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ORIGINAL PAPER

Association between late gadolinium enhancement and global longitudinal strain in patients with rheumatic mitral stenosis

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Abstract

The correlation between the extent of myocardial fibrosis and subclinical left ventricle (LV) systolic dysfunction in rheumatic mitral stenosis (MS) has not been widely studied. We sought to evaluate the correlation between the extent of LV myocardial fibrosis quantified by late gadolinium enhancement (LGE) using cardiac magnetic resonance (CMR) and global longitudinal strain (GLS) by speckle tracking echocardiography (STE) in patients with rheumatic MS. We prospectively evaluated 36 consecutive rheumatic MS patients who were planning to undergo mitral valve surgery. Then we evaluate the correlation between the extent of LV myocardial fibrosis quantified by LGE CMR and the systolic LV function by GLS using STE. Thirty-six patients with mean age of 45.7 ± 9.9 years old, showed mean LGE was $4.9 \pm 2.7\%$. The mean LV ejection fraction (EF) measured by CMR was $50 \pm 10.8\%$, and the mean LV GLS was $13.5 \pm 3.9\%$. There was a moderate correlation between GLS and LGE (r −0.432, $p = 0.009$). There were no correlations between GLS with mitral valve area (MVA) with r 0.149, $p = 0.385$, mean mitral valve gradient (MVG) with r -0.078, $p = 0.653$, and LVEF (r 0.299, $p = 0.076$). There was a moderate correlation between LGE and GLS in patients with rheumatic MS.

Keywords Myocardial fibrosis · Global longitudinal strain · Late gadolinium enhancement · Cardiac magnetic resonance · Rheumatic mitral stenosis

Abbreviations

BMI	Body Mass Index
CMR	Cardiac magnetic resonance
GLS	Global longitudinal strain
LGE	Late gadolinium enhancement
LA	Left atrium
LAVI	Left Atrial Volume Index
LV	Left ventricular
LVEDVi	Left Ventricular End-Diastolic Volume Index
LVEF	Left ventricular ejection fraction
LVESVi	Left Ventricular End-Systolic Volume Index
LVMI	Left Ventricular Mass Index
mPAp	Mean pulmonary arterial pressure
MS	Mitral stenosis
MVA	Mitral valve area
MVG	Mitral valve gradient
RHD	Rheumatic heart disease
RV	Right ventricle
RVEDVi	Right Ventricular End-Diastolic Volume Index
RVEF	Right ventricular ejection fraction
RVESVi	Right Ventricular End-Systolic Volume Index
STE	Speckle tracking echocardiography
TAPSE	Tricuspid annular plane systolic excursion

Introduction

In general, patients with rheumatic mitral stenosis (MS) have good left ventricular (LV) systolic function measured by ejection fraction (EF) which routinely used in daily practice. However, subclinical LV systolic dysfunction can be detected using tissue Doppler imaging (TDI) or speckle tracking echocardiography (STE) [1–3].

In rheumatic heart disease (RHD), the inflammatory process of the valve results from cross-reactions between streptococcal antigens and heart valves and also myocardial tissue. The anatomical damage of the valve will develop

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into MS due to exposure to recurrent rheumatic fever. In addition, there is myocardial remodeling process due to chronic inflammation that occurs in RHD. The process of damage to the LV structure is characterized by increased myocardial interstitial space by collagen deposition and loss of cardiac muscle fibers resulting in replacement fibrosis. These changes had occurred before the LV systolic function decreased clinically or clinical symptoms occur [4, 5]. Based on this theory, myocardial fibrosis has been one of the theories proposed in the pathophysiology of LV systolic dysfunction in rheumatic MS [6].

Cardiac Magnetic Resonance (CMR) is a noninvasive modality for detecting myocardial fibrosis. Left ventricular longitudinal strain correlates with the degree of myocardial fibrosis in other valvular diseases that give a direct burden of volume or pressure or both on the left ventricle, such as aortic stenosis, aortic regurgitation, and mitral regurgitation [7–10]. However, this phenomenon has not been studied in MS case. We hypothesize that the LV systolic dysfunction measured by GLS using STE is negatively correlated with LV myocardial fibrosis volume quantified by LGE using CMR in patients with rheumatic MS.

Methods

We prospectively evaluated 36 consecutive rheumatic MS patients who were going to undergo mitral surgery at National Cardiovascular Center Harapan Kita during April–June 2018. Patients with concomitant congenital heart disease, coronary heart disease, any significant aortic valve abnormality, significant mitral regurgitation, diabetes mellitus, and hypertension were excluded. Further exclusion criteria include any contraindication for CMR (creatinine > 2 g/dL, metallic implant, and unable to lay still during the examination) and suboptimal imaging data. All patients underwent CMR and Echocardiography examination within a week period of time. Institutional review board approval was approved prior to enrollment with written informed consent obtained from all patients.

