INTRODUCTION

Two-thirds of the world's populations live in developing countries where a high prevalence rheumatic heart disease exists. Up to 30 million school children and young adults have chronic rheumatic heart disease worldwide, and nearly a third or more of these have mitral stenosis which has been regarded almost synonymous to rheumatic heart disease, as rheumatic heart disease is the etiology of mitral stenosis in most of the patients [1-5].

The importance of restoration of left atrial function arises from the fact that normal left atrial function is pivotal for maintaining optimal overall cardiac function as it plays different roles throughout the cardiac cycle. Left atrial function is responsible for 30% of left ventricular filling and cardiac output; it boosts pumping during late ventricular diastole augmenting therefore left ventricular filling. During ventricular systole and isovolumic relaxation, it functions as a reservoir adapting inflow volume from pulmonary veins then acts as a passive conduit during early ventricular diastole and diastasis, thus to say normal function of the left atrium is a requirement for optimal overall cardiac function[6, 7].

Recent reports have consistently showed that left atrial size and volume are strong predictors for major adverse clinical outcomes in various cardiovascular diseases. Moreover,

functional assessment of Left Atrium has been emerging as a marker of cardiovascular outcomes[6].

Balloon Mitral Valvuloplasty is considered the treatment of choice for patients with hemodynamically significant Mitral Stenosis[8], yet the immediate results on left atrial pressure overload relief is not fully detected by conventional 2D & Doppler studies.

Speckle-tracking echocardiography (STE) allows direct and angle-independent analysis of myocardial deformation, thus providing sensitive and reproducible indices of myocardial fiber dysfunction that overcome most of the limitations of Doppler-derived strain measures. Two dimensional strain and strain rate imaging have been developed for the quantitative assessment of global and regional myocardial function. This technique is based on gray-scale images that are analyzed by the dedicated software system. Two dimensional strain imaging has been frequently used to investigate left ventricular function, with fewer studies on global and segmental left atrial function, although the left atrial speckle tracking imaging has been found to be a feasible and reproducible method of left atrial functional assessment [9-12].

The quantification of change in left atrial function secondary to balloon mitral valvuloplasty in patients with mitral stenosis hasn't been extensively studied and we aim to present an insight on the restoration of left atrial function following balloon mitral valvuloplasty with the use of Speckle-Tracking Echocardiography[13].

Aim of the Work

The aim of the present study is to measure the improvement of left atrial reservoir function, in patients with symptomatic moderate to severe mitral stenosis, after undergoing percutaneous balloon mitral valvuloplasty using speckle tracking imaging by comparing peak atrial longitudinal strain and peak systolic strain rate before and after the procedure, in correlation with standard echocardiographic and invasive hemodynamics parameters of success of percutaneous balloon mitral valvuloplasty, as well as volumetric parameters of left atrium.

Chapter 1
INTERPLAY OF RHEUMATIC MITRAL STENOSIS AND LEFT ATRIUM

Pathology and pathophysiology of rheumatic mitral stenosis

In rheumatic heart disease (RHD), all four valves may become damaged, nevertheless the mitral valve (MV) is virtually always affected, but the reasons for this propensity are unclear. Perhaps greater mechanical stress on the MV causes the inflammatory process to be manifested more severely there than on other valves[14]. About 25% of all patients with RHD have isolated mitral stenosis (MS), and about 40% have combined MS and mitral regurgitation (MR). Multivalvular involvement is seen in 38% of MS patients, with the aortic valve affected in about 35% and the tricuspid valve in about 6%[15].

With acute rheumatic fever, there is inflammation and edema of the leaflets, with small fibrin-platelet thrombi along the leaflet contact zones. Subsequent scarring leads to obliteration of the normal leaflet architecture and the characteristic rheumatic mitral valve deformity including leaflet thickening by fibrous tissue and/or calcific deposits, fusion of the commissures, and chordal shortening and fusion[15].

