Original Article

Strain patterns in primary mitral regurgitation due to rheumatic heart disease and mitral valve prolapse

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1. Introduction

Rheumatic heart disease (RHD) continues to be a major public health issue in many developing countries and studies have re-ported mitral regurgitation (MR) as a common valvular lesion. Mitral valve prolapse (MVP) is a common etiology of MR in developed countries, occurring in 2% of the population in the United States. There are striking pathophysiological differences in the MR due to RHD and MVP and their natural histories are different. RHD causes MR in the early part of the disease and progression of MR is due to accumulation of inflammatory cells and cytokines promoting a progressive cycle of valvular interstitial cell activation, fibrotic leaflet remodelling and interstitial neo-vascularization leading to leaflet tip prolapse and mitral annular dilatation. There is evidence of elevated chronic inflammatory markers in RHD compared to controls suggestive of chronic low-grade persistent carditis. Although there is no chronic inflammatory carditis and left atrial pathology, an association of MVP with cardiomyopathy has been hypothesized.

Despite the pathological differences in MR due to the two conditions, it is unclear if the patterns of left ventricular (LV) and left atrial (LA) remodelling are different. As the guidelines written by professional cardiac societies for surgical decision making in severe
MR are predominantly based on studies in patients with MVP, their applicability to patients with rheumatic MR, which is a major problem in developing countries, remains unclear. This is important because in developing nations the predominant etiology of severe MR could still be rheumatic.19

Left ventricular global longitudinal strain (GLS), assessed with two-dimensional speckle-tracking echocardiography (STE), detects subtle LV systolic dysfunction in patients with MR with preserved LVEF.20 Recent work has shown that GLS appears to be a better predictor of events compared to conventional parameters like LVEF and LV dimensions. Measuring GLS preoperatively may help predict the optimal timing for surgery and also may predict postoperative outcomes in patients with severe primary MR.11 LA remodelling has been documented as an important predictor of cardiovascular events,21 independently related to stroke and death, as well as systolic and diastolic heart failure.11 Studies on LV and LA strain in MR due to RHD and studies comparing the two conditions are not available. It is also unclear if the strain parameters differ between the two conditions and whether separate thresholds are required in RHD MR for surgical decision-making. Using T1 mapping and determination of extracellular volume (ECV), patients with asymptomatic MR in MVP demonstrate a spectrum of myocardial fibrosis with reduced myocardial deformation on cardiac MRI.14 In patients with RHD compared to controls, very few patients had LGE and biochemical evaluation for serum markers of collagen turnover indicated a predominance of collagen degradation rather than increased synthesis and myocardial fibrosis.15 How these changes are reflected in values of T1 and ECV in RHD are unclear, but worth exploring, as abnormal values may help understand pathophysiology, demonstrate correlation with strain parameters and improve clinical decision-making.

Hence, we hypothesized that, due to the pathophysiological differences between RHD and MVP, the strain values in the LA and LV are different and parameters specific to MR due to RHD may have to be developed and applied in clinical decision-making in countries where the disease is prevalent.

2. Methods

2.1. Data source and study population

The study was conducted in a University-hospital over 12 months from May 2017 to April 2018. After statistical calculations, 50 patients in the age range between 18 and 75 years with chronic severe MR who attended the outpatient department in the study period were studied. Those with an LVEF <40%, MR, of Carpenter type I or IIIB, coexistent moderate or severe valvular disease, coronary artery disease (CAD) by the history of angina or ECG changes suggestive of CAD, atrial fibrillation, left ventricular hypertrophy (LVH), hypertrophic cardiomyopathy (HCM), dilated cardiomyopathy (DCM), prior open heart surgery, congenital heart disease with MR, and poor 2D or 3D Echo windows, were excluded. Controls were age and sex-matched and were selected from normal 2D TTE studies performed in our department (Fig. 1).

