocyte necrosis, interstitial fibrosis and disorganization of atrial muscle bundles.[30] Consequent to these changes (structural remodeling), the atrial myocytes lose their normal contraction and relaxation functions.[31] Hemodynamically, narrowing of mitral orifice poses increased resistance to LA emptying i.e. increased LA afterload. The combination of these structural and hemodynamic changes leads to progressive impairment of LA mechanical functions, which has an adverse impact on the long term prognosis of these patients.[32] Triposkiadis *et al*. demonstrated that LA volumes in MS patients were significantly larger, while LA emptying fractions (both active and passive) were substantially reduced compared to normal patients.[2] Kono *et al*. suggested that intrinsic LA dysfunction is present even in early stages of mitral stenosis, when LA pressure is only slightly elevated.[33] Inaba *et al*. revealed that follow-up study is needed to determine whether LA dysfunction is a predictor for the development of cardiovascular events (e.g. stroke, thromboembolism, atrial arrhythmias).[32] We found that phasic LA volumes showed a significant correlation with age; severity of mitral stenosis; trans-mitral gradients; pulmonary artery pressure; LV dimensions, volumes and ejection fraction. This suggests that LA remodeling in mitral stenosis progresses with increasing age, progression of disease and worsening hemodynamics.

The impact of BMV on LA mechanical functions in MS patients has not been extensively studied so far. Few studies that have been conducted in

Table 1: Pearson Correlation Analysis of Phasic LA Volumes

Parameter	V_{max}		V_{min}		V_p	
	r	p	r	p	r	p
Age	**0.549**	**0.004**	**0.473**	**0.017**	**0.515**	**0.008**
LA diameter	0.774	**<0.001**	0.680	**<0.001**	0.662	**<0.001**
LVIDD	-0.436	**0.029**	-0.298	0.148	-0.386	0.057
LVIDS	-0.501	**0.011**	-0.412	0.041	-0.483	**0.015**
LVEDV	-0.258	0.213	-0.153	0.467	-0.225	0.279
LVESV	-0.403	**0.046**	-0.335	0.102	-0.403	**0.046**
LVEF	0.452	**0.023**	0.448	**0.025**	0.489	0.013
Wilkins score	0.517	**0.008**	0.428	**0.033**	0.479	**0.015**
MVA-2D	-0.603	**0.001**	-0.667	<0.001	-0.612	0.001
MVA-PHT	-0.646	**<0.001**	-0.609	0.001	-0.596	**0.002**
PDG	0.673	**<0.001**	0.686	<0.001	0.644	**0.001**
MDG	0.708	**<0.001**	0.725	<0.001	0.677	<0.001
PASP	0.682	**<0.001**	0.631	0.001	0.627	0.001

Note: r = correlation coefficient, p = p- value. LA: Left atrium, LVIDD: Left ventricular diastolic diameter, LVIDS: Left ventricular systolic diameter, LVEDV: Left ventricular end diastolic volume, LVESV: Left ventricular end systolic volume, LVEF: Left ventricular ejection fraction, MVA-2D: Mitral valve area-planimetry, MVA-PHT: Mitral valve area- Pressure half time, PDG: Peak diastolic gradient, MDG: Mean diastolic gradient, PASP: Pulmonary artery systolic pressure.