In earlier stages of the disease, the relatively flexible leaflets open in diastole into a curved shape because of

restriction of motion at the leaflet tips. This diastolic doming is most evident in the motion of the anterior leaflet and is less prominent as the leaflets become more fibrotic and calcified.

The symmetrical commissural fusion results in a small central oval orifice in diastole that on pathologic specimens is shaped like a fish mouth or buttonhole because the anterior leaflet is not in the physiological open position. Superimposed calcification immobilizes leaflets and narrows the orifice further. With end stage disease, the thickened leaflets may be so adherent that they cannot open or shut, leading to combined MS and MR[15].

Normally, the LA has 3 phasic functions as it acts as a reservoir, conduit and pump booster during ventricular systole, early ventricular diastole and late diastole, respectively[15].

In mitral stenosis, LA volume during diastole increases progressively because of the tight MV which leads to a decreased LA contractility as the wall stress is beyond the physiological limits of Frank-Starling mechanism. Compensatory LA pressure elevation leads to stretching of LA wall; resulting in LA stiffness and dilatation. This leads to an impairment in both reservoir and conduit function. The changes in LA reservoir function in patients with MS may be due to disorganization of the atrial muscle bundles and atrial fibrosis[16].

The passive filling of LV during early diastole gets impaired in MS due to the compensatory increase in heart rate to overcome the obstacle to LV, which in turn decreases the duration of early ventricular diastole[17].

An increase in LA pump function usually appears as a compensatory mechanism to the decrease in LA reservoir and conduit function, as it occurs with aging[18]. Though, Stefanidis et al found that LA active emptying in patients with MS decreased due to LA fibrosis and obstruction to blood flow during active emptying[19]. Inci et al has shown no improvement in LA pump booster function till 1 year of follow-up after percutaneous balloon mitral valvuloplasty (BMV)[20].

The combination of mitral valve disease and atrial inflammation secondary to rheumatic carditis causes LA dilatation and fibrosis and disorganization of the atrial muscle bundles leading to disparate conduction velocities and inhomogeneous refractory periods and thereby precipitation of atrial fibrillation (AF) that is often episodic at first but then becomes more persistent. AF causes diffuse atrophy of atrial muscle, further atrial enlargement, and further non-homogenous refractoriness and conduction. These changes, in turn, lead to irreversible AF[15].

Though MS has shown to affect all three phasic functions of LA, only reservoir function appears to improve after BMV, both early and on the 1 year follow-up intervals[13, 20, 21].

Echocardiographic assessment in rheumatic mitral stenosis

In the contemporary era, adequate assessment of MS and associated lesions can be obtained in the vast majority of patients by transthoracic echocardiography (TTE). It is the most accurate approach to the diagnosis and is used also for quantification of hemodynamic severity by measuring mean pressure gradient (MPG), mitral valve area (MVA), and pulmonary artery pressure (PAP) or right ventricular systolic pressure (RVSP) [15, 22].

Transesophageal echocardiography (TEE) is recommended when transthoracic images are suboptimal. It is also indicated for exclusion of left atrial thrombus and evaluation of MR severity when balloon mitral valvuloplasty (BMV) is considered[22]. However, in few patients with non-diagnostic noninvasive studies or discrepant clinical and echocardiographic findings, it is essential to further characterize MS hemodynamics with catheterization as the next best approach.

Transthoracic echocardiography is recommended for all patients with MS at initial presentation, for reevaluation of changing symptoms or signs, and at regular intervals (according to disease severity) for monitoring disease progression[22].

