Severity of Mitral Stenosis and Left Ventricular Mechanics: A Speckle Tracking Study

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Key Words

Echocardiography · Left ventricular function · Mitral stenosis

Abstract

Background: It has been shown that mitral stenosis (MS) impairs left ventricular (LV) systolic function; however, this issue has not been studied comprehensively. We aimed to evaluate the role of 2D strain in the assessment of subclinical LV systolic dysfunction in patients with MS. **Methods:** Seventy-two patients with isolated MS (mild, moderate and severe) and 31 healthy control subjects constituted the study population. 2D echocardiography images were obtained from LV apical 4-chamber (4C), long axis (LAX), and 2-chamber (2C) views. Peak longitudinal strain and strain rate (Sr) were obtained from 4C, LAX, and 2C views. Global strain and Sr were calculated by averaging the three apical views. **Results:** There were no significant differences in LV ejection fraction and LV systolic or diastolic dimensions between the groups. Patients with MS had significantly lower LV longitudinal strain and Sr measurements than the control group. In addition, there were no significant differences in MS subgroups with respect to LV strain and Sr measurements. **Conclusion:** We demonstrated that patients with MS had lower LV func-

tions using 2D strain imaging, and this is independent of the hemodynamic severity of MS. In the detection of subclinical LV dysfunction in patients with MS, 2D strain imaging appears to be useful.

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Introduction

Although there is a downward trend in the prevalence of mitral stenosis (MS) in developed countries, it stands out as a huge public health problem in developing countries [1–3]. It is accepted that isolated MS does not impair left ventricular (LV) systolic function [3], but in some publications it has been shown that MS impairs LV systolic function [4–6]. In the assessment of LV systolic function, a number of imaging techniques – such as echocardiography, MRI, scintigraphy and CT – have been used [7–9]. In the echocardiographical assessment of LV function, the ejection fraction (EF), tissue Doppler imaging (TDI), Doppler strain, and 2D strain have been widely used [10–12]. EF is the most widely used index of contractile function, but due to the visual component, assessment of endocardial excursion is subjective and has high interobserver variability [13]. TDI and Doppler strain are

characterized with the limitations of angle dependence, limited spatial resolution, and deformation analysis in one dimension [10]. 2D strain is a novel technique which evaluates LV systolic functions more objectively and quantitatively, and does not have the limitations seen in EF, TDI, and Doppler strain; thus, it has become more commonly used in recent years [11, 12]. In the diagnosis of LV dysfunction due to MS, some studies have shown EF, TDI, and Doppler strain to be useful [14–17]. However, studies related to the use of 2D strain, a more objective technique in the diagnosis of LV systolic function in MS, are very limited [18]. In this study, we aimed to evaluate the role of 2D strain in the assessment of subclinical LV systolic dysfunction and the relationship between stenosis severity and LV dysfunction in patients with MS.

Methods

Study Population

In our study, 72 patients with isolated MS and 31 healthy control subjects (group 1) constituted the study population. The 72 patients with MS were classified as those with mild MS (36 patients, group 2), moderate MS (24 patients, group 3), and severe MS (12 patients, group 4). Patients with hypertension, diabetes mellitus, atrial fibrillation, atrioventricular conduction anomalies, moderate to severe valvular heart diseases other than MS, chronic obstructive pulmonary disease, segmental wall motion abnormalities, impaired LV systolic function ($EF \leq 50\%$), and history of coronary artery disease were excluded from the study. Written informed consent was obtained from the patients, and the study was approved by the institutional review board.

Echocardiographic Measurements

All patients underwent an echocardiographic examination using the GE Vivid 7 system (GE Vingmed Ultrasound AS, Horten, Norway) with a 3.5-MHz transducer. All data were transferred to a workstation for further offline analysis (EchoPAC PC; GE Vingmed Ultrasound AS). LV-EF was calculated using the Simpson's formula from measurement of end-diastolic and end-systolic volumes on apical 4-chamber views [19]. Left atrium posterior-anterior dimension was measured from the parasternal long axis (LAX) view. Pulmonary artery pressure (PAP) was measured from the apical 4-chamber view and was derived from the tricuspid regurgitant jet velocity using the simplified Bernoulli equation assuming a right atrial pressure of 10 mm Hg. Conventional stenotic indices, such as planimetric mitral valve area (MVA-pln), were calculated by pressure half time (MVA-pht); maximum and mean mitral valve pressure gradient (maximum and mean MVPG) were measured as previously described [20]. MS severity is based on a variety of hemodynamic data, using mean MVPG, systolic PAP, and valve area as follows: mild (area $>1.5 \text{ cm}^2$, mean MVPG $<5 \text{ mm Hg}$, or systolic PAP $<30 \text{ mm Hg}$), moderate (area $1.0\text{--}1.5 \text{ cm}^2$, mean MVPG $5\text{--}10 \text{ mm Hg}$, or systolic PAP $30\text{--}50 \text{ mm Hg}$), and severe (area $<1.0 \text{ cm}^2$, mean MVPG $>10 \text{ mm Hg}$, or systolic PAP $>50 \text{ mm Hg}$). Mitral valve Wilkins score was mea-

sured as described by Wilkins et al. [21]. All images were evaluated by two experienced cardiologists (M.K., I.H.T.) who were blinded to the patients' clinical characteristics.

