Early Impairment Left Ventricular Mechanics in Children With Mitral Valve Prolapse

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Early impairment of left ventricular (LV) function has been reported in some inherited connective tissue diseases such as Marfan syndrome or rheumatic heart disease in pediatric patients. However, there is no study about cardiac strain in pediatric patients with primary mitral valve prolapse (MVP). The aim of this study was to evaluate the LV functions in pediatric patients with primary MVP, mild or moderate mitral regurgitation (MR), and normal LV ejection fraction. The study group included 72 consecutive patients (40 female, mean age: 13.1 ± 5.2 with primary MVP who had mild or moderate MR, and normal systolic function (LV ejection fraction ≥60%) were compared with 40 healthy children using conventional echocardiography, tissue Doppler imaging, and 2-dimensional speckle tracking echocardiography. Patients were divided into subgroups according to the MR severity: mild (n:34), and moderate (n:38) and leaflet thickness: classical (n: 40), and nonclassical (n: 32). The children with MR had significantly lower values for global early diastolic strain rate ([SRe] patients: 1.40 ± 0.25 vs controls: 1.62 ± 0.54; p = 0.001), and E/SRe (patients: 72.7 ± 5.6 vs controls: 62.1 ± 4.9; p <0.04) when compared with the control group. In subgroup analysis, SRe (mild: 1.49 ± 0.38 vs moderate: 1.32 ± 0.31; p <0.001) was lower in MVP patients with moderate MR compared to mild MR, and E/SRe (mild: 69.4 ± 5.1 vs moderate: 75.1 ± 6.4; p <0.001) value was higher in MVP patients with moderate MR compared to mild MR. Diatolic strain parameters, SRe, and E/SRe are more sensitive markers of early subtle myocardial injury in pediatric patients with primary MVP. **(Am J Cardiol 2019;123:1992−1998)**

Mitral valve prolapse (MVP) occurs in 5% of the healthy pediatric population and is the most common cardiac diagnosis in childhood.[1] In the case of asymptomatic patients with signs of ventricular remodeling, surgery is recommended by current guidelines.[2] Generally, 2-dimensional echocardiography, color flow, and Doppler parameters using the proximal isovelocity surface area are the recommended approach to quantify ventricular remodelling.[3] However, this approach has been shown to have lower accuracy in the presence of noncircular effective regurgitant orifice area, and eccentric, multiple, or late-systolic jets are common conditions in patients with mitral regurgitation (MR).[3] Moreover, the interobserver reproducibility of these indices to distinguish severe from nonsevere MR is <50%.[4] In these instances, cardiac magnetic resonance imaging can play a useful role. However, it has some limitations like not being widely available and being expensive. Speckle tracking echocardiography (STE) is a relatively new echocardiographic technique which is useful for assessing the early changes in regional and global systolic and diastolic myocardial function in children.[5] The aim of this study is to assess the ability of the subtle differences in left ventricular (LV) strain models to characterize subclinical LV dysfunction in children with mild to moderate MVP.

Methods

The study group included asymptomatic 66 consecutive patients aged <18 years with primary MVP and MR but with normal systolic function (LV ejection fraction [EF] ≥60%) who were selected at the pediatric cardiology clinic of University Hospital. The severity of MR was defined using the echocardiography using the latest guideline.[6] Patients who had technically inadequate STE recordings, severe MR or concomitant another valve regurgitation, LVEF under 60%, suspected rheumatic heart disease, arrhythmia, heritable disorders of the connective tissue, genetic diseases, and undergone cardiac surgery for whatever reason were excluded from the study. The control group was recruited from the local population. They were referred to pediatric cardiology clinics for evaluation of an innocent murmur with no cardiac abnormality by clinical evaluation and echocardiography. They were examined by the same pediatric cardiologist; and the participants who had normal ECG and normal standard echocardiography findings were included in the study. The study was conducted in accordance with the Declaration of Helsinki, and was approved by the local ethics committee (Ethical Approval number: 2017/52). All parents gave their informed consent forms.

The patient and control groups were evaluated with 2D standard transthoracic echocardiography using the same echocardiography device (Vivid E7 dimension, GE Healthcare, Norway) in standard precordial positions.[7] MVP was evaluated from the parasternal long axis view. The patients were divided into subgroups according to the MR severity (mild or moderate) and leaflet thickness (classical or nonclassical MVP). The severity of MR detected by color

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Doppler were defined as mild, moderate, and severe when the length of the jet was >1.5 cm, 1.5 to 2.9 cm, and >3 cm, respectively.[8,9] Thickening of the mitral leaflets >5 mm and leaflet displacement >2 mm indicated classic MVP and nonclassical MVP if leaflet thickness was lower than 5 mm. The samples were stored (EchoPAC software products 12.1; GE Vingmed Ultrasound AS), and digital images were analyzed offline by an investigator who was blinded to the medical diagnosis. All of the LV volumes and EF were measured using the Simpson Method. LV end-systolic diameter (LVIDs), LV posterior wall diameter, LV end-diastolic diameter (LVIDd), and left atrial diameter (LAd) (mm) were measured and adjusted to body surface area of the children.

