Indian Heart Journal 73 (2021) 85–90

Contents lists available at ScienceDirect

Indian Heart Journal

journal homepage: www.elsevier.com/locate/ihj

Original Article

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

Gopalan Nair Rajesh [a], S.G. Shyam Lakshman [a, *], Haridasdan Vellani [a], Chakanalil Govindan Sajeev [a], Boban Thomas [b]

[a] DM Cardiology, Government Medical College, Kozhikode, Kerala, India
[b] DM Cardiology, Centro Hospitalar Barreiro Montijo, Barreiro, Portugal

ARTICLE INFO

Article history:
Received 23 May 2020
Accepted 7 November 2020
Available online 12 November 2020

Keywords:
Global longitudinal strain
Left atrial strain
Mitral valve prolapse
Rheumatic heart disease

ABSTRACT

Objective: Left atrial (LA) and left ventricular (LV) remodelling are the adaptive changes that occur in primary mitral regurgitation (MR) and are related to its clinical outcomes. Despite the pathophysiological differences in MR in rheumatic heart disease (RHD) and mitral valve prolapse (MVP), whether the pattern of LV and LA remodelling is different between the two conditions remains unknown. Hence, we compared the LA and LV strain pattern in MR due to RHD, the predominant etiology in developing countries topatients with MVP and age and sex-matched controls.

Methods: A total of 50 patients of severe MR which included 30 MVP MR and 20 RHD MR were assessed by strain imaging by speckle tracking echocardiography (STE) and were compared with age and sex-matched controls. 2D STE was used for LA and 3D STE was used for LV strain analysis. LA and LV strain parameters were compared between MVP MR and RHD MR groups.

Results: 30 patients with MVP and 20 with RHD were studied. 60% (n = 30) were symptomatic. Mean GLS was −17.2 ± 4.4% compared to −20 ± 3.2% among controls and mean LA strain was 17.35 ± 10.3% compared to 51.34 ± 11.5% among controls which were significantly lower (both $p < 0.01$). No significant difference in LA strain and GLS was found between MVP and RHD subgroups (LA strain 20.45 ± 11.9% and 14.63 ± 8.85%; $p = 0.08$; GLS - 18.25 ± 4.3% and-16.2 ± 4.6%; $p = 0.12$). PALS in the RHD group was lower compared to MVP($p = 0.08$) which showed a trend towards significance. LV strain parameters showed no significant difference among the MVP and RHD groups.

Conclusion: LA and LV strain parameters showed no significant difference in MR due to either RHD or MVP. There was a trend towards lower LA strain in RHD which needs validation with large multicentric studies. The current strain parameters from MVP with the prognostic value may be applied to MR of RHD etiology, pending confirmation of our results by other groups.

1. Introduction

Rheumatic heart disease (RHD) continues to be a major public health issue in many developing countries and studies have reported mitral regurgitation (MR) as a common valvular lesion.[1] Mitral valve prolapse (MVP) is a common etiology of MR in developed countries, occurring in 2% of the population in the United States.[2] 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 neovascularization leading to leaflet tip prolapse and mitral annular dilatation.[3,4] There is evidence of elevated chronic inflammatory markers in RHD compared to controls suggestive of chronic low-grade persistent carditis.[5,6] Although there is no chronic inflammatory carditis and left atrial pathology, an association of MVP with cardiomyopathy has been hypothesized.[7,8]

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

* Corresponding author. DM Cardiology, Department of Cardiology, Government Medical College, Calicut, Kerala, 673008, India.
E-mail address: drshyam.kmc.lakshman@gmail.com (S.G. Shyam Lakshman).

https://doi.org/10.1016/j.ihj.2020.11.010

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.[9]

Left ventricular global longitudinal strain (GLS), assessed with two-dimensional speckle-tracking echocardiography (STE), detectssubtle LV systolic dysfunction in patients with MR with preserved LVEF.[10] 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,[12] independently related to stroke and death, as well as systolic and diastolic heart failure.[13] 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 strainvalues in the LA and LV are different and parameters specific to MR due to RHD mayhave 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 $\leq$40%, MR, of Carpentier type I or IIIB, coexistent moderate or severevalvular 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 3 D 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.

