Use of strain and strain rate echocardiographic imaging to predict the progression of mitral stenosis: a 5-year follow-up study

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Abstract

Objective: Little information is available about echocardiographic progression of mitral stenosis (MS). The aim of this study was to investigate whether the left ventricular (LV) strain is a favorable method predicting the progression of MS.

Methods: Forty-eight patients with isolated mild-to-moderate MS were enrolled in this prospective cohort study. LV global longitudinal strain (GLS) and strain rate (GLSR) were measured by two-dimensional echocardiography (2-DE) at the baseline. Mitral valve area (MVA) was evaluated during the 5-year follow-up. The change in MVA from the beginning to the end of the surveillance period was determined as an indicator of progression. Pearson's correlation test was used, and significant differences between the groups were analyzed using the Student's t-test or the Mann–Whitney U test. At the end of follow-up, we evaluated the correlation between the change in MVA and both GLS-GLSR. GLS and GLSR are predictive factors for MS progression, whether or not it has been tested according to the receiver operating characteristics curve analysis.

Results: A meaningful correlation was detected between the change in MVA with both GLS and GLSR (r=0.924 and r=0.980, respectively, $p<0.001$). The cut-off value for GLS was identified as –16.98 (sensitivity 81%, specificity 96%, $p<0.001$) and for GLSR as –1.45 (sensitivity 95%, specificity 100%, $p<0.001$). Patients with MS having a value under (mathematically above) these cut-off values showed more rapid progression.

Conclusion: The progression of MS can be predicted by GLS and GLSR measurements, which are evaluated via strain echocardiography. *(Anatol J Cardiol 2016; 16: 772-7)*

Keywords: mitral stenosis, rheumatic heart disease, progression, strain imaging, echocardiography

Introduction

Despite the decreasing frequency of mitral stenosis (MS) in developed countries, it is still common, especially in developing countries (1). Although there have been improvements in its diagnosis and management, MS is still leading to morbidity. After MS develops, the mean decrease of the valve area is nearly 0.1 cm^2 per year (2).

Recently, there have been some clinical studies on the incidence and progression of MS and rheumatic heart disease (3, 4). However, there are no adequate data available on which patients will see more rapid progressions. A few laboratory studies have investigated the indicators of MS progression (5, 6), and little data exist involving echocardiographic parameters leading to the deterioration of MS.

It is known that left ventricular (LV) systolic functions are generally well preserved in patients with MS (1, 7). However, some studies have shown impaired LV systolic functions in patients with pure MS (8–10). Rheumatic myocarditis, known as a myocardial factor, could be the mechanism responsible for LV dysfunction, and we also speculate that it may cause the progression of MS. However, there are no studies published investigating the relationship between the progression of MS and the LV strain which shows subclinical LV systolic dysfunction.

In this study, we aimed to evaluate the role of the LV two-dimensional (2-D) strain in predicting the progression of MS because the estimation of the progression of MS can be important to decide the frequency of control visits and to plan optimal management of the patient.

Methods

Study population

At the beginning of the study, 63 patients with mild-to-moderate isolated MS were enrolled to this prospective cohort study between January 2008 and September 2009. Twelve patients who could not come to follow-up appointments were excluded

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from the study. Three patients were also excluded during the strain analysis (Fig. 1).

A total of 48 patients were followed up in this period. This study was carried out by the Department of Cardiology at the Ankara University Faculty of Medicine. All of the patients were in sinus rhythm and have a functional capacity of New York Heart Association (NYHA) class I or II. Patients with coronary artery disease, diabetes mellitus, hypertension, atrial fibrillation/flutter, moderate-to-severe valvular disease other than MS, NYHA functional class III–IV, chronic obstructive pulmonary disease, and impaired LV systolic function [LV ejection fraction (LVEF) <50%] were excluded from the study.

The study protocols have been approved by the local Ethics Committee and were performed in accordance with the Declaration of Helsinki. All patients provided written informed consent before enrollment.