The CMR studies were performed using 1.5 T MRI technology (Philips® Achieva 1.5 T, Amsterdam, Netherland) with identical standard and protocol to all patients. Image acquisition was performed using ECG-gated Steady-State Free Precession (SSFP) to multiple planes of the heart (long axis, short axis, four chambers, and three chambers). Late gadolinium enhancement imaging was carried out 10 min after intravenous injection of 0.1 mmol/kg body weight [11]. All volume and mass measurements were indexed to body surface area. The CMR data were analyzed off-line on a dedicated MR workstation with integrated software (CVI42®, Calgary, Canada). Fibrosis quantification was performed by a cardiovascular imaging specialist from a short-axis stack of LGE imaging using manual adjustment semi-automatically for each segment of the LV [12]. First, the endocardial and epicardial contours of the LV wall were manually traced. Second, the area of fibrotic was manually detected and tracked using manual adjustment option. Third, we analyzed 3D LGE images slice by slice and calculated the volume of the fibrotic tissue as a percentage of the total LV tissue. The LGE % is presented as a percentage of LGE mass to LV mass accumulated for each segment. Analysis of cardiac CMR examinations in the form of the LGE protocol was carried out by one examiner for all cases. Using Bland Altman plot, interobserver and intraobserver variability for calculating myocardial fibrosis were $p = 0.66$ and $p = 0.14$, respectively (supplement 1).

Echocardiographic examinations were done using the General Electric Vivid E9 system (GE Vingmed Ultrasound AS, Horten, Norway) with a 3.5 MHz transducer. All data were analyzed in a workstation (EchoPAC PC; GE Vingmed Ultrasound AS). Mitral stenosis severity is evaluated based on the 2009 EAE/ASE Recommendations Echocardiographic of Assessment of Valve Stenosis for Clinical Practice [13].

Strain imaging of 2-D speckle tracking echocardiography images was obtained and reported as the average of peak longitudinal strain of all segments obtained from the LV apical 4-chamber, apical long axis, and apical 2-chamber views. All images were obtained during breath hold and stored in cine-loop format from 3 to 5 consecutive beats. The frame rate for images was between 50 and 90 frames/s. The endocardial border was determined manually, and then the software system created an automatic epicardial tracing for each view. The regions of interest (ROI) included the whole thickness of the LV and the automatic process was started, allowed the system to read and measure each region. Inadequate tracking segments were automatically excluded, and the investigator could correct the contour manually to achieve optimal tracking. The tracking quality of the remaining segments was controlled visually to ensure adequate automatic tracking. Only segments with optimal tracking quality were included. Segments with suboptimal tracking quality were dismissed from the analysis. All images were evaluated by one experienced cardiologist who was blinded to patient clinical characteristics and CMR results.

Statistical analysis

A continuous variable was presented as a mean ± standard deviation in normally distributed and median (interquartile range) in non-normally distributed data. Correlation between variables was tested by Pearson test for normally distributed continuous variables and Spearman test for non-normally distributed continuous variables. All statistical analysis was performed using IBM SPSS statistics 20 (SPSS Inc, Chicago, USA). A p value of less than 0.05 was considered statistically significant.

Results

Thirty-six patients were included in the study. The mean age was 45.7 ± 9.9 years and female dominated (72.2%, 26/36). All patients have severe MS with mean MVA was 0.7 ± 0.2 cm^2 and mean MVG 11.4 ± 4.1 mmHg. Majority of patients were in atrial fibrillation (80.6%, 29/36) and average LVEF by CMR was 50 ± 10.8%. Complete clinical characteristics of all patients are summarized in Table 1.

Analysis of LGE and GLS was performed in all patients. Mean LGE was 4.9 ± 2.7% and mean GLS was − 13.5 ± 3.9%. Figure 1 illustrates the calculation of global longitudinal strain by 2D echocardiography and Fig. 2 for calculating LGE by MRI from one patient in this study.

There was a moderate negative correlation between GLS and estimated volume of myocardial fibrosis (r − 0.432, p = 0.009) as seen in Fig. 3. In addition, GLS is not significantly correlated with either MVA (r 0.149, p = 0.385), mean MVG (r − 0.078, p = 0.653), and LVEF (r 0.299, p = 0.076) as seen in Table 2.