During diastole, using pulsed-wave Doppler at the tips of mitral leaflets, the early mitral inflow (E), late mitral inflow (A) peak velocities, and the deceleration time of the E-wave were measured as previously reported.[10] The early diastolic (E'-wave) and late diastolic (A'-wave) velocities were measured at the lateral parts of the mitral annuli on the apical 4-chamber views. Gray images were obtained from apical 4-chamber, 3-chamber, 2-chamber, and parasternal short-axis (level of the papillary muscle) views based on the recommendations of the current guideline.[11] Under ECG monitoring, and at a frame rate of 60 to 100 frames/s, the images were acquired digitally and were stored. The images were randomized with special numbers in a single-blinded way, and were subsequently analyzed completely blinded for clinical datum. The endomyocardial borders of the LV were marked manually at the end of systole. Epicardial marking was performed by the computer automatically. The records were verified in real-time, and were corrected manually when optimal tracking was needed. Longitudinal, transverse, and radial strain and strain rates (SRs) were assessed from 6 basal and 6 midventricular segments of the LV included apical, mid, and basal segments of the LV; and anterior, septal, and inferior segments at the short-axis view of the LV. Global systolic strain (GS), global systolic SR, global early diastolic SR (SRe) and late diastolic SR, Peak basal and apical rotation, peak LV twist, and peak LV torsion were automatically calculated as the averaged value of all 17 segments. The ratio of early mitral inflow velocity to global SRe (E/SRe) was computed as the E velocity divided by the global SRe value.

Numerical values are expressed as mean ± standard deviation, and categorical data are given as percentages. SPSS 22.0 was used for the statistical analysis. The Kolmogorov−Smirnov test was used to determine whether the data were distributed normally. The unpaired student's t test was used to compare the means of normally distributed data, whereas the Mann-Whitney U test was used for non-normal distributions. Correlations in the quantitative data were analyzed using Pearson's correlation test. The results are given with a 95% confidence interval, and are considered significant at $p < 0.05$. Multivariable linear regression analyses were performed to assess the relation between

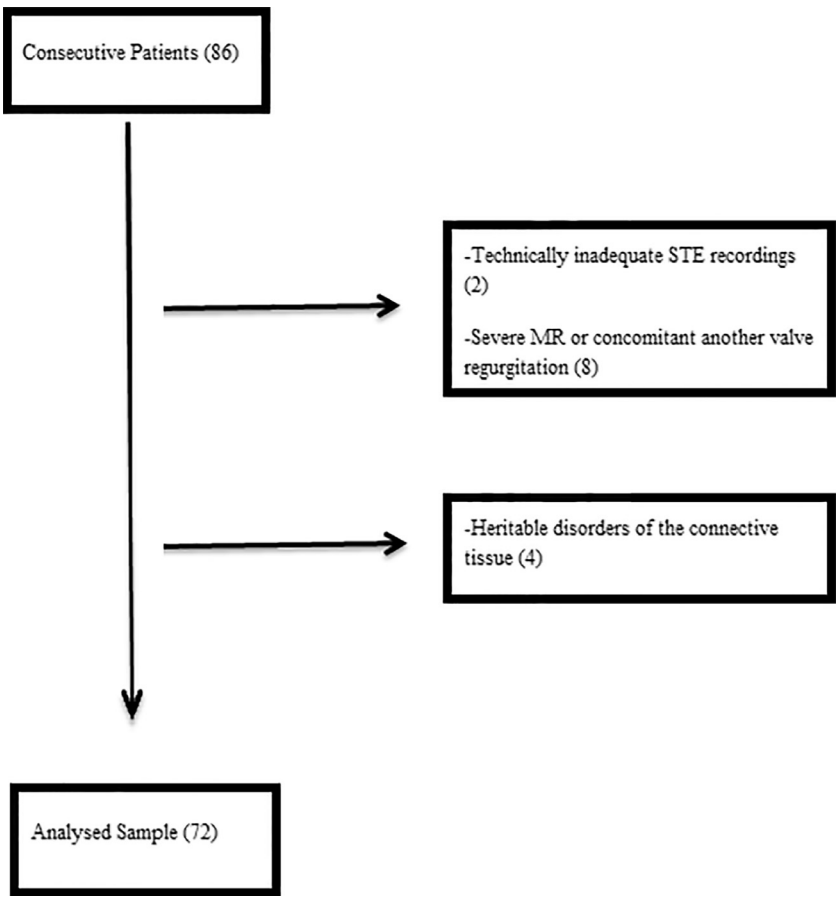

Figure 1. Patient selection flow chart. The final study population consisted of selected patients who were scanned by standard echocardiography.