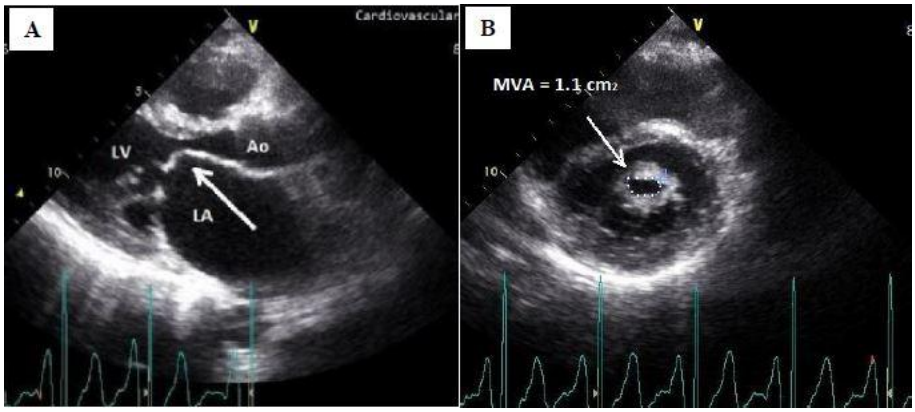

Figure (1): 2D echocardiography in a patient with rheumatic mitral valve stenosis
A: PLAX view showing doming of anterior mitral valve leaflet
B: PSAX view showing narrowing of mitral orifice (MVA = 1.1 cm^2)

Mitral valve area is the most chief echocardiographic parameter, measured using direct planimetry from two-dimensional short axis images and calculated by the Doppler pressure half-time (PHT) method. Mean diastolic pressure gradient calculation using Doppler velocities is useful in assessment of severity, particularly in patients in sinus rhythm[(22)].

Assessment of MV morphology and scoring is important for choosing the management strategy by providing an overall impression whether the valve is favorable or unfavorable for BMV and predicting its hemodynamic results and outcome.

Anatomical features of rheumatic MV that can be evaluated include: leaflet thickening, restriction of opening, diastolic leaflet doming, commissural fusion, chordal thickening, fusion, and shortening, and calcification of the

valve apparatus[23]. Left atrial size, associated MR, concomitant valvular lesions, PAP, left ventricle (LV) size and systolic function, and right ventricle (RV) size and systolic function are also valuable echocardiographic measures.

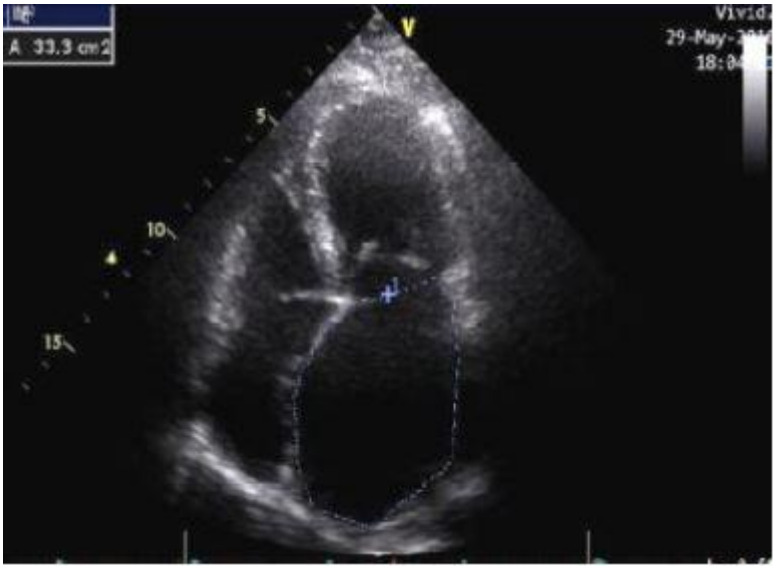

Figure (2): Left atrial enlargement in MS. Transthoracic echocardiography, apical 4-chamber view (A4C).

Aiming at better patient selection for therapeutic options, different approaches have been developed to combine the different anatomical features of MS. The most widely used scoring system is the Wilkins score, which combines mobility, thickness, calcification, with subvalvular apparatus scarring in 16-points scale. The total score is the sum of the four items and ranges between 4 and 16[23].

Another approach is the Cromier score which relies on a global assessment of MV anatomy[24]. So that three groups are classified according to the best surgical alternative.