Table 1 Baseline characteristics

Variables	Value (N = 36)
Age (years)	45.7 ± 9.9
Sex (n)	
Male	10 (27.8%)
Female	26 (72.2%)
BMI (kg/m^2)	23.1 ± 4.4
Heart rhythm (n)	
Sinus *rhythm*	7 (19.4%)
Atrial fibrillation	29 (80.6%)
Baseline echocardiographic data	
Mean MVG (mmHg)	11.4 ± 4.1
MVA (cm^2)	0.7 ± 0.2
mPAp (mmHg)	36.5 ± 14
TAPSE (mm)	16.3 ± 5.1
GLS (%)	− 13.5 ± 3.9
Baseline CMR Data	
LVEF (%)	50 ± 10.8
RVEF (%)	44.3 ± 10.2
LVEDVi (ml/m^2)	74 (50–174)
LVESVi (ml/m^2)	36.5 (18–140)
RVEDVi (ml/m^2)	87 (44–175)
RVESVi (ml/m^2)	45 (24–112)
LVMI (g/m^2)	47.8 ± 13.5
LAVI (ml/m^2)	162 (81–462)
LGE (%)	4.9 ± 2.7

BMI Body Mass Index, *MVG* mitral valve gradient, *MVA* mitral valve area, *mPAP* mean pulmonary artery pressure, *TAPSE* tricuspid annular plane systolic excursion, *GLS* global longitudinal strain, *LVEF* left ventricular ejection fraction, *RVEF* right ventricular ejection fraction, *LVEDVi* Left Ventricular End Diastolic Volume Index; *LVESVi* Left Ventricular End Systolic Volume Index, *RVEDVi* Right Ventricular End Diastolic Volume Index, *RVESVi* Right Ventricular End Systolic Volume Index, *LVMI* Left Ventricular Mass Index, *LAVI* Left Atrial Volume Index, *LGE* late gadolinium enhancement

Discussion

In our study, the average GLS of our patients was − 13.5 ± 3.9%. It was lower than normal reference values and even lower compared to other MS patients in previous studies which was approximately − 17% [1, 2]. This could probably due to older age subjects and the higher prevalence of AF in our population, suggesting the rheumatic process has been progressing in longer period and reached in more advanced stage. The prevalence of AF in our population was 80.6%, 29/36 compared to other studies which were between 29 and 43% [14, 15]. Lee et al. demonstrated that in patients with non-valvular heart diseases, those with AF have more impaired GLS compared to non-AF patients [16]. However, further study is needed to see this phenomenon in valvular heart disease. In addition, the average LVEF measured by CMR in our patients was borderline normal (50 ± 10.8%), with some of them have reduced LVEF. Other studies also reported that LV dysfunction is detected in approximately 25% of MS patients [1, 17].

Several mechanisms have been proposed to explain the occurrence of LV dysfunction in rheumatic MS, include [6]; (1) reduced filling of LV from mechanical obstruction due to stenotic mitral valve, (2) chronic inflammation leading to abnormal wall motion from endomyocardial fibrosis, (3) scarring of the subvalvular apparatus leading to wall motion abnormalities, (4) reduced LV compliance leading to profound diastolic function, (5) increased afterload leading to remodeling (6) abnormal right-left septal interaction from pulmonary hypertension, and (7) concomitant disease such as systemic hypertension and coronary artery disease.

The CMR examination showed that all patients included in this study showed positive LGE with the average myocardial fibrotic volume of 4.9 ± 2.7%. In rheumatic MS, some studies suggested the association between rheumatic process and myocardial fibrosis [6, 18]. Pancardiac inflammation is the essential pathophysiology during acute rheumatic fever which involved endocardium, myocardium, and pericardium. Long-term effects which caused by the chronic inflammation may lead to valve injury and stenosis, chronic inflammation and scarring of the endocardium and myocardium. The association between acute and chronic inflammation is