2.2. Echocardiographic protocol

Transthoracic echocardiography was performed with Vivid E9 echo machine (GE-VingMed, Horten, Norway) using a 3.5-MHz multiphase array probe. Chamber dimensions were measured in M Mode. The proximal isovelocity surface area (PISA), the effective regurgitant orifice area (EROA), regurgitant volume and the regurgitant fraction were calculated as per recommendations.16 Indexed LV end-diastolic volume (LVEDVi), indexed LV end-systolic volume (LVESVi) were measured from apical 4 chamber views.

2.3. Speckle tracking echocardiography and strain analysis

Offline analysis was done by Echo Pac software 2.02. Three-dimensional (3D) strain for left ventricular (LV) myocardial deformation analysis based on 3D LV data sets integrating speckle-tracking with three-dimensional echocardiography, enabled the calculation of all LV Strain components from a single apical LV 3D data set. A semi-automated epicardial tracking was performed to delineate the region of interest for strain analysis (3D STE). Three-dimensional STE was used to determine the end-systolic global longitudinal strain (GLS), global circumferential strain (GCS), global area strain (GAS) and global radial strain (GRS). Following a frame-by-frame analysis, a final 17-segment bulls-eye map of strain values was displayed. Global strain values were automatically calculated by the software and were not determined in the presence of more than three uninterpretable segments (Fig. 2).

For assessment of LA strain and strain rate, digital cineloops of two-dimensional (2D) greyscale LA images of three consecutive cardiac cycles were acquired both in the standard apical four- and two-chamber views, during breath-hold with a stable electrocardiographic recording, and were stored for offline analysis. Care was taken to obtain true apical images using standard anatomic landmarks in each view to not foreshorten the left atrium and allowing reliable delineation of the atrial endocardial border. The frame rate for greyscale imaging was 60 frames/sec with adequate spatial definition and to enhance the feasibility of the frame-to-frame tracking technique.17

2D LV strain software was used for calculating LA strain as there was no vendor-specific or dedicated software for LA strain available. In line with current11 recommendations, the LA endocardial border was manually traced using a point-and-click approach in the apical four- and two-chamber views. To trace the region of interest in the discontinuities of the LA wall, corresponding to the pulmonary veins and LA appendage, the direction of LA endocardial and epicardial surfaces at the junction with these structures was
extrapolated. Subsequently, following segmental tracking quality analysis and eventual manual adjustment of the region of interest, longitudinal strain curves were generated by the software for each atrial segment. The onset of the QRS complex was used as the reference point for the LA strain analysis. When the R wave was used, all strain values were positive, and there were two peaks, the first one corresponding to reservoir function (first peak between R wave and T wave) and the second one to the atrial contractile function (starting on the P wave); the difference between reservoir strain and atrial contractile strain values measured the conduit strain. Peak atrial longitudinal strain (PALS) and strain rate was measured at the end of the LA reservoir phase and was calculated by averaging the peak values observed in all LA segments (Fig. 3).

Thirty patients were randomly selected for the evaluation of the inter-observer variability of LV and LA STE measurements by two independent observers. For intraobserver variability, thirty random measurements were taken and were repeated one week apart.

### 2.4. Statistical analysis

The sample size for the total number of MR cases, calculated with a standard normal variate at 5% type I error, with a precision of 4% for quantitative and qualitative variables, was 48. As this is a pilot study comparing MVP MR and RHD MR, the authors believe that the number included was adequate to achieve the desired power. The maximum number of severe mitral regurgitation over
the study period was included in the study. Quantitative data are expressed as mean ± SD. Qualitative data are expressed in numbers and percentages. Student’s t-test was used for comparisons of independent samples and was used for comparisons of means and paired Student’s t-test was used for subgroup analysis. Comparisons of qualitative variables were performed using the chi-square test. Pearson’s test was used to assess correlation. Inter-observer and intra-observer variability were assessed by the intra-class correlation coefficient. All statistical tests were 2-tailed with a p-value < 0.05 considered significant. All statistical tests were carried out in IBM-SPSS 22 (SPSS Institute, Chicago, IL, USA).