Two-Dimensional Echocardiography

2D echocardiography images were obtained from LV apical 4-chamber (4C), LAX (long axis) and 2-chamber (2C) views. All images were obtained during breath hold, and stored in cine-loop format from three consecutive beats. The frame rate for images was between 50 and 90 frames/s. All data were transferred to a workstation for further offline analysis. After defining the endocardial border manually, an epicardial tracing was automatically developed by the software system for each view. If the automatically obtained tracking segments were adequate for analysis, the software system was allowed to read the data, whereas analytically inadequate tracking segments were either corrected manually or excluded from the analysis. Strain measurements were reported as the peak longitudinal strain (LS) for 4C, LAX, and 2C views, and global strain (GS) was calculated by averaging the three apical views (fig. 1). Strain rate (Sr) measurements were reported as the peak Sr for 4C, LAX, 2C views and global strain rate (GSr) was calculated by averaging the three apical views (fig. 2).

Statistical Analysis

Continuous variables are expressed as means $\pm$ SD. The level of significance was 0.05. The Kolmogorov-Smirnov test was used for the normality test of all variables. To compare parametric continuous variables, Independent Student's t test or one-way ANOVA were used; for non-parametric variables the Mann-Whitney U or Kruskal-Wallis tests were used. For categorical variables, the χ^2 test was used. Correlations between variables were tested by Pearson or Spearman correlation tests where appropriate. For inter-observer variability for 2D strain parameters, Bland-Altman analysis was used. Statistical analyses were performed using SPSS (SPSS Inc., Chicago, Ill., USA) version 15.0 for Windows.

Results

The study population consisted of 103 patients (age 40.9 ± 8.3 years, 75.7% female). There were no significant differences between MS patients and control subjects regarding age and gender. The other clinical and echocardiographic characteristics are shown in table 1. There were no significant differences in LV-EF and LV systolic/diastolic dimensions between the groups. Systolic PAP increased significantly from group 1 through to group 4. The median New York Heart Association (NYHA) class of group 3 and 4 was significantly higher than that of group 1 and 2.

In the analysis carried out between control subjects and MS groups, LV-GS, 4C-LS, LAX-LS, and 2C-LS values were found to be significantly lower in the patients' group. In addition, all Sr values other than LV-LAX-Sr were found to be significantly lower in patients with MS than control subjects (table 2; fig. 3a).

Fig. 1. Apical 4C-LS measurement.

Fig. 2. Apical 4C-Sr measurement.

Table 1. Clinical and echocardiographic features according to severity

	Group 1 (n = 31)	Group 2 (n = 36)	Group 3 (n = 24)	Group 4 (n = 12)	p value
Age, years	39.2 ± 7.8	43.3 ± 9.8	40.3 ± 7.1	39.6 ± 6.1	n.s.
Female/male	26/5	27/9	16/8	9/3	n.s.
Ejection fraction, %	64 ± 2.5	64.7 ± 2.3	63.8 ± 2.52	62.8 ± 2.0	n.s.
PAPs, mm Hg	20 ± 3.8	34.7 ± 5.4	42.1 ± 6.4	49.1 ± 5.9	<0.01 ^a
MVA-pln, cm ²	–	2.1 ± 0.29	1.3 ± 0.17	0.86 ± 0.08	<0.001 ^a
Maximum gradient, mm Hg	–	10.4 ± 3.9	17.3 ± 5.5	25.5 ± 4.0	<0.001 ^a
Mean gradient, mm Hg	–	4.8 ± 2.2	9.0 ± 3.4	14 ± 2.0	<0.001 ^a
Left atrial diameter, cm	2.7 ± 0.3	4.1 ± 0.4	4.6 ± 0.72	4.6 ± 0.37	<0.05 ^a
NYHA (median)	1	1	2	2	<0.05
Echo score	–	5.9 ± 1.1	7.7 ± 1.6	8.1 ± 0.57	<0.001 ^{b, c}
LV end-diastolic diameter, cm	4.58 ± 0.35	4.56 ± 0.35	4.79 ± 0.36	4.6 ± 0.49	n.s.
LV end-systolic diameter, cm	2.65 ± 0.33	2.69 ± 0.31	2.75 ± 0.40	2.55 ± 0.55	n.s.
β-Blockade (no)	–	1	2	2	n.s.
Diuretic (no)	–	–	2	3	n.s.