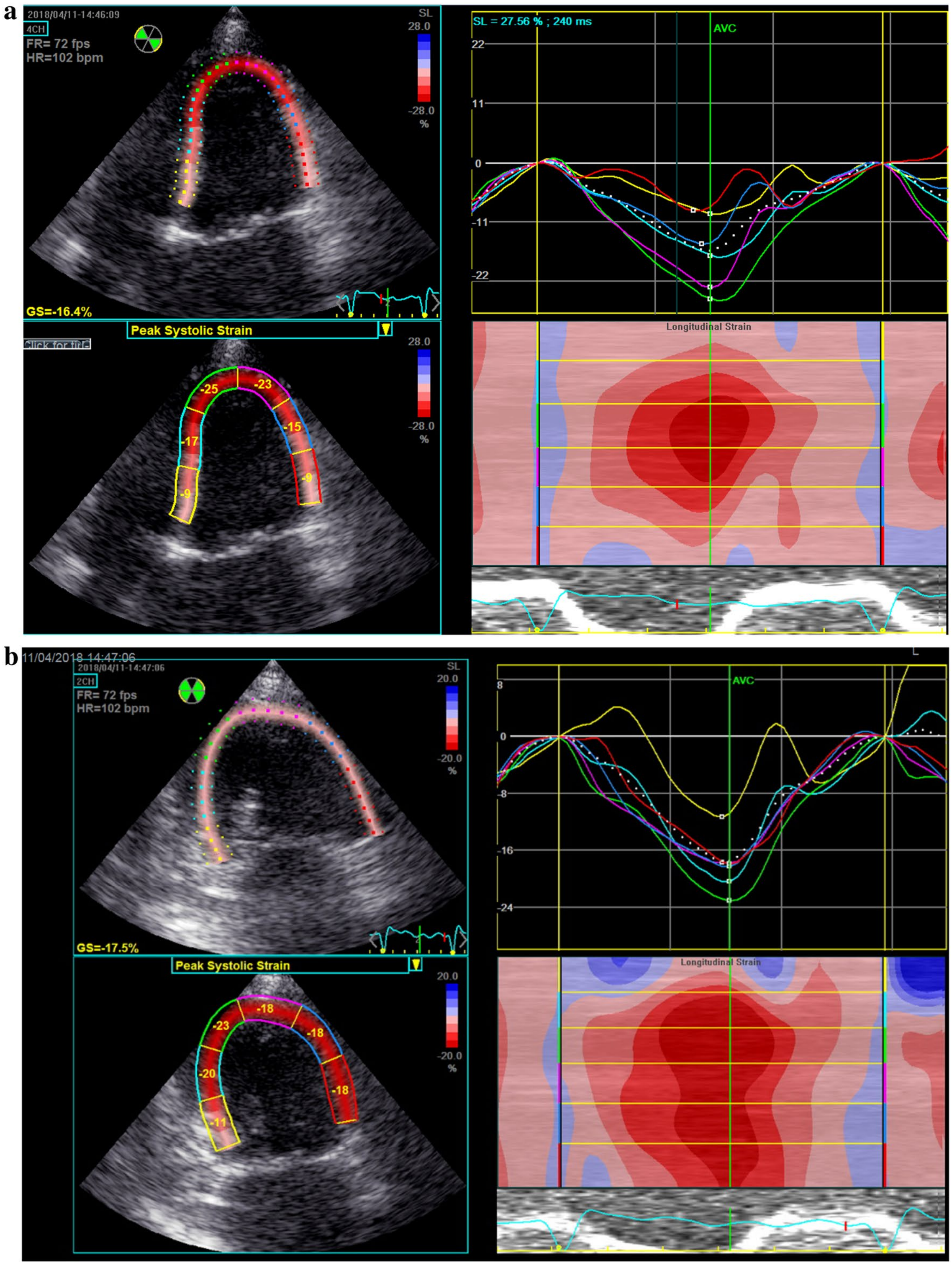

Fig. 1 Measurement of global longitudinal strain obtained from apical 4 chambers peak systolic strain (**a**), 2 chambers peak systolic strain (**b**), 3 chambers peak systolic strain (**c**), and the average of all peak systolic strains (**d**)

represented by the presence of fibrinoid necrosis followed by the appearance of histiocytes and giant cells in the granulomatous phase. The chronic inflammation with resultant fibrosis often called “myocardial factor” [6]. In RHD, there is also overexpression of transforming growth factor-beta 1 (TGF-β1). TGF-β1 stimulates fibroblasts to proliferate c