Transthoracic echocardiography was performed for each patient by a cardiologist (A.O.), and strain analyses were obtained. All echocardiographic parameters were re-evaluated by the same cardiologist after 5 years. The strain analysis using speckle tracking echocardiography was performed just once at the beginning of the study due to the lack of a software system in the EchoLab. Serial 2-D and Doppler echocardiography were obtained, and the mitral valve area (MVA) was calculated by the same cardiologist during a 5-year follow-up. The change in MVA (cm^2) from the beginning to the end of the surveillance period was determined as the indicator of progression. More changes in MVA were considered to show a more rapid deterioration. The patients were separated into groups according to this parameter, and at the end of the follow-up period, we evaluated the correlation of the change in MVA with both global longitudinal strain (GLS) and global longitudinal strain rate (GLSR).

Echocardiographic analysis

A transthoracic echocardiographic examination was carried out using GE Vivid 7 (GE, Horten, Norway) with a 3.5-MHz transducer. Standard parasternal long- and short-axis views and apical two- and four-chamber views were recorded for all patients. The LV dimension, interventricular wall thickness (IVS), LV posterior wall (PW) thickness, and left atrial (LA) diameters were measured by the cardiologist from the M-mode images in a parasternal long-axis view (11). Continuous wave Doppler technique was used to record peak tricuspid regurgitant velocities, and then estimated systolic pulmonary artery pressure (PAP) was calculated using modified Bernoulli equation. The modified Simpson's method was used by the same cardiologist to calculate LVEF on apical four-chamber views (12). The planimetric and pressure half-time method was used to estimate MVA, and the mean value of these two measurements was determined as the final MVA. Continuous wave Doppler echocardiography was performed to calculate the maximum and mean transmitral gradients.

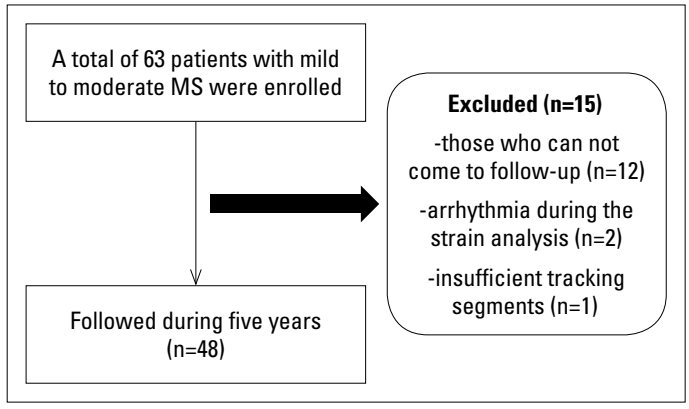

Figure 1. Flow diagram of patients. The diagram includes detailed information on the excluded patients

Longitudinal 2-D strain and strain rate analysis

GLS echocardiography images were obtained by a cardiologist (A.O.) from standard apical four-chamber, three-chamber, and two-chamber views of LV from the apex. Three stable cardiac cycles were recorded for each view and all data were sent to a work station using a software system (EchoPAC PC, GE Ultrasound, Waukesha, Wisconsin, USA) for further offline analysis. Two patients who had some rhythm disturbances were excluded. The frame rates used for GLS analysis were 60–80 frames/s. The system used the conventional 2-D grayscale echocardiographic images, and the activity of the speckles was tracked throughout the myocardial tissue. The regions of interest (ROIs) were manually outlined by marking the endocardial borders at the mitral annulus level and at the apex of each digital loop. The software system generated the epicardial surface automatically. ROI was corrected manually, if necessary. After any manual adjustment, ROI was divided into six segments. Each segment was scored automatically by the software according to the image quality. Whether the tracking quality for each segment could be considered acceptable or not was determined by the software. If the automatically obtained tracking segments were sufficient for analysis, the software system read each region; insufficient tracking segments were automatically excluded for one patient, and the investigator corrected the contour manually to achieve optimal tracking. The peak systolic strain values in an 18-segment LV model were used in the present study. The end-systole was accepted as an aortic valve closure in the apical long-axis view. The results for all three planes were then combined in a single bulls-eye summary that provided GLS (Fig. 2). Measurements were repeated at least three times, and the average of these measurements was calculated. GLSR was measured by the same technique.