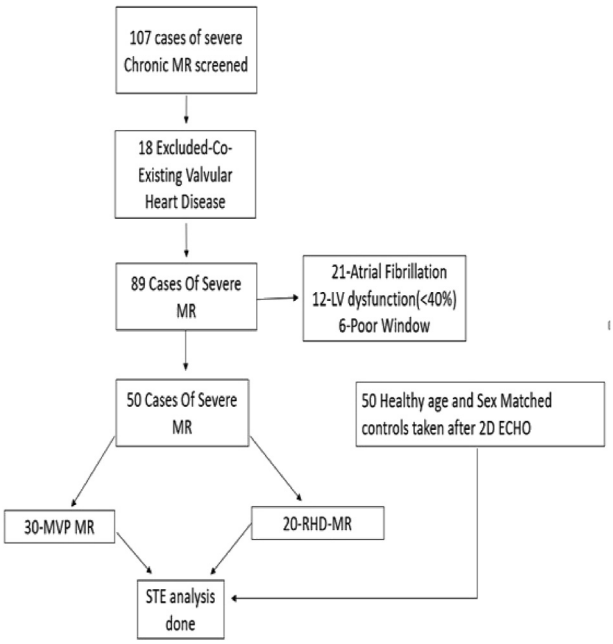

Fig. 1. Figure depicting the methodology of Study.

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-holdwith 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 current[16] 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

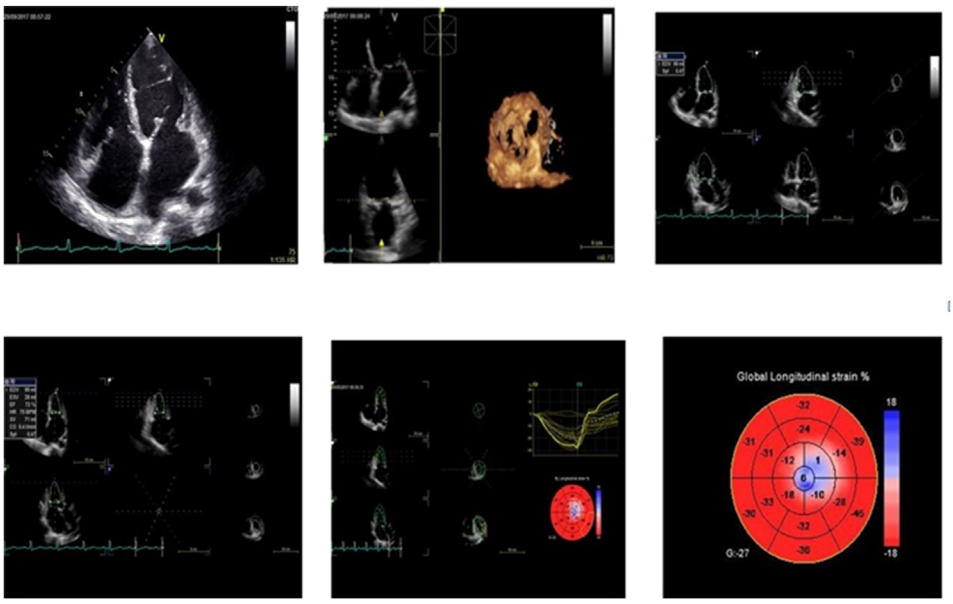

Fig. 2. 3 D LV speckle tracking echocardiographic analysis and Bulls Eye Plot.

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.[18] 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

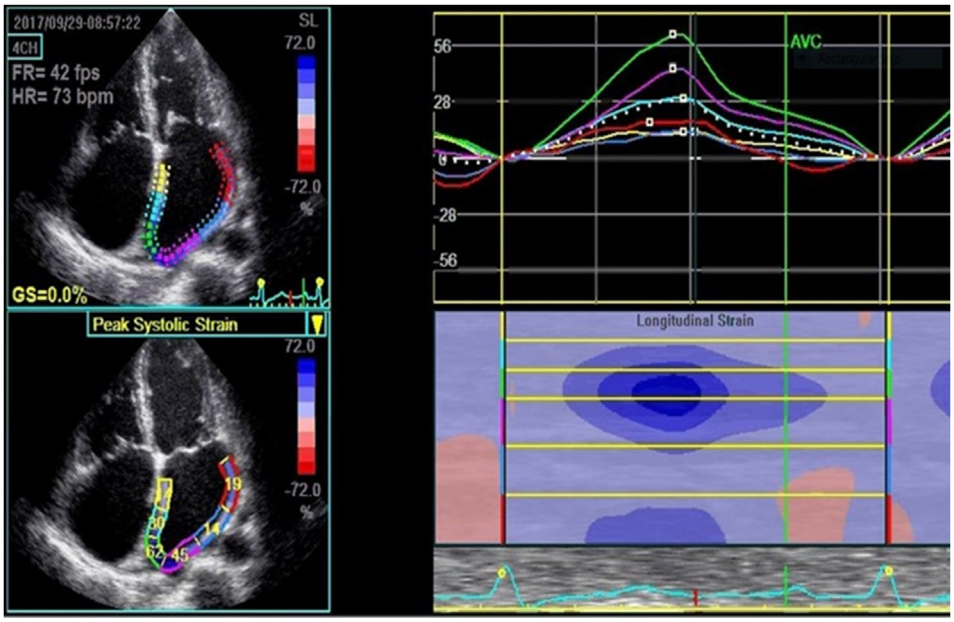

Fig. 3. 2D LA speckle tracking echocardiographic analysis for PALS.