Table 2: Pearson Correlation Analysis of LA Functions

Parameter	LATEF		LAEI		LAAEF		LAPEF	
	r	p	r	p	r	p	r	p
Age	-0.056	0.792	-0.042	0.841	0.027	0.898	-0.094	0.655
LA diameter	-0.083	0.694	-0.084	0.689	-0.223	0.285	0.079	0.709
LVIDD	-0.141	0.502	-0.152	0.468	-0.215	0.302	-0.009	0.967
LVIDS	-0.007	0.974	-0.001	0.997	-0.136	0.517	0.103	0.624
LVEDV	-0.128	0.543	-0.135	0.521	-0.197	0.346	-0.005	0.982
LVESV	0.012	0.956	0.019	0.929	-0.143	0.495	0.133	0.526
LVEF	-0.170	0.417	-0.194	0.354	0.030	0.887	-0.250	0.228
Wilkins score	0.000	0.999	0.047	0.824	0.091	0.664	-0.063	0.766
MVA-2D	0.369	0.070	0.346	0.090	0.355	0.081	0.190	0.362
MVA-PHT	0.166	0.429	0.156	0.457	0.186	0.373	0.062	0.768
PDG	-0.289	0.161	-0.288	0.163	-0.325	0.113	-0.113	0.591
MDG	-0.310	0.132	-0.309	0.132	-0.352	0.084	-0.120	0.566
PASP	-0.143	0.496	-0.145	0.489	-0.167	0.426	-0.050	0.814
V_{max}	-0.198	0.342	-0.184	0.379	-0.112	0.595	-0.158	0.452
V_{min}	-0.593	**0.002**	-0.578	**0.003**	-0.386	0.057	-0.457	**0.021**
V_p	-0.455	**0.022**	-0.437	**0.029**	-0.131	0.533	-0.482	**0.015**

Note: r = correlation coefficient, p = p- value. LA: Left atrium, LATEF: LA total emptying fraction, LAEI: LA expansion index, LAAEF: LA active emptying fraction, LAPEF: LA passive emptying fraction, LVIDD: Left ventricular diastolic diameter, LVIDS: Left ventricular systolic diameter, LVEDV: Left ventricular end diastolic volume, LVESV: Left ventricular end systolic volume, LVEF: Left ventricular ejection fraction, MVA-2D: Mitral valve area-planimetry, MVA-PHT: Mitral valve area- Pressure half time, PDG: Peak diastolic gradient, MDG: Mean diastolic gradient, PASP: Pulmonary artery systolic pressure.

Table 3: Acute Impact of BMV on LA Volumes and Functions

Parameter	Pre-BMV (mean ± SD)	Post-BMV (mean ± SD)	Difference (mean)	p-value
V_{max} (ml/m²)	79.00 ± 12.30	67.95 ± 14.93	11.05	**< 0.001**
V_{min} (ml/m²)	53.50 ± 10.37	43.30 ± 11.44	10.21	**< 0.001**
V_p (ml/m²)	65.54 ± 11.45	54.36 ± 12.03	11.18	**< 0.001**
LATEV (ml/m²)	25.50 ± 5.29	24.66 ± 5.84	0.84	0.440
LATEF (%)	32.43 ± 5.69	36.63 ± 6.34	-4.20	**0.001**
LAEI (%)	49.11 ± 13.54	59.46 ± 17.35	-10.36	**0.002**
LAAEF (%)	18.46 ± 4.28	20.76 ± 7.60	-2.30	0.127
LAPEF (%)	17.16 ± 5.26	19.84 ± 5.58	-2.68	0.057

Note: BMV: Balloon Mitral Valvotomy; Vmax: Maximal left atrial volume, Vmin: Minimal left atrial volume, Vp: Left atrial volume at the onset of p-wave, LATEV: Left atrial total emptying volume, LATEF: Left atrial total emptying fraction, LAEI: Left atrial expansion index, LAAEF: Left atrial active emptying fraction, LAPEF: Left atrial passive emptying fraction.