Statistical analysis

SPSS 16.0 (Statistical Package for Social Sciences) software was used for the statistical analysis. Categorical variables were expressed as percentages, whereas numeric variables were shown as arithmetic mean±standard deviation (SD). Quantita-

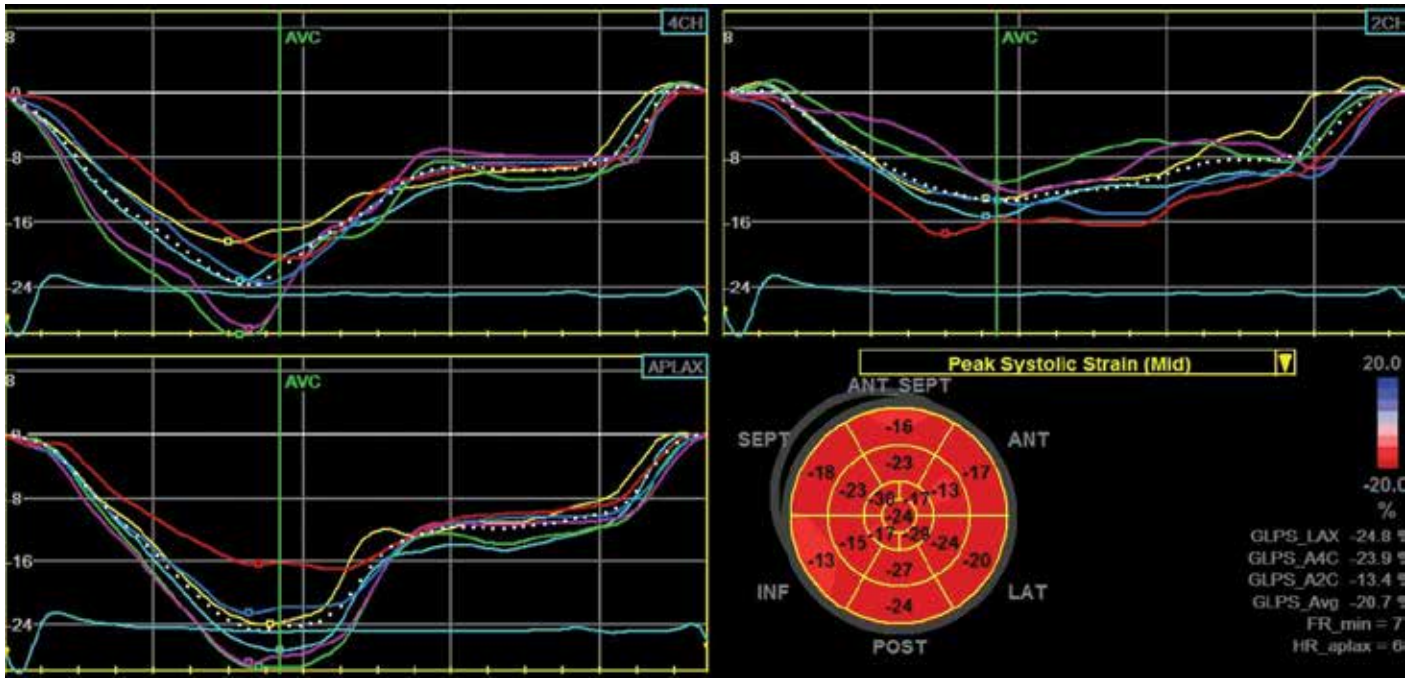

Figure 2. Assessment of LV function using Speckle-tracking echocardiography and measurement of GLS and bulls-eye image of left ventricle

tive variables with a normal distribution were evaluated by applying the one-sample Kolmogorov–Smirnov test. All numeric variables had a normal distribution. Pearson's correlation test was used to assess linear relationships between continuous variables. Significant differences between the groups for obtained measurements were analyzed using the Student's t-test or the Mann–Whitney U test. GLS and GLSR are predictive factors of progression, whether or not it has been tested according to the receiver operating characteristics (ROC) curve analysis. The cut-off value was calculated according to the Youden index for variables with hallmark. A p value <0.05 was accepted to be statistically significant.