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 because of 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 measured by TR jet velocity. Mean PASP among two groups were 28.4 ± 4.2 and 34.8 ± 7.2 respectively (p < 0.05). The baseline echocardiographic parameters are detailed in Table 1.

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 1.9 ± 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 LVstrain 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). GLS 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 LVIDs (r = −0.3, p < 0.05) {Table 4}. GLS 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 (intra-class 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 carditis.[5,6] Reports of decrease in regional septal myocardial deformation indices in subjects with MVP suggest the co-existence of primary cardiomyopathy.[20] Kitkungvan and co-workers have reported that in primary MR, LV fibrosis was more prevalent in MVP than non MVP.[21] 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 MVR 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.[22]

Table 1
Baseline echocardiographic parameters in RHD and MVP Groups.

Echocardiographic Parameters	MVP(n = 30) Mean ± SD	RHD (n = 20) Mean ± SD	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	0.8202

LA-Left Atrium; LVIDd-LV internal dimension in diastole; LVIDs-LV internal dimension in systole; EF-Ejection 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.

LV and LA strain	Cases (n = 50)		Controls (n = 50)		
patterns	Mean	SD	Mean	SD	p
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	0.9	1.43	0.44	p < 0.05

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

Table 3
Comparison of LV and LA strain parameters among MVP and RHD MR.

LV and LA strain	MVP/RHD				P value
Patterns	MVP(n = 30)		RHD (n = 20)		
	Mean	SD	Mean	SD	
GLS (%)	−18.25	4.3	−16.2	4.6	0.123
GRS (%)	35.3	15.3	35.9	15.8	0.893
GCS (%)	−13.6	5.4	−13.4	5.4	0.874
GAS (%)	−31.2	8.2	−29.2	8.7	0.413
PALS (%)	20.45	11.9	14.63	8.85	0.080
LA Strain Rate	2.24	1.1	1.60	0.66	0.124

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

Table 4
Correlation of LV and LA strain with other echocardiographic parameters.

LV and LA strain	LVIDd		LVIDs		EF	
Parameters	r	p	r	p	r	p
GLS	0.980	0.010	0.690	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

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

In patients with asymptomatic severe MR with preserved LV function, GLS has prognostic value.[13,23–25] In the study by Mascle et al[26] 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. 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.

What is already known?

LV and LA strain has prognostic value in MR due to MVP.

What this study adds:

As 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.

Declaration of competing interest

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

Acknowledgement

We would like to thank Dr Tiny Nair, PRS Hospital, Trivandrum, Kerala, India for his suggestions for the manuscript.