3. Results

Over 12 months, after 107 patients with chronic severe MR were screened, 18 patients were excluded due to coexisting moderate and severe disease affecting the other valves, 21 due to atrial fibrillation, 12 due to LV dysfunction (EF < 60), and 6 due to poor echo window. The remaining 50 cases, 30 due to MVP (60%) and 20 due to RHD (40%) and were studied (Fig. 1). Despite the large prevalence of RHD in India, it is often not possible to find patients with truly isolated severe MR due to RHD. As isolated severe MR is less common in RHD compared to multivalvular involvement,19 and as we evaluate close to 150,000 patients annually in our outpatient department, MVP still predominated in our study.

The mean age was 45.6 ± 15.6 years, and 64% in the study group and 62% in the control group were males. 60% (n = 30) of all patients were symptomatic. Predominant symptom was dyspnea in 73% (n = 22), followed by palpitations in 70% (n = 21). Heart failure symptoms were present in 23% (n = 7) of the symptomatic patients, 22 eventually underwent mitral valve surgery (MVS). The mean LV dimensions in diastole and systole in MVP and RHD groups were 56.4 ± 5.7 mm and 41.1 ± 5.4 mm and 59.7 ± 7.9 and 39.6 ± 5.6 respectively and were matched (p = 0.0759; p = 0.3634). Mean EF by Simpson’s method in two groups were 61.3 ± 7.2 and 69.3 ± 7.4 respectively (p < 0.05). Only two patients had LV dysfunction echocardiographically, but nine had pulmonary hypertension respectively (p < 0.05). Only two patients had LV dysfunction echocardiographically, but nine had pulmonary hypertension respectively (p < 0.05). Only two patients had LV dysfunction echocardiographically, but nine had pulmonary hypertension respectively (p < 0.05). Only two patients had LV dysfunction echocardiographically, but nine had pulmonary hypertension respectively (p < 0.05). Only two patients had LV dysfunction echocardiographically, but nine had pulmonary hypertension respectively (p < 0.05). Only two patients had LV dysfunction echocardiographically, but nine had pulmonary hypertension respectively (p < 0.05). Only two patients had LV dysfunction echocardiographically, but nine had pulmonary hypertension respectively (p < 0.05). Only two patients had LV dysfunction echocardiographically, but nine had pulmonary hypertension respectively (p < 0.05). Only two patients had LV dysfunction echocardiographically, but nine had pulmonary hypertension respectively (p < 0.05).

The mean ± SD for GLS was −17.2 ± 4.4%, GRS was 35.5 ± 15.3%. GCS was −13.5 ± 5.4% and GAS was −29.8 ± 8.3% in all patients. The mean ± SD for PALS and atrial strain rate was 17.35 ± 10.3% and 19 ± 0.9 respectively. Compared to controls, all LV and LA strain parameters except GRS and GAS (p = 0.08, p = 0.216) were significantly lower (p < 0.05). There was a trend towards lower GRS among MR patients compared to controls as depicted in Table 2 (p = 0.08). Comparing LV strain parameters there was no difference between the MVP and RHD groups (mean ± SD for GLS, GRS, GCS, GAS in the MVP group were −18.25 ± 4.3%, 35.3 ± 15.3%, −13.6 ± 5.4%, −31.2 ± 8.2% respectively and in the RHD group were −16.2 ± 4.6%, 35.9 ± 15.9%, −13.4 ± 5.4%, −29.2 ± 8.7%, respectively). LA long strain and strain rate were similar in MVP and RHD subgroups (20.45 ± 11.9%, 2.24 ± 1.1 and 14.63 ± 8.85%, 1.6 ± 0.66, respectively (p = 0.08, p = 0.124, respectively) (Table 3). However, LA strain among RHD and MVP subgroups also showed a trend towards lower PALS among the RHD group compared to MVP (p = 0.08). GCS had a positive correlation systolic and diastolic LV dimensions (r = 0.9; P < 0.05, r = 0.7; p < 0.05) whereas GCS and GAS showed a positive correlation with LVIDs (r = 0.5, p < 0.05; r = 0.6, p < 0.05) (Table 4). GRS showed a negative correlation with LVIDs (r = −0.535, p < 0.05) but not with LVIDd. PALS had a negative correlation with LVID (r = −0.3, p < 0.05) (Table 4). GRS was the only LV strain parameter which showed correlation with EF whereas PALS did not show correlation with EF (Table 4).