independent variables, including thickening of the mitral leaflets, severity of MR, age, BMI, LVM, LV, LAd, IVRT, Mitral E, Mitral A, E/A, E/E' ratios with dependent variables, including strain, SRs, E, E/SRe ratio, twist, and torsion measures.

Results

In the initial sample of 86 patients, 2 were excluded because of technically inadequate STE recordings, 8 patients had severe MR or concomitant another valve regurgitation, and 4 had heritable disorders of the connective tissue (Figure 1). The study included 72 patients, of whom 44 (61 %) were girls. Clinical, demographic results of subjects are listed in Table 1. There was no statistically significant difference between the groups with respect to age, gender, weight, height, BMI, and office blood pressures (Table 1). Sixty-two MVP patients had auscultatory findings, 52 of them had midsystolic click, and 10 of them had no murmur. In the study group, in 72 patients with MVP, 34 patients had mild MR, 38 patients had moderate MR. Forty patients had prolapse of anterior leaflet, 14 had prolapse of posterior leaflet, and 18 had prolapse of both leaflets. None of the patients with MVP and control subjects had LV systolic or diastolic diameter >95th percentile or EF <5th percentile (Figure 2). LV dimensions, systolic, and diastolic functions of LV are shown in Table 2. In the assessment of LV dimensions adjusted to the body surface area, the patients with moderate MR had significantly higher LAd, LVIDd, and Mitral E/E' ratio and lower Mitral E/A ratio compared to the mild MR and control groups. There was no significant difference for standard 2-dimensional and Doppler parameter between mild MR and control groups. In patients with MVP, mitral leaflet thickness had no correlation to LAd, LV systolic, and diastolic dimensions ($p > 0.05$).

In comparison with controls, global longitudinal strain (GLS) parameters of the LV were not significantly different between patients with MVP and controls (Figure 2). Also, there was no significant difference for GS, SRs, and late diastolic values according to MR severity (Table 3). However, patients with MVP showed significantly lower values for global SRe (MVP: 1.40 ± 0.25 vs control: 1.62 ± 0.54; $p < 0.001$) and higher values for E/SRe (MVP: 72.7 ± 5.6 vs control: 62.1 ± 4.9; $p < 0.001$) when compared with the controls. In subgroup analysis, SRe (mild: 1.49 ± 0.38 vs moderate: 1.31 ± 0.24; $p < 0.001$) was lower in MVP patients with moderate MR compared to mild MR, and E/SRe (mild: 69.4 ± 5.1 vs moderate: 75.1 ± 6.4; $p < 0.001$) value was higher in MVP patients with moderate MR compared to mild MR (Figure 3). In the multivariate analysis, increased LAd, LVIDd, and Mitral E/E' ratio and decreased Mitral E and Mitral E/A ratio were independently associated with decreased SRe. E/SRe correlated positively with LAd, LVIDd, Mitral E and E/E' ratio (Table 4). No significant difference was found between classical and nonclassical MVP subgroups in terms of strain parameters ($p > 0.05$). LV twist and torsion showed no statistically significant difference between the patients with MVP and controls. Also, according to the severity of MR and thickening

Table 1
Demographic characteristics of the groups

	MVP (n = 72)	Control (n = 40)	p value
Age (years)	13.1 ± 5.2	12.8 ± 3.1	0.44
Gender (Female/Male)	44 F/28 M	23 F/17 M	0.48
Height (cm)	155.1 ± 14.4	150.3 ± 12.1	0.35
Weight (kg)	40.1 ± 4.2	45.4 ± 7.6	0.24
BMI (kg/m2)	20.2 ± 1.8	22.9 ± 2.5	0.36
Office Systolic blood pressure (mmHg)	104 ± 12.6	105 ± 12.4	0.80
Office Diastolic blood pressure (mmHg)	63.4 ± 2.1	68.6 ± 4.5	0.25

Values are expressed as mean ± standard deviation.