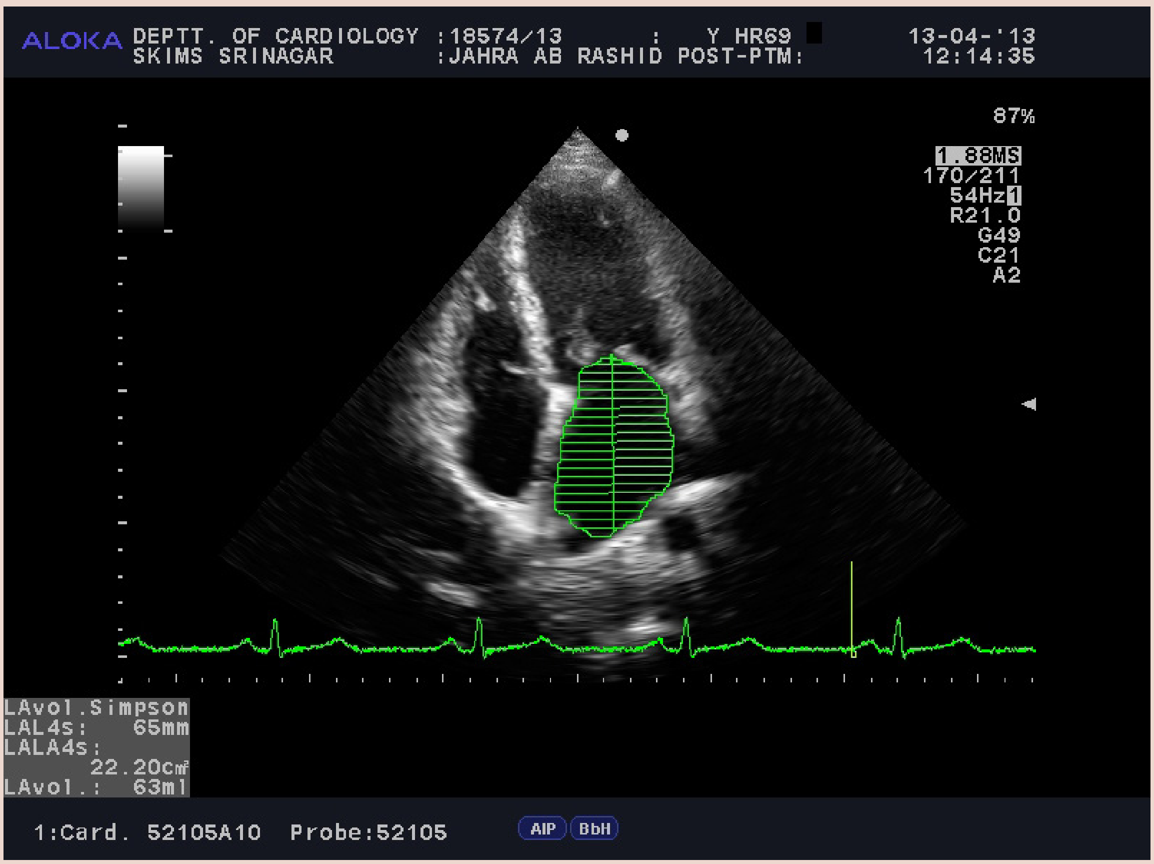

Figure 1: Measurement of LA volume at the onset of p-wave (V_p) by modified Simpson's method in apical 4-chamber view.

this regard have demonstrated conflicting results. Stefanadis *et al.* found that successful percutaneous balloon mitral valvuloplasty led to significant increase in LA pump function in patients with sinus rhythm, a significant increase in LA reservoir function in patients with atrial fibrillation and a significant reduction in LA stiffness in all patients.[34] Bitigen *et al* demonstrated that phasic LA volumes and total emptying volume decrease while conduit volume increases after BMV.[8] Vieira *et al* showed a significant reduction in LA volumes and LAEF 72 hours and 1 year after the procedure.[9] It must be stressed that the parameters used to assess the left atrial functions were different in each of these studies with no established standards used to define various components of LA function. After thorough research of the available literature we carefully selected only those parameters which are well substantiated by quality evidence as reliable measures of LA function in many diseases other than rheumatic mitral stenosis.[21-28] We observed significant decrements in V_{max}, V_{min} and V_p in the immediate post-BMV period. Also, LAEF and LAEI