No significant intra-observer variability was observed for STE-derived LV parameters and LA strain parameters (intraclass correlations GLS-r = 0.82, GRS-r = 0.89, PALS-r = 0.58, LA longitudinal SR-r = 0.98). Inter-observer variability was insignificant for LV and LA measurements (intraclass correlation-GLS-r = 0.88, PALS-r = 0.58, LA longitudinal SR-r = 0.96). During follow-up, 22 patients (44%) underwent mitral valve surgery. Four patients died, three of whom had refused surgery and one due to prosthetic valve dysfunction due to poor drug compliance.

4. Discussion

To the best of our knowledge, this is the first study comparing LA and LV strain of severe MR due to RHD or MVP. As expected in chronic severe MR, we demonstrated a reduction in both LV and LA strain values compared with age and sex-matched controls. However, there was no difference among LA and LV strain in patients with severe MR due to either MVP or RHD even though RHD has an element of chronic indolent or sub-acute cardiitis. Reports of decrease in regional septal myocardial deformation indices in subjects with MVP suggest the co-existence of primary cardiomyopathy. Kitkungvan and co-workers have reported that in primary MR, LV fibrosis was more prevalent in MVP than non MVP. Despite these different pathophysiological parameters cardiac chamber involvement seems to be similar. The decision about MV surgical timing is unclear in those with normal LV function like our cohort with mean EF > 60%. Commonly used parameters to decide for MVP are angle-dependent measurements. In recent years, quantification of myocardial deformation by STE has emerged as a reliable and reproducible estimate of regional and global myocardial function, beyond ejection fraction and chamber dimension.

Table 1

| Echocardiographic Parameters | MVP(n = 30) | RHD (n = 20) | P Value |
|-------------------------------|------------|-------------|---------|
| LA diameter (mm) | 46.8 ± 7.8 | 48.7 ± 9.2 | 0.4360 |
| Aortic diameter (mm) | 24.8 ± 4.2 | 31.2 ± 4.6 | <0.05 |
| LVIDd (mm) | 56.4 ± 5.7 | 59.7 ± 7.9 | 0.0759 |
| LVIDs (mm) | 41.1 ± 5.4 | 39.6 ± 5.6 | 0.3634 |
| LV EF (%) | 61.3 ± 7.2 | 69.3 ± 7.4 | <0.05 |
| E/A ratio | 1.5 ± 0.3 | 1.58 ± 0.3 | 0.4232 |
| PASP(mm Hg) | 28.4 ± 4.2 | 34.8 ± 7.2 | <0.05 |
| HR (beats/min) | 93.8 ± 21.2 | 66.2 ± 12.1 | <0.05 |
| ED Vol (ml) | 84.8 ± 22.5 | 85.5 ± 23.3 | 0.9278 |
| ES Vol (ml) | 38.5 ± 16.2 | 36.8 ± 14.4 | 0.7059 |
| ED mass (gm) | 114.1 ± 16.4 | 118.4 ± 18.2 | 0.3538 |
| ES mass (gm) | 119.1 ± 113.6 | 120.3 ± 21.8 | 0.8020 |

LA- Left atrium; LVIDd- LV internal dimension in diastole; LVIDs- LV internal dimension in systole; EF- Ejecation Fraction; E/A- Mitral peak E/A Velocity; HR- Heart rate; ED Vol- End Diastolic Volume; ES Vol- End systolic Volume. ED mass- End Diastolic Mass; ES Mass- End Systolic Mass.