d

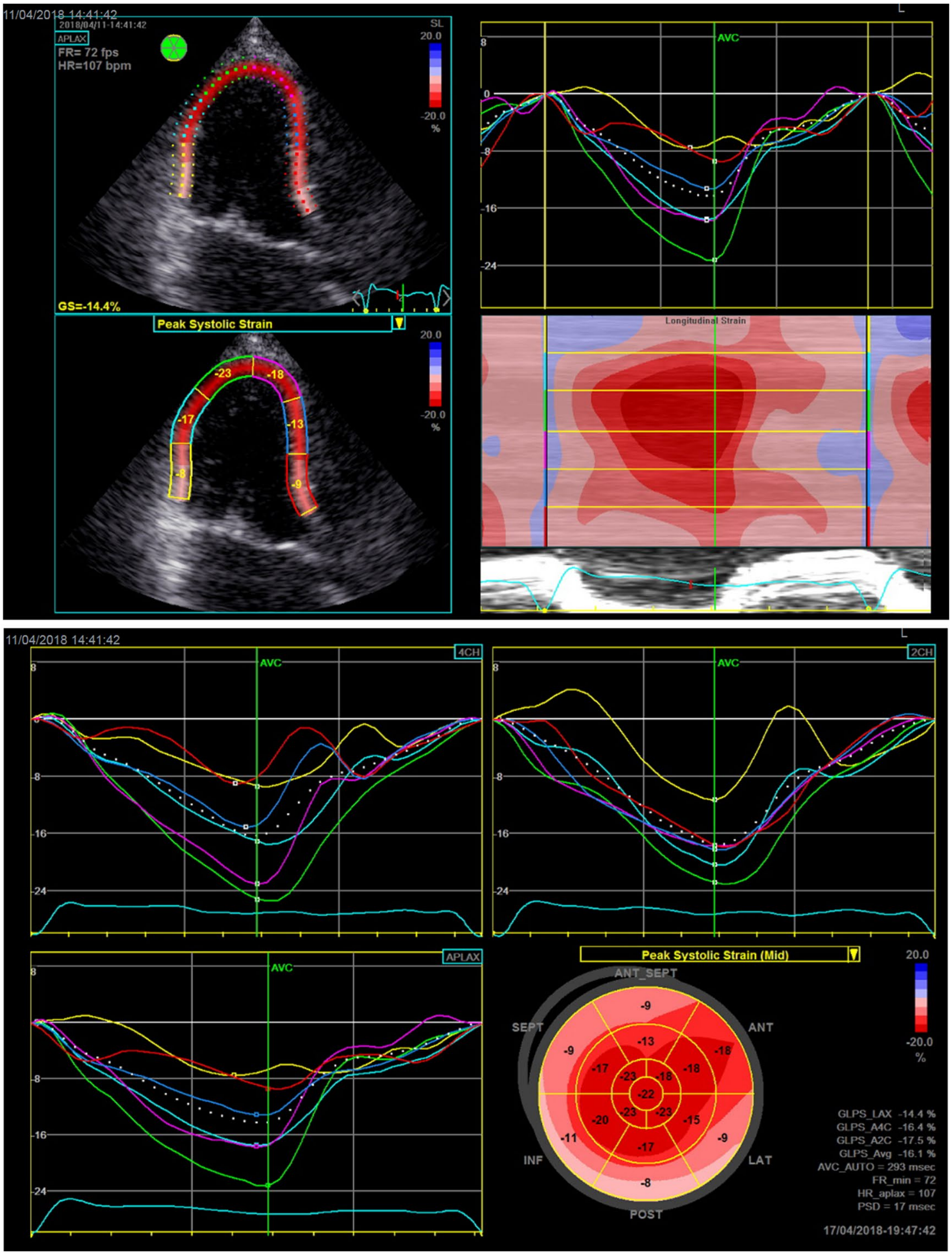

Fig. 1 (continued)

and creates extracellular matrix components. With repeated injury such as chronic inflammation in RHD, the sustained increase of TGF-β1 will lead to tissue fibrosis [19, 20].

So far, there was no LGE study on rheumatic MS to draw comparisons from, but our finding showed lower value compared to similar studies in different populations. The average LGE of our patients (4.9 ± 2.7%) were lower compared to subjects with pressure overload state such as aortic stenosis and hypertrophic cardiomyopathy, which were 8 ± 5% and 11 ± 12%, respectively [8, 12].