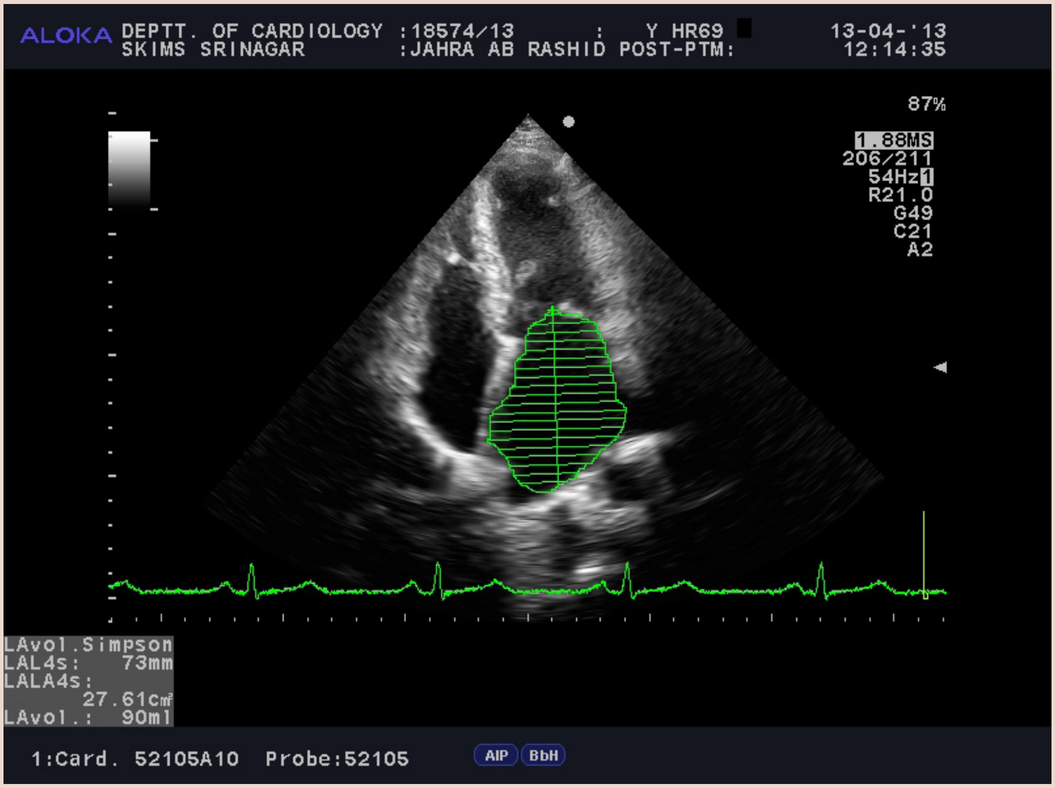

Figure 2: Measurement of maximal LA volume (V_{max}) by modified Simpson's method in apical 4-chamber view.