Results

Sixty-three patients with a diagnosis of mild-to-moderate isolated MS were planned to be included in this study. However, twelve patients who could not come to follow-up visits were excluded from the study and another three patients were excluded during the strain analysis because of poor view quality. In total, 48 patients with isolated mild-to-moderate MS (83% female, mean age 40.6±4.5 years) were included in the study. These patients were followed up for 5 years. No patient died in this follow-up period. The echocardiographic parameters of the patients at baseline and 5-year follow-up are shown in Table 1.

When the echocardiographic parameters were compared between the baseline and 5-year values, significant differences were not seen in IVS, PW, LV end-diastolic diameter, LV end-systolic diameter, and LVEF. The left atrial diameter, pulmonary artery pressure (PAP), mitral valve gradient (MVG) peak, and MVG mean increased significantly (4.9±0.8 vs. 5.1±0.8, p<0.001; 36.3±9.2 vs. 42.2±11.7, p<0.001; 10.9±2.7 vs. 13.1±3.7, p<0.01; 4.7±1.3 vs. 6.4±2.3, p<0.01, respectively) at the end of the surveillance period. MVA was significantly reduced after this time (1.8±0.4 vs. 1.6±0.4, p<0.01). We found that the progression rate of MS is 0.04 cm^2/year. The GLS value was measured as –16.74±1.45, and the GLSR value as –1.39±0.13 at the initial evaluation (Table 1).

Table 1. The demographic and conventional echocardiographic characteristics of patients at baseline and 5-years later

Parameters	MS basal	MS control	*P*
IVS, cm	0.87±0.13	0.88±0.11	0.505
PW, cm	0.83±0.11	0.86±010	0.076
LVEDD, cm	4.7±0.6	4.8±0.5	0.195
LVESD, cm	3.1±0.5	3.3±0.5	0.085
LVEF, %	63±8	62±6	0.067
LA diameter, cm	4.9±0.8	5.1±0.8	<0.001
PAP, mm Hg	36.3±9.2	42.2±11.7	<0.001
MVA, cm^2	1.8±0.4	1.6±0.4	<0.01
MVG peak, mm Hg	10.9±2.7	13.1±3.7	<0.01
MVG mean, mm Hg	4.7±1.3	6.4±2.3	<0.01
GLS	-16.74±1.45	–	–
GLSR	-1.39±0.13	–	–

GLS - global longitudinal strain; GLSR - global longitudinal strain rate; IVS - interventricular septum; LA - left atrium; LV - left ventricle; LVEDD - LV end-diastolic diameter; LVEF - left ventricular ejection fraction; LVESD - LV end-systolic diameter; MVA - mitral valve area; MVG - mitral valve gradient; PAP - pulmonary artery pressure; PWT - posterior wall thickness

Our study displayed a meaningful correlation between the change in MVA with both GLS and GLSR (r=0.924 and r=0.980, respectively, p<0.001) (Fig. 3A, B). Meanwhile we did not statis-

tical analysis as separated into groups according to MVA. The statistical analysis of the relationship between the severity of MS and GLS was not performed due to the small number for our study population, and previous studies (13) have failed to display a correlation between MVA and GLS. To determine the best cut-off value for GLS in predicting the progression of MS (the change in MVA), an ROC curve analysis was used. The cut-off value for GLS was –16.98 (sensitivity 81%, specificity 96%, p<0.001), while that for GLSR was –1.45 (sensitivity 95%, specificity 100%, p<0.001). The patients with MS having a value under (mathematically above) these cut-off values showed a more rapid progression. Figure 4A, B shows the ROC curve analysis for GLS and GLSR; the area under the curve (AUC) was calculated as 0.940 and 0.973, respectively (p<0.001).

Discussion

In this representative study, we demonstrated that GLS and GLSR of LV were correlated with the progression of MS.

In our study, we found that MVA was reduced by 0.04 cm^2/year during the follow-up period. According to a study[2] performed in 1996, the mean decrease of the valve area is nearly 0.1 cm^2 per year after MS develops. On the other hand, we have not found any data on this issue in our country (Turkey). Also, we do not encounter such a fast progression in our clinical practice. We interpreted this difference to be a result of lack of new data in the literature and reduced virulence of the bacteria that caused the acute rheumatic fever over time, but there is no scientific data to support our hypothesis.