Table (1): Wilkins score for assessment of mitral valve stenosis by echocardiography

Grade	Mobility	Thickening	Calcification	Subvalvular Thickening
1	Highly mobile valve with only leaflet tips restricted	Leaflets near normal in thickness (4-5 mm)	A single area of increased echo brightness	Minimal thickening just below the mitral leaflets
2	Leaflet midportions and base portions have normal mobility	Midleaflets normal, considerable thickening of margins (5-8 mm)	Scattered areas of brightness confined to leaflet margins	Thickening of chordal structures extending to one of the chordal length
3	Valve continues to move forward in diastole, mainly from the base	Thickening extending through the entire leaflet (5-8 mm)	Brightness extending into the mid portions of the leaflets	Thickening extended to distal third of the chords
4	No or minimal forward movement of the leaflets in diastole	Considerable thickening of all leaflet tissue (>8-10 mm)	Extensive brightness throughout much of the leaflet tissue	Extensive thickening and shortening of all chordal structures extending down to the papillary muscles

(From Otto CM: Valvular Heart Disease. Elsevier, Philadelphia, 2004.)

Other scoring systems have been described but are not widely used. A common limitation of scoring systems is the lack of information on the location of leaflet thickening and calcification, specifically in relation to the commissures, which may influence the results of BMV[25]. Another drawback of the current scoring systems is that the importance of subvalvular apparatus impairment is probably underestimated[26].

Table (2): Cromier score for assessment of mitral valve stenosis

Echocardiographic Group	Mitral Valve Anatomy
Group 1	Pliable noncalcified anterior mitral leaflet and mild subvalvular disease (i.e., thin chordae ≥ 10 mm long)
Group 2	Pliable noncalcified anterior mitral leaflet and severe subvalvular disease (i.e., thickened chordae < 10 mm long)
Group 3	Calcification of mitral valve of any extent, as assessed by fluoroscopy, whatever the state of subvalvular apparatus

(From Otto CM: Valvular Heart Disease. Elsevier, Philadelphia, 2004.)

Hence, a novel echocardiographic scoring system has recently been described by Rifaie et al[27] for MV assessment, depending on commissural site of calcification and the degree of subvalvular fibrosis and evaluated for predicting immediate outcome following BMV. It includes:

(a) Scoring of calcification as follows:

Calcification was identified by localized areas of bright echo reflection affecting MV leaflets, seen in parasternal short-axis view at MV level.

- The absence of calcification was given a score of 0.

- Calcification localized to leaflet margins was given a score of 2
- That extending to leaflet bodies was given a score of 4
- That involving the commissures (one or both) was given a score of 6.

(b) Scoring of subvalvular involvement as follows:

Subvalvular involvement was identified by thickening of chordae tendinae and/or papillary muscles, seen in parasternal long-axis (PLAX) and apical four chamber (A4C) views.

- The absence of subvalvular involvement was given a score of 0.
- Thickening of less than half the chordal length was given a score of 2.
- That involving half or more the chordal length was given a score of 4.
- That involving the whole chordal length and PM was given a score of 6.

Calcification score was expressed out of 6 and the score of subvalvular involvement was expressed out of 6. The total novel score is the sum of the calcification score and the score of subvalvular involvement, expressed out of 12.

Chapter 2

EVALUATION OF LEFT ATRIUM BY ECHOCARDIOGRAPHY

Left atrial dimensions

The complex LA physiology, as well as the pathological implications, has raised the need for a more extensive echocardiographic examination. The first parameter to be used for LA assessment was the LA antero-posterior (AP) diameter measured in the parasternal long axis view at LV end-systole by using either B-mode or M-mode; M-mode measurements are performed from the leading edge of the anterior LA wall to the leading edge of the posterior wall[28].

Current guidelines adopted by the American Society of Echocardiography recommend the use this parameter to describe LA enlargement as mild (41-46 mm in men or 39-42 mm in women), moderate (47-51 mm in men or 43-46 mm in women) or severe (≥52 mm in men or ≥47 mm in women) [29].