Table 2

| Comparison of LV and LA strain among MR Cases and Controls. |
|-----------------|-----------------|----------------|
| Patterns | Mean | SD | Mean | SD |
| GLS (%) | −17.2 | 4.4 | −20.0 | 3.2 | p < 0.05 |
| GRS (%) | 35.5 | 15.3 | 31.6 | 5.6 | p = 0.087 |
| GCS (%) | −13.5 | 5.4 | −16.5 | 7.9 | p = 0.05 |
| GAS (%) | −29.8 | 8.3 | −32.2 | 3.7 | p = 0.216 |
| PALS (%) | 17.352 | 10.3 | 51.34 | 11.5 | p = 0.05 |
| LA Strain Rate | 1.9 | 0.5 | 1.43 | 0.44 | p = 0.05 |

GCS- Global circumferential strain; GAS- Global area strain; PALS- Peak atrial Longitudinal Strain;
GLS: Global longitudinal strain; GRS: Global radial strain; GCS: Global circumferential strain; GAS: Global area strain; PALS: Peak atrial longitudinal strain.

5.1. Limitations

Although the study by Mascle et al.29 demonstrated preoperative variations in GLS in MR correlated with preoperative variations in GLS, findings also suggest that despite the pathophysiological differences in LV and LA strain does not differ in MR due to RHD in comparison to MVP, the same strain parameters may be used in RHD MR which is commoner in India.

5. Conclusion

In patients with asymptomatic severe MR with preserved LV function, GLS has prognostic value.13,23 In the study by Mascle et al.29 preoperative variations in GLS in MR correlated with preoperative echocardiographic parameters and post-operative LV dysfunction with similar findings in the present study. Left atrial strain has been shown to correlate with LA fibrosis in previous studies. In the present study, there were no significant differences in LA reservoir strain and LA strain rate among the two subgroups. But, these studies on LV and LA strain have included patients mainly with MVP making it hard to extrapolate their conclusions to patients with RHD. Our findings also suggest that despite the pathophysiological differences between the two subgroups, a separate cut-off for strain parameters for severe MR due to RHD or MVP is probably not required.

5.1. Limitations

Table 3

Comparison of LV and LA strain parameters among MVP and RHD MR.

| Parameters | MVP (n = 30) | RHD (n = 20) | P value |
|------------|--------------|--------------|---------|
| GLS (%)    | –18.25       | –16.2        | 0.123   |
| GRS (%)    | 15.3         | 15.8         | 0.893   |
| GCS (%)    | 13.6         | 13.4         | 0.874   |
| GAS (%)    | –31.2        | 29.7         | 0.413   |
| PALS (%)   | 20.45        | 11.9         | 0.080   |
| LA Strain Rate | 2.24       | 1.1          | 0.124   |

Table 4

Correlation of LV and LA strain with other echocardiographic parameters.

| Parameters | LVIDd | LVIDs | EF | r | p | r | p | r | p |
|------------|-------|-------|----|---|---|---|---|---|---|
| GLS        | 0.980 | 0.010 | 0.090 | 0.030 | 0.347 | 0.044 |
| GRS        | –0.007 | 0.962 | –0.535 | 0.036 | 0.257 | 0.071 |
| GCS        | 0.072 | 0.619 | 0.540 | 0.041 | –0.232 | 0.105 |
| GAS        | 0.057 | 0.692 | 0.615 | 0.038 | –0.170 | 0.237 |
| PALS       | –0.178 | 0.217 | –0.313 | 0.046 | –0.064 | 0.657 |
| LA Strain Rate | 0.160 | 0.267 | 0.045 | 0.754 | –0.131 | 0.365 |

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5. Conclusion

Speckle tracking echocardiography, a reliable non-invasive and angle-independent modality to quantify LA and LV deformation indices, showed that there is no significant difference in LA and LV strain indices in severe MR due to either RHD or MVP, despite significant pathophysiological differences. There was a trend towards lower left atrial strain in RHD compared to MVP. Currently identified prognostic strain parameters in patients with primary MR, predominantly due to MVP, may be used for clinical decision-making for patients with RHD pending confirmation of results by other groups.

5.1. Limitations

This was a single center study. Large multicentric studies may be required to confirm our results in severe primary MR due to RHD. Duration of MR could not be ascertained which may have an impact on LV and LA strain. Prospective validation of ventricular and atrial strain indices is required to confirm their usefulness in the prediction of the need for cardiac surgery in patients with RHD, and its preoperative and postoperative outcomes.

Declaration of competing interest

The authors report no relationships that could be construed as a conflict of interest.

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