LV function in patients with MS has been investigated, and subclinical LV dysfunction was shown using speckle-tracking echocardiography in some patients with MS (13).

The possible pathophysiological mechanisms of LV dysfunction in patients with MS include abnormal motion of IVS caused by right ventricular overload, decrease of preload, elevation of afterload, and alteration of right and LV interactions (9, 14). In addition, regional wall motion abnormalities, rigidity of the mitral valve apparatus due to scarring, and generalized LV dysfunction as a result of rheumatic myocarditis, known as a myocardial factor, could be the mechanisms responsible for this situation (15, 16).

Previous studies have continuously showed that both myocardial and mechanical factors play important roles in the reduction of LV systolic function in patients with MS (14, 15).

Strain is a measure of myocardial fiber shortening, and strain rate measures the velocity of deformation. These two methods

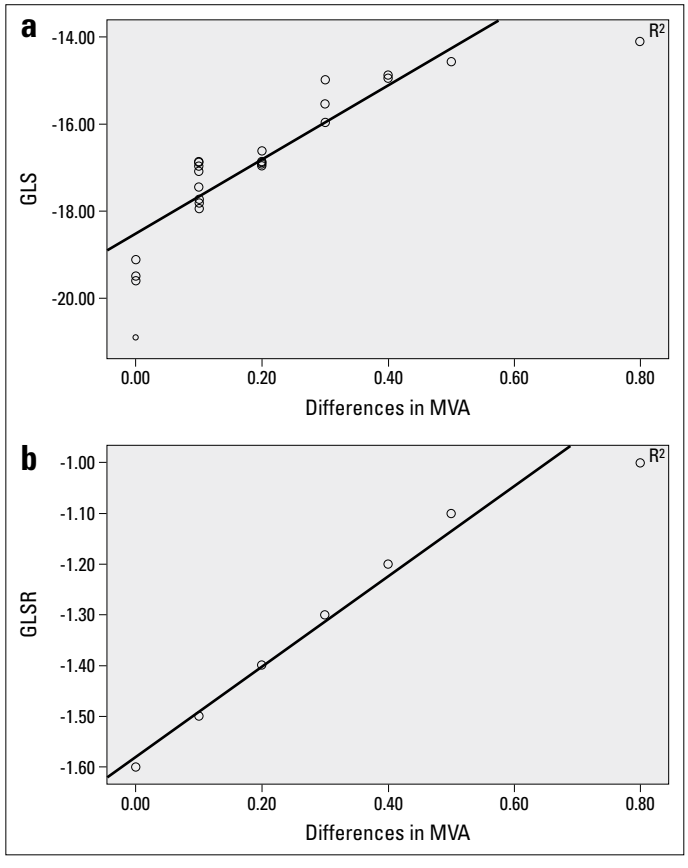

Figure 3. The patients were grouped according to their valve narrowing progression. A significant correlation between the change in MVA (cm^2) with both GLS (a) and GLSR (b) is shown. GLS - global longitudinal strain; GLSR - global longitudinal strain rate; MVA - mitral valve area