Where indicated, data presented as means ± SD.

^a All between-group differences statistically significant. ^b Group 2 vs. 3 statistically significant. ^c Group 2 vs. 4 statistically significant.

Table 2. LV-2D strain and Sr measurements of control subjects and patients with MS

	Control (n = 31)	MS (n = 72)	p value
4C-LS, %	19.6 ± 2.5	17.0 ± 1.8	<0.001
LAX-LS, %	19.4 ± 2.2	16.8 ± 1.6	<0.001
2C-LS, %	19.7 ± 2.2	16.6 ± 1.6	<0.001
4C-Sr, s ⁻¹	1.62 ± 0.34	1.28 ± 0.38	<0.001
LAX-Sr, s ⁻¹	1.41 ± 0.26	1.27 ± 0.39	0.07
2C-Sr, s ⁻¹	1.56 ± 0.37	1.34 ± 0.41	0.01
GS, %	19.6 ± 2.0	16.8 ± 1.54	<0.001
GSr, s ⁻¹	1.53 ± 0.21	1.30 ± 2.8	<0.001

Table 3. LV-2D strain and Sr measurements of control subjects and subgroups of MS patients

	Group 1 (n = 31)	Group 2 (n = 36)	Group 3 (n = 24)	Group 4 (n = 12)	p value
4C-LS, %	19.6 ± 2.5	17.5 ± 1.91	16.9 ± 1.56	15.9 ± 1.37	<0.001 ^{a, b, f}
LAX-LS, %	19.4 ± 2.2	17.5 ± 1.48	16.3 ± 1.56	15.9 ± 1.34	<0.001 ^{a, b, f} , 0.03 ^c , 0.02 ^e
2C-LS, %	19.7 ± 2.2	17.2 ± 1.92	16.1 ± 1.1	16.2 ± 1.18	<0.001 ^{a, b, f}
4C-Sr, s ⁻¹	1.62 ± 0.34	1.34 ± 0.29	1.32 ± 0.48	1.02 ± 0.35	0.01 ^{a, b} , <0.001 ^f , 0.04 ^e
LAX-Sr, s ⁻¹	1.41 ± 0.26	1.33 ± 0.41	1.21 ± 0.26	1.22 ± 0.54	0.158
2C-Sr, s ⁻¹	1.56 ± 0.37	1.34 ± 0.46	1.32 ± 0.32	1.38 ± 0.44	0.09
GS, %	19.6 ± 2.0	17.4 ± 1.66	16.4 ± 1.19	16.0 ± 1.18	<0.001 ^{a, b, f}
GSr, s ⁻¹	1.53 ± 0.21	1.34 ± 0.25	1.28 ± 0.25	1.21 ± 0.37	0.01 ^a , 0.002 ^f , 0.004 ^b

^a Group 1 vs. 2; ^b group 1 vs. 3; ^c group 2 vs. 3; ^d group 3 vs. 4; ^e group 2 vs. 4; ^f group 1 vs. 4.

Fig. 3. Comparison of LV-GS and LV-GSr values between patients with MS vs. control subjects (a) and between subgroups of MS patients vs. control subjects (b).

Table 4. Correlations between GS and GSr values and echocardiographic parameters

	GS		GSr	
	r	p	r	p
MVA-pln	0.30	0.008	0.22	0.05
PAPs	-0.32	0.005	0.01	0.40
Left atrial diameter	-0.10	0.37	-0.10	0.37
Mean gradient	-0.26	0.03	0.01	0.98
Maximum gradient	-0.24	0.04	0.05	0.65
Echo score	-0.04	0.69	0.11	0.33
Ejection fraction	0.40	0.001	0.40	0.001

In the analysis carried out with respect to the severity of MS and considering the values of LV-GS, 4C-LS, LAX-LS, and 2C-LS, it was observed that while group 1 had significantly higher values than the other groups, there were not any significant differences between group 2, group 3, and group 4 except for LV-LAX-LS values of group 2, and these values were significantly higher than those of group 3 and group 4 (table 3; fig. 3b).

In the analysis carried out according to the severity of MS for the values LV-GSr, 4C-Sr, LAX-Sr, and 2C-Sr, it was noted that while group 1 had significantly higher values than the other groups, there were not any significant differences between group 2, group 3, and group 4 (table 3; fig. 3b).