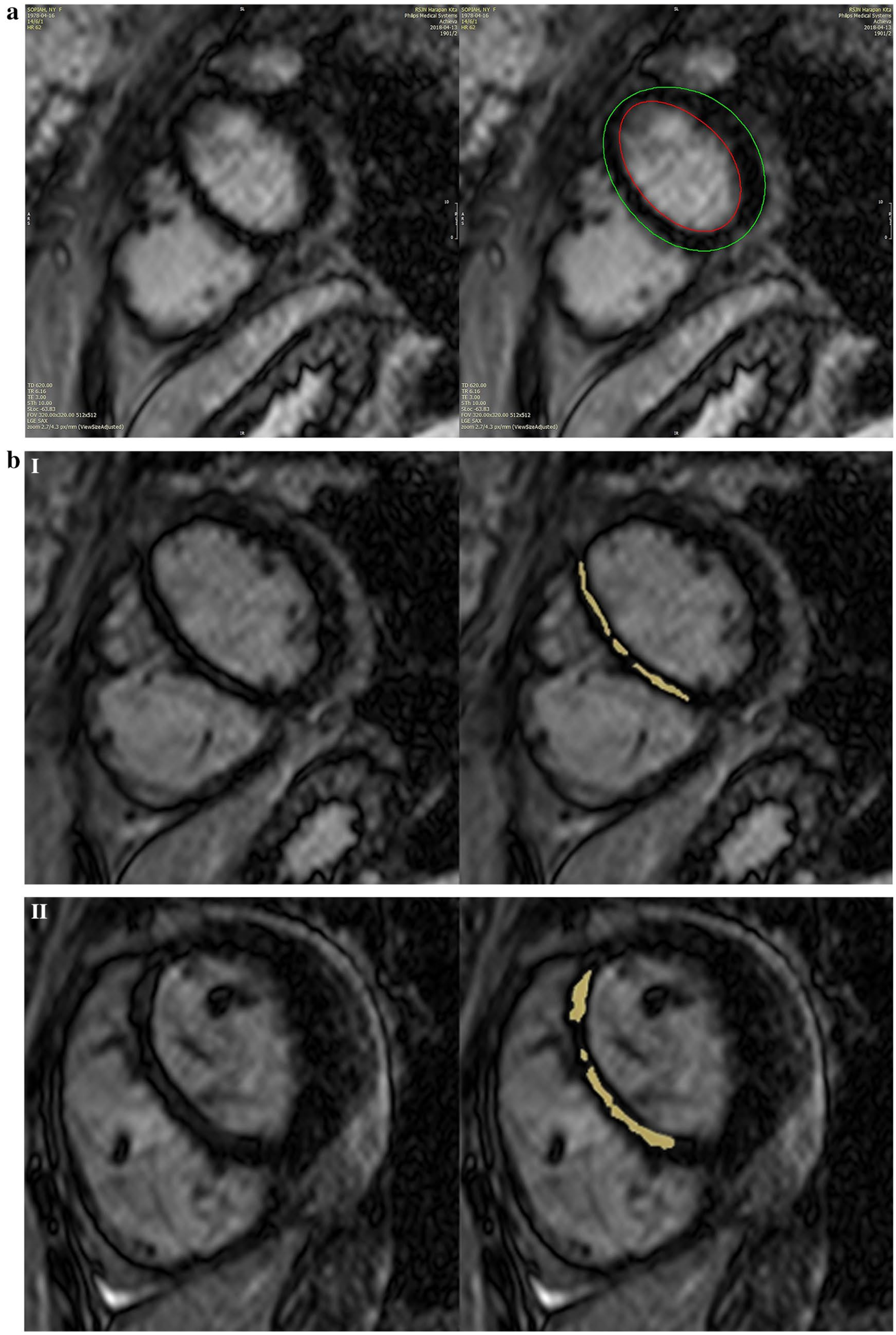

Fig. 2 LGE examination from a patient. Endocardium and epicardium borders were manually contoured (**a**), LGE examinations were manually tracked slice by slice (**b**)