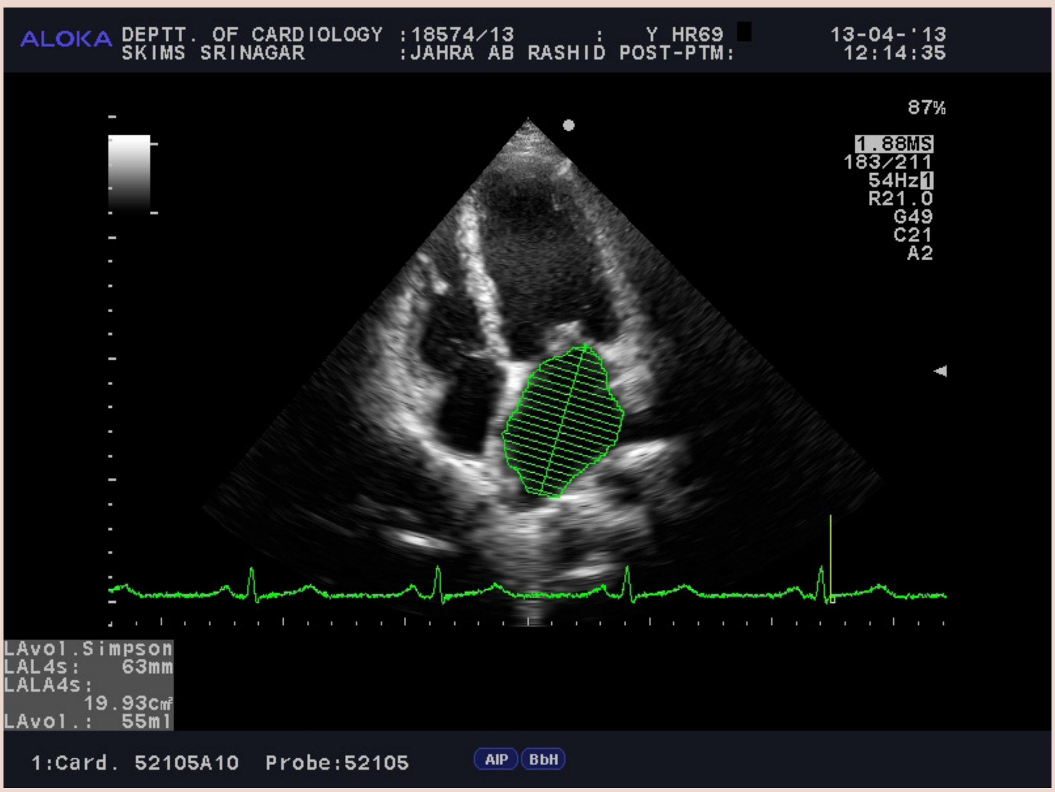

Figure 3: Measurement of minimal LA volume (V_{min}) by modified Simpson's method in apical 4-chamber view.

increased significantly after the procedure. Although LAPEF increased after BMV, this change did not achieve statistical significance (p= 0.057). There was no significant improvement in LAAEF early after BMV. Our findings suggest an early improvement in LA reservoir and conduit functions but no significant improvement in pump function after successful BMV. The mechanisms of modulation of LA functions following BMV have not been well elucidated. The major acute hemodynamic impact of BMV on the LA is a decrease in the mitral valve afterload, as reflected by an increase in the mitral valve area, a decrease in the peak and mean trans-mitral diastolic pressure gradients and a decrease in pulmonary artery systolic pressure. These changes are followed by decrease in LA volumes and increase in LAEF, which might reflect a tight relationship among pressure, volume and function.[9] The rapid recovery of LA reservoir and conduit functions following BMV suggests that these functions are predominantly dependent on LA volumes and afterload. The failure of immediate improvement in LA pump function after BMV could be attributed to the lack of acute changes in LA structure, including fibrosis of atrial wall, disorganization of atrial muscle bundles and intrinsic contractile dysfunction of atrial myocytes.[35] The prospects of long term reverse LA structural remodeling following BMV and possible further improvement in these functions remains unanswered as of now. Long term prospective studies are required to evaluate whether these changes translate into clinical benefits like reduced incidence of atrial fibrillation and risk of systemic thromboembolism.

LIMITATIONS

The main limitations of our study were as follows:

This study was carried out at a single centre and the study sample was relatively small. The limited sample size was mainly due to the strict inclusion criteria adopted for this study to avoid the confounding effect of other variables on the results of this study.

We only studied the immediate impact of successful BMV on LA mechanical functions. Long term effects and clinical implications thereof were not evaluated in this study.

The parameters used to assess LA mechanical functions were not entirely independent. Real time 3D echocardiography and strain rate imaging may be superior for assessing LA functions.

Manual tracking of LA wall for measuring LA volumes is prone to inter and intra-observer variability. These may reduce the reproducibility of these measurements.

CONCLUSION

Successful BMV leads to early improvement in left atrial reservoir and conduit functions, without significantly affecting left atrial pump function in patients with severe mitral stenosis and normal sinus rhythm. Potential long term reverse LA structural remodeling, possible further recovery of these functions following BMV and the clinical implications thereof need to be studied further.

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SOURCE OF SUPPORT

Nil

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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