References

1. Marcus RH, Sareli P, Pocock WA, Barlow JB. The spectrum of severe rheumatic mitral valve disease in a developing country: correlations among clinical presentation, surgical pathologic findings, and hemodynamic sequelae. *Ann Intern Med*. 1994;120(3):177–183.
2. Iung B, Vahanian A. Epidemiology of valvular heart disease in the adult. *Nat Rev Cardiol*. 2011;8(3):162–172.
3. Cunningham MW. Streptococcus and rheumatic fever. *Curr Opin Rheumatol*. 2012;24(4):408–416.
4. Marcus RH, Sareli P, Pocock WA, et al. Functional anatomy of severe mitral regurgitation in active rheumatic carditis. *Am J Cardiol*. 1989;63(9):577–584.
5. Yaman IH, Dagdemir A, Baysal K. Serum intercellular adhesion molecule-1 levels in acute rheumatic fever. *Ann Trop Paediatr*. 2003;23(3):167–171.
6. Hafez M, El-Morsy Z, El-Shennawy F, et al. Susceptibility to overproduction of cytokines in acute rheumatic carditis and their role in the pathogenesis. *J Med Sci*. 2002;2(2):65–73.
7. GulottaSJ, Gulco L, Padmanabhan V, Miller S. The syndrome of systolic click, murmur, and mitral valve prolapse-a cardiomyopathy? *Circulation*. 1974;49(4):717–728.
8. Scampardonis G, Yang S, Maranhão V. Left ventricular abnormalities in prolapsed mitral leaflet syndrome: review of eighty-seven cases. *Circulation*. 1973;48:287–297.
9. Watkins DA, Johnson CO, Colquhoun SM, et al. Global, regional, and national burden of rheumatic heart disease, 1990–2015. *N Engl J Med*. 2017;377(8):713–722.
10. Kim M-S, Kim Y-J, Kim H-K, et al. Evaluation of left ventricular short- and long-axis function in severe mitral regurgitation using 2-dimensional strain echocardiography. *Am Heart J*. 2009;157(2):345–351.
11. Kim HM, Cho G-Y, Hwang I-C, et al. Myocardial strain in prediction of OutcomesAfter surgery for severe mitral regurgitation. *J Am CollCardiolImg*. 2018;11(9):1235–1244.
12. Kizer JR, Bella JN, Palmieri V, Liu JE, Best LG. Left atrial diameter as an independent predictor of first clinical cardiovascular events in middle-aged and elderly adults: the Strong Heart Study (SHS). *Am Heart J*. 2006;151(2):412–418.
13. Gottdiener JS, Kitzman DW, Aurigemma GP. Left atrial volume, geometry, and function in systolic and diastolic heart failure of persons≥ 65 years of age (the Cardiovascular Health Study). *Am J Cardiol*. 2006;97(1):83–89.
14. Podlesnikar T, Delgado V, Bax JJ. Cardiovascular magnetic resonance imaging to assess myocardial fibrosis in valvular heart disease. *Int J Cardiovasc Imag*. 2018;34(1):97–112.
15. Meel R, Nethononda R, Libhaber E, Dix-Peek T, Peters F, Essop M. Assessment of myocardial fibrosis by late gadolinium enhancement imaging and biomarkers of collagen metabolism in chronic rheumatic mitral regurgitation. *Cardiovasc J Afr*. 2018;29(3):150–154.
16. Mor-Avi V, Lang RM, Badano LP, et al. Current and evolving echocardiographic techniques for the quantitative evaluation of cardiac mechanics: ASE/EAE consensus statement on methodology and indications endorsed by the Japanese Society of Echocardiography. *Eur J Echocardiogr*. 2011;12(3):167–205.
17. Serri K, Reant P, Lafitte M, Berhouet M. Global and regional myocardial function quantification by two-dimensional strain: application in hypertrophic cardiomyopathy. *JAmCollCardiolImg*. 2006;47(6):1175–1181.
18. Cameli M, Lisi M, Giacomin E, et al. Chronic mitral regurgitation: left atrial deformation analysis by two-dimensional speckle tracking echocardiography:

mitral regurgitation and left atrial strain. *Echocardiography*. 2011;28(3):327–334.
19. Manjunath CN, Srinivas P, Ravindranath KS, Dhanalakshmi C. Incidence and patterns of valvular heart disease in a tertiary care high-volume cardiac centre: a single centre experience. *Indian Heart J*. 2014;66(3):320–326.
20. Malev E, Zemtsovsky E, Pshepiy A, Timofeev E, Reeva S, Prokudina M. Evaluation of left ventricular systolic function in young adults with mitral valve prolapse. *Exp Clin Cardiol*. 2012;17(4), 165-68.
21. Kitkungvan D, Nabi F, Kim RJ, et al. Myocardial fibrosis in patients with primary mitral regurgitation with and without prolapse. *J Am CollCardiolImg*. 2018;72(8):823–834.
22. Marwick TH. Measurement of strain and strain rate by echocardiography: ready for prime time? *J Am CollCardiolImg*. 2006;47(7):1313–1327.
23. Mentias A, Naji P, Gillinov AM, et al. Strain echocardiography and functional capacity in asymptomatic primary mitral regurgitation with preserved ejection fraction. *J Am CollCardiolImg*. 2016;68(18):1974–1986.
24. Lancellotti P, Cosyns B, Zacharakis D, et al. Importance of left ventricular longitudinal function and functional reserve in patients with degenerative mitral regurgitation: assessment by two-dimensional speckle tracking. *J Am Soc Echocardiogr*. 2008;21(12):1331–1336.
25. Witkowski TG, Thomas JD, Debonnaire PJMR, et al. Global longitudinal strain predicts left ventricular dysfunction after mitral valve repair. *Eur Heart J Cardiovasc Imaging*. 2013;14(1):69–71.
26. Mascle S, Schnell F, Thebault C, et al. Predictive value of global longitudinal strain in a surgical population of organic mitral regurgitation. *J Am Soc Echocardiogr*. 2012;25(7):766–772.