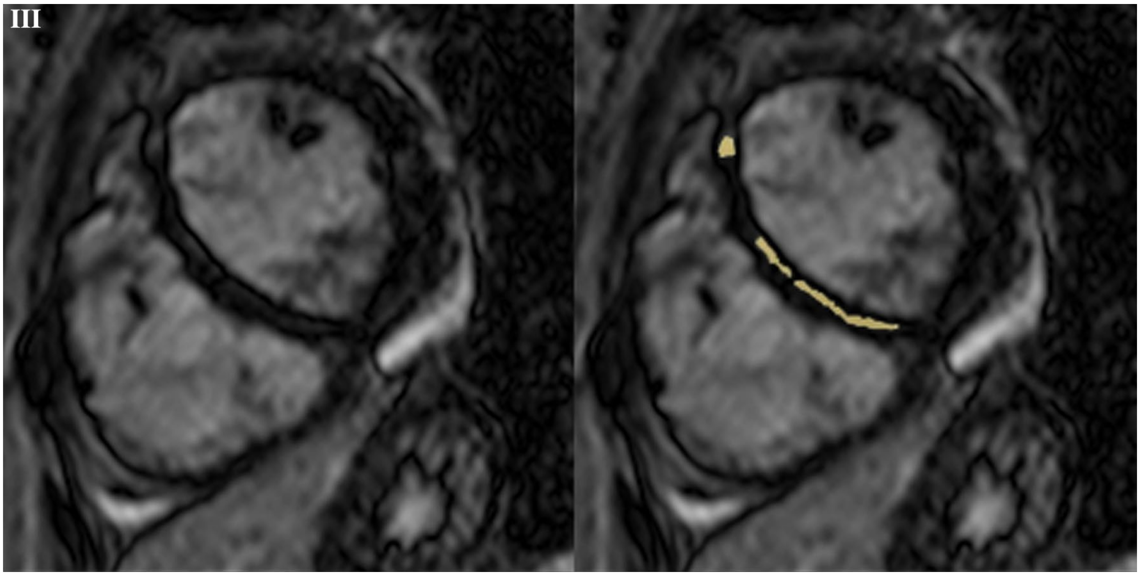

Fig. 2 (continued)

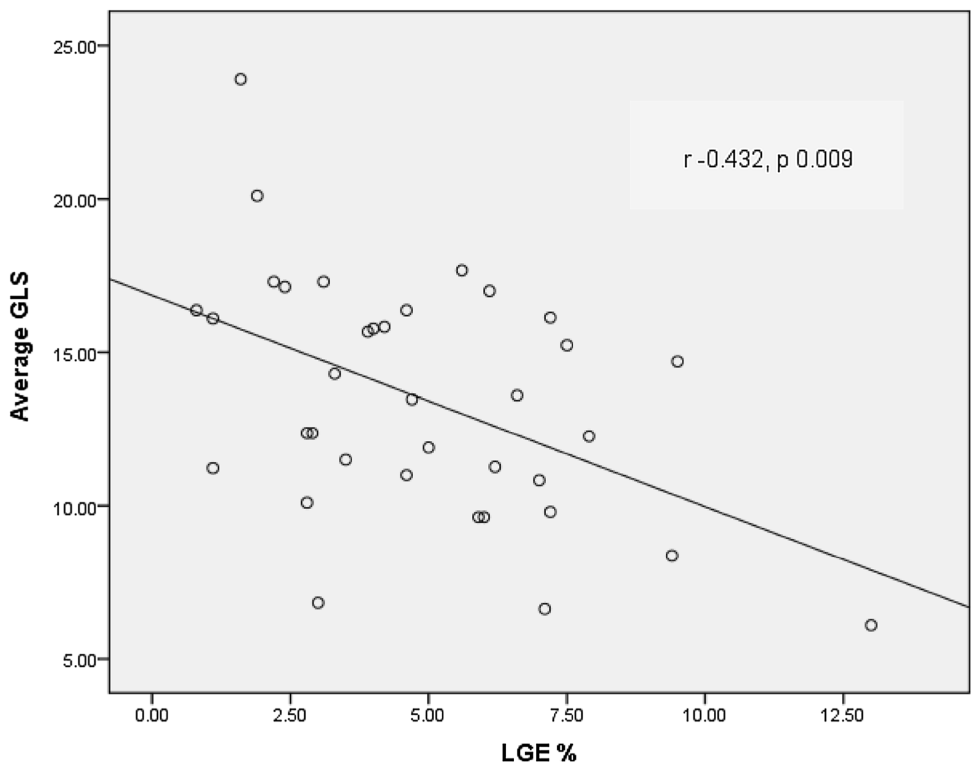

Fig. 3 Scatterplot diagram illustrates correlation between GLS and LGE

Further, in pure volume overload states in patients with chronic severe mitral regurgitation (MR) and mitral valve prolapse, LGE showed even higher value, with 40% and 63% respectively [21, 22]. Several mechanisms have been proposed, include; (1) greater supply–demand mismatch in pressure-overload states resulting in ischemia and fibrosis, (2) pro-fibrotic pathways are activated to a larger extent in pressure overload states compared to volume-overload states, and (3) predominant pathology in MR may be extracellular volume (ECV) loss rather than excessive collagen deposition [23]. Smaller percentage of LGE in rheumatic MS leads to a suspicion that pressure or volume overload condition probably gives more influence to development myocardial fibrosis rather than rheumatic process per se.