AP diameter measurement is easily obtained and does not require high-quality equipment or exceptional skills, but its accuracy is reduced; LA enlargement is predominant in the superior-inferior or medial-lateral axis, due to the fact that the LA is positioned between the aortic root and the tracheal bifurcation[30].

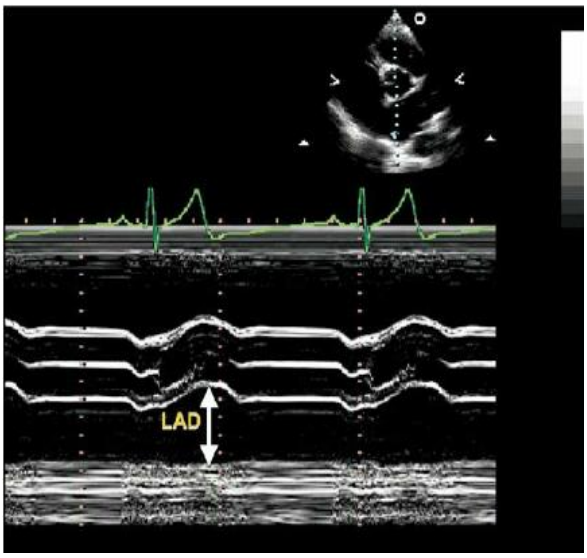

Figure (3): Left atrial diameter (LAD) measured by M-Mode in PLAX view

Despite this major impediment, data from the Framingham Heart Study suggested that an incremental enlargement by 5 mm of the LA AP diameter was associated with high risk (39%) of developing atrial fibrillation (AF) during follow-up. In addition to that, the Cardiovascular Health Study reported that the risk for developing atrial fibrillation was four times bigger in patients with a LA AP diameter >50 mm[30].

LA size assessment represents a significant predictor of morbidity and mortality in many cardiovascular conditions; it has been shown recently that indexed LA volume is a more robust cardiovascular risk marker than LA area or diameter[29].

LA size changes occur in all directions and, similarly to the left ventricle, a single dimension (i.e. LA antero-posterior diameter), despite being used for a long time and provided of a prognostic value, is not an accurate representation of actual LA size[31].

Although 2D-derived LA volumes show a systematic underestimation vs. 3D Echocardiography (3DE) and cardiac magnetic resonance imaging (CMR) they have satisfactory intra- and inter-observer variability and can be used in clinical trials[32].

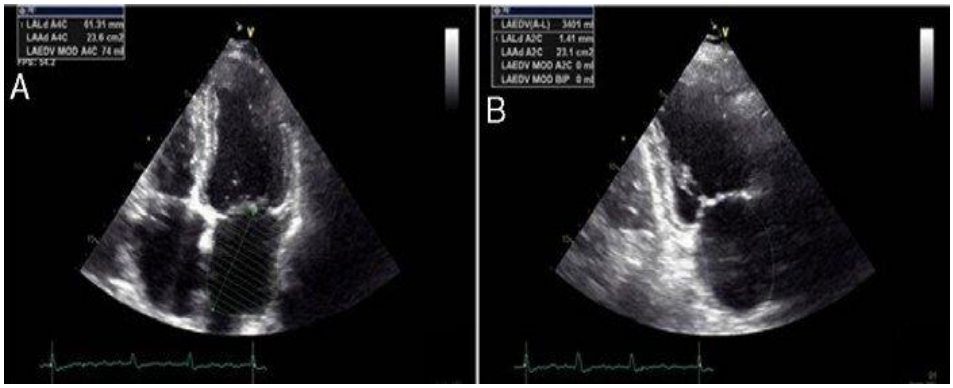

Figure (4): Assessment of left atrial volume using Simpson's method in A4C and Apical 2-chamber (A2C) views

How to increase accuracy and reproducibility of LA measurement?

Performance recommendations

While recording apical views for computing LA volume, care should be taken to maximize base and length of the LA