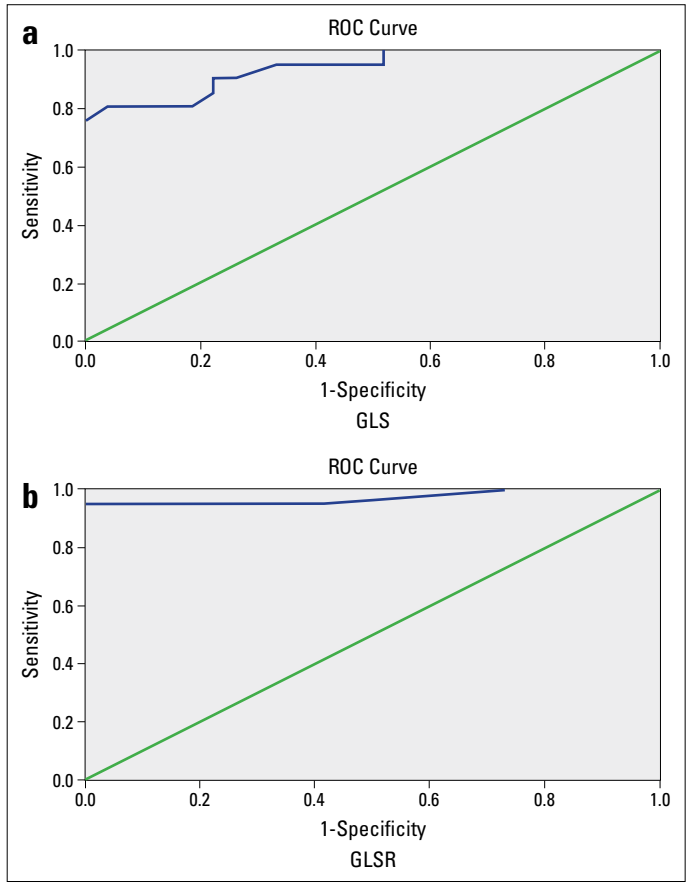

Figure 4. (a) Receiver operating characteristic curves for GLS (AUC 0.940, 95% CI 0.813–0.980, p<0.001). (b) Receiver operating characteristic curves for GLSR (AUC 0.973, 95% CI 0.881–0.980, p<0.001).

are complementary for assessing LV function (17, 18). Additionally, 2-D strain is a simple and readily available method to assess systolic strain from standard 2-D images. Therefore, 2-D strain imaging may be used to detect subclinical heart disease. Furthermore, 2-D strain demonstrated that GLS and GLSR are reduced in patients with MS from those in normal subjects—evidence of subclinical LV dysfunction, which was interpreted as a rheumatic myocardial factor (19).

A biopsy study proved the impact of this myocardial factor on subclinical LV dysfunction in patients with pure rheumatic MS (20). The reduction of myofilaments, degeneration of myofibrils, disarray, and reduction of myofibrils were shown to different degrees in all patients (20).

In a biopsy study conducted by Dörtlemez (21) in our country, 30 patients with pure MS were evaluated with biopsy of LV during the operation. There was no rheumatic activity according to the clinical and laboratory findings in these patients during that time. Histopathological changes in the LV myocardium were detected in 60% of the patients.

The abovementioned studies (19–21) indicate that the influence of rheumatic myocarditis (myocardial factor) on subclinical LV dysfunction is significant in patients with MS.

Despite the innovations in imaging of the mitral valve, echocardiographic evaluation is still the primary imaging modality in diagnose and follow-up (22, 23). Strain analysis can be easily done during the echocardiographic examination.

We have shown previously that GLS and GLSR for LV were markedly impaired in patients with MS compared to those in normal subjects (13). In this study, MS patients with lower GLS and GLSR values at the baseline experienced a more rapid progression over time. According to these results, we can speculate that rheumatic carditis can lead to a decrease of normal myocardial cells. Fibrosis and calcification can be substitute its place as a result of rheumatic process, but we do not have histopathological data to prove this.

This suggests myocardial involvement in disease progression. To the best of our knowledge, this study is the only one using strain echocardiography to estimate the progression of MS. Our study revealed GLS and GLSR in MS patients may be used to predict the progression of the disorder. There are currently no studies published on the prediction of the progression of MS.

Study limitations

A limited number of patients was included in the study. This study was conducted in a single center. We did not evaluate the patients hemodynamically. We do not have histopathological data showing the myocardial involvement. Patients with severe MS were not included this study because of the risk of long-term follow-up without intervention. We did not have a control group in our study and we have no strain data in the fifth year. We performed neither circumferential nor radial strain analyses.

Conclusions

GLS and GLSR measurements of LV can be used to estimate the progression of rheumatic MS. The cut-off value for GLS was identified as –16.98, while for GLSR, this was identified as –1.45. The patients with MS who had a value under these cut-off values showed a more rapid progression. However, further studies are needed to validate our findings.

Conflict of interest: None declared.

Peer-review: Externally peer-reviewed.

Authorship contributions: Concept – C.T.K., A.O.; Design – C.T.K., A.O.; Supervision – Ç.E., A.O.; Data collection&/or processing – N.Ö., A.A.; Analysis and/or interpretation – D.M.G.; Literature search – A.A.; Writing – D.M.G.; Critical review – C.T.K.

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