Table 2 Correlation between GLS and MVA, mean MVG, LVEF, LGE

Parameter	Correlation coefficient (r)	Significance (p)
GLS and MVA	0.149	0.385
GLS and mean MVG	−0.078	0.653
GLS and LVEF	0.299	0.076
GLS and LGE	−0.432	0.009

GLS global longitudinal strain, *MVA* mitral valve area, *MVG* mitral valve gradient, *LVEF* Left ventricular ejection fraction, *LGE* late gadolinium enhancement

However, some studies reported the association between rheumatic process and endomyocardial fibrosis. A macroscopic necropsy study (1950–1961) on 111 cases of RHD in Uganda, there were 11 cases that both conditions (endomyocardial fibrosis and rheumatic heart disease) were present and 6 cases were *likely* present [24]. The degree concurrence of these two conditions in the necropsy population strongly suggests an association between rheumatic heart disease and endomyocardial fibrosis. Further necropsy study was conducted for the years 1950–1965 in all cases in which endomyocardial fibrosis or RHD had been clearly established. They found 26 cases have characteristic macroscopical lesions of both rheumatic heart disease and endomyocardial fibrosis [18].

In this study, LV myocardial fibrosis presented by LGE and subclinical LV dysfunction assessed by GLS showed moderate negative correlation ($r -0.432$, $p=0.009$). It suggested that greater fibrosis correlates with more significant subclinical LV dysfunction. A study by Lee et al. showed that regardless of LV systolic function, using electron microscope, there were varying degrees of ultrastructural pathologic alterations in pure MS patients. It occurred in myocardial muscle cells in all examined specimens (myocardial factor), but these impairments did not correlate with the severity of MS. Further, those patients with abnormal LV function always exhibited more extensive loss of myofibrils resulting from either disproportion of the mitochondria to myofibril ratio or myofibrillar degeneration [4]. Sengupta et al. showed that mitral annular velocities measured by TDI immediately improved after percutaneous mitral balloon valvuloplasty, but not the LVEF. This finding leads to the consideration that systolic dysfunction in MS depends on myocardial factors rather than hemodynamic factors [25]. Although it is believed that the pathophysiology of LV systolic dysfunction is not based on just one mechanism, our study and other previous findings considered that the mechanism of LV dysfunction in this group of patients could be explained by the theory of myocardial factor, including chronic inflammation further causing endomyocardial fibrosis.

No correlation was found between subclinical LV dysfunction calculated by GLS with LV ejection fraction derived by CMR ($r=0.299$, $p=0.076$). The absolute value of average GLS ($-13.5\pm3.9\%$) in our patients suggest worse subclinical LV dysfunction than the value of average LVEF ($50\pm10.8\%$) which is borderline LV dysfunction. The explanation is because the volume-based measurement of LVEF is fundamentally different from direct measurement of myocardial motion by GLS, hence the reliability and precision of these measurements are also different. LVEF is an insensitive marker of LV systolic function which depends on loading condition and might be unable to detect early LV dysfunction until the degree of myocardial dysfunction has become more significant to cause decreased EF.

Our study showed that GLS was not correlated with MVA and mean MVG which represent MS severity. This finding is similar to other studies [1, 2, 4]. Bilen et al. state that MS have reduced LV longitudinal strain and strain rate compare to normal subject, but the reduction does not differ among groups based on the degree of MS severity [1]. Further, Ozdemir et al. found no correlation between the GLS and strain rates with either MVA or diastolic transmitral gradients [2]. All of these findings further suggest that myocardial factors affect subclinical LV dysfunction in patients with MS rather than hemodynamic factors.

In light of all the findings of our present study and other previous studies, it is suggested that the deterioration in subclinical LV function in patients with rheumatic MS could be based on myocardial factor, including endomyocardial fibrosis as a result of rheumatic process, rather than being structural adaptations in response to hemodynamic derangement.

Limitations

The potential limitation of our study was relatively small sample size and the lack of variation of the severity of the MS. All patients were in a condition which indicated for surgical intervention. So, the study did not represent an overall population of rheumatic MS. High prevalence of atrial fibrillation may probably still affect the measurements, even though care has been taken to avoid unreliable data. Age and gender [26], obesity with diabetic [27] could affect GLS. Our patients had a good BMI, none of them were obese, and diabetic was excluded. However, we did not evaluate whether age and gender would affect the correlation between GLS and LGE.

Conclusion

Several mechanisms have been proposed to explain the occurrence of LV dysfunction in rheumatic MS. Concordance with other previous studies, our study found that subclinical LV systolic dysfunction measured by GLS using STE has a moderate negative correlation with the extent of LV myocardial fibrosis quantified by LGE using CMR. This suggested that the deterioration in subclinical LV function in patients with rheumatic MS could be affected by myocardial factor, including endomyocardial fibrosis as a result of the rheumatic process. However, further studies are needed to confirm these findings.

Compliance with ethical standards

Conflict of interest All authors declare that there are no conflicts of interest.

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