In the correlation analysis, there was a moderate correlation between LV-GS with MS indexes (MVA-pln, mean and maximum gradients). No correlation was found

between LV-GSr with either left atrial diameter or echo scores. While there was a moderate correlation between LV-GSr with MVA-pln and EF, there was no correlation between the other parameters. (table 4; fig. 4 and 5).

Bland-Altman analysis showed that inter-observer agreement was high.

Discussion

Our study results indicate that patients with MS had significantly lower measurements of both LV strain and Sr when compared with healthy subjects. Furthermore, both LV strain and Sr measurements did not change as the severity of MS increased. LV-GS values were more closely correlated with both PAPs and conventional mitral stenotic indices than LV-GSr values.

In recent years, 2D strain imaging has increasingly been used in the assessment of global ventricular function. Being angle-independent, reproducible, and able to provide quantitative data further increases the utility of 2D strain imaging in evaluation of ventricular functions in clinical settings [11, 12, 22]. In a number of studies, the superiority of 2D strain over TDI and Doppler strain in the assessment of LV regional and global functions has been shown. Examples include ischemic/non-ischemic cardiomyopathy [23] and hypertrophic cardiomyopathy [24]. However, there is only one 2D strain imaging study in the literature related to MS [18].

The existence of LV dysfunction in a quarter of patients with MS has been shown in many studies [4–6, 25]. Many hemodynamic and myocardial factors have been

Fig. 4. Correlation between LV-GS and conventional stenotic indices (MVA-pln, **a**; mean gradient, **b**) and PAPs (**c**).

Fig. 5. Correlation between LV-GSr and conventional stenotic indices (MVA-pln, **a**; mean gradient, **b**) and PAPs (**c**).

put forward regarding the LV dysfunction in MS, including reduction in LV filling, chronic myocardial inflammation, scarring of subvalvular apparatus, reduction of LV compliance and diastolic dysfunction, increased afterload, abnormal right-left septal interaction, and pulmonary hypertension [26, 27]. A study by Sengupta et al. [27] showed that mitral annular velocities measured by TDI immediately improved after percutaneous mitral

balloon valvuloplasty, but not EF, and this improvement correlated with the changes in MVA. This finding leads to the consideration that systolic dysfunction in MS depends on myocardial factors rather than hemodynamic factors. Similarly, a unique electron microscopy study in pure MS patients by Lee et al. [28] showed that regardless of LV function, varying degrees of ultrastructural pathologic changes occurred in myocardial muscle cells in all

examined specimens (myocardial factor), but these impairments did not correlate with the severity of MS. In addition, those patients with abnormal LV function always exhibited more extensive loss of myofibrils. Both of these studies have shown that LV systolic dysfunction in MS is dependent on myocardial factors rather than hemodynamic factors. In our study, we similarly found that patients with MS had lower GS and GSr values when compared with healthy subjects, but there were no significant differences between mild-moderate and advanced groups when considering the severity of MS. These results suggest that subclinical LV dysfunction in patients with MS depends on myocardial factors rather than hemodynamic factors.

Subclinical LV dysfunction related to MS has been evaluated via several different methods. Gash et al. [5] detected that ejection phase indices decreased in patients with LV dysfunction when compared with those who do not have LV dysfunction. Kurtulus et al. [14] used TDI (for the first time), Dogan et al. [17] and Simsek et al. [16] used Doppler strain, and Ozdemir et al. [18] used 2D strain imaging (for the first time) in the assessment of subclinical LV dysfunction in patients with MS. In almost all of these studies, mild and moderate MS patients were included in the studies, while the number of severe MS patients was either very small or excluded. To the best of our knowledge, this study is the first in the literature that includes severe MS patients and has carried out a subgroup analysis. In the analysis, it was observed that subclinical LV dysfunction evaluated by GS and GSr was

not related to the severity of MS. In the correlation analysis, we found out that there was a moderate correlation between GS and conventional stenotic indices and correlation was moderate only between GSr and MVA. The fact that the number of patients with severe MS was relatively low ($n = 12$) may affect the generalization of the results of this study in a negative way.

Limitations

The most important limitation of our present study is the relatively small sample size, particularly in the severe MS group, so the results of this group may not be generalized. However, this study is the only one that includes such a high number of patients with severe MS in the literature. In addition, Doppler strain and segmentary 2D strain analysis were not carried out, and short axis images were not recorded.

Conclusion

In conclusion, when compared with healthy subjects, patients with MS had lower LV functions using 2D strain and Sr analysis, and this was independent of the hemodynamic severity of the obstruction. The most probable reason for this finding is rheumatic myocardial involvement or so-called myocardial factor. In the detection of subclinical LV dysfunction in patients with MS, 2D strain imaging appears to be useful.

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