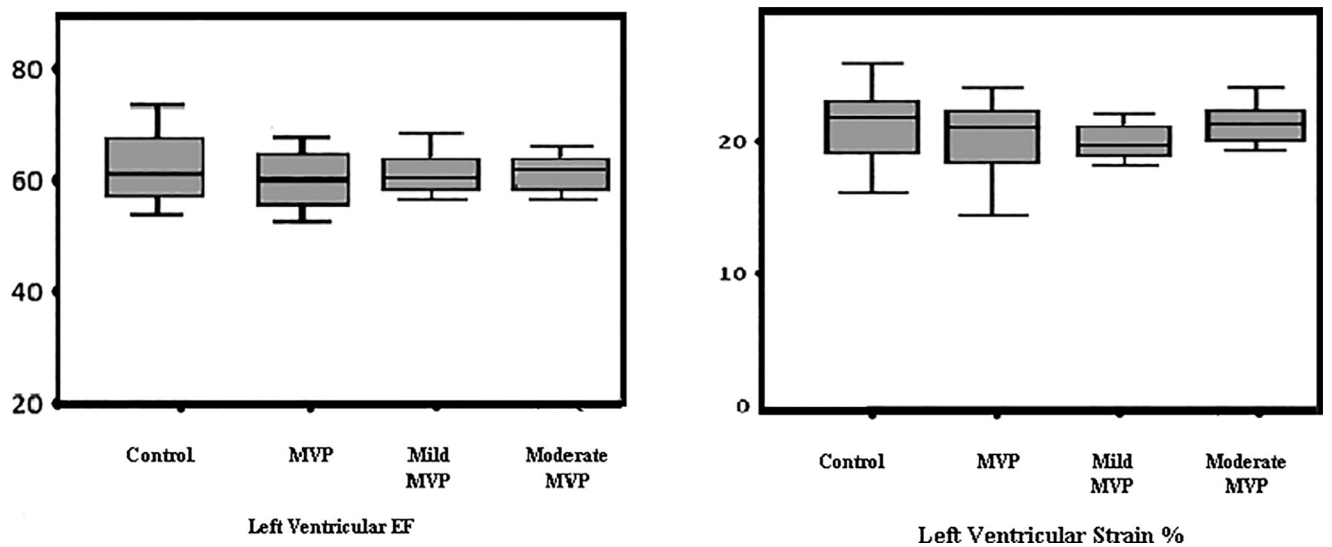

Figure 2. The children with MVP showed similar values of ejection fraction and global strain as compared to controls and each others. MVP = mitral valve prolapse.

Table 2
Echocardiographic measurements of groups and subgroups according to mitral regurgitation severity

	Groups			MR severity		
	MVP (n = 72)	Control (n = 40)	p value	Mild (n = 34)	Moderate (n = 38)	p value
EF (%)	61.4 ± 3.6	62.1 ± 3.1	0.40	61.0 ± 2.8	62.44 ± 2.6	0.52
FS (%)	30.9 ± 2.1	31.1 ± 2.6	0.24	30.7 ± 2.6	31.8 ± 1.9	0.63
IVSd (mm/m^2)	6.4 ± 1.2	6.0 ± 1.4	0.08	6.4 ± 1.3	6.5 ± 1.3	0.82
LVIDs (mm/m^2)	21.1 ± 4.3	20.6 ± 4.1	0.10	21.0 ± 3.2	21.4 ± 3.3	0.58
LVIDd (mm/m^2)	34.4 ± 6.1	32.9 ± 3.4	0.24	32.9 ± 5.2	39.1 ± 7.2*,†	0.01
LPWD (mm/m^2)	4.9 ± 0.8	4.6 ± 0.7	0.06	4.7 ± 0.8	5.1 ± 1.1*,†	0.04
LVMI (g/m 2.7)	43.44 ± 9.11	42.11 ± 7.87	0.21	43.17 ± 7.9	43.51 ± 9.1	0.62
Mitral E (m/s)	0.95 ± 0.14	1.01 ± 0.19	0.12	0.99 ± 0.10	0.91 ± 0.09*,†	0.02
Mitral A (m/s)	0.57 ± 0.12	0.54 ± 0.09	0.52	0.56 ± 0.05	0.59 ± 0.13	0.20
Mitral E/A	1.66 ± 0.39	1.68 ± 0.41	0.14	1.64 ± 0.32	1.58 ± 0.28*,†	0.03
E/E'	9.3 ± 2.1	9.2 ± 2.5	0.09	9.1 ± 1.9	10.8 ± 3.5*,†	0.01
DT (ms)	140.4 ± 27.1	140.1 ± 24.16	0.72	140.2 ± 28.6	140.8 ± 24.85	0.64
IVRT (ms)	62.1± 13.1	65.7 ± 16.3	0.48	61.7 ± 15.1	63.6 ± 16.8	0.09
LAd (mm/m^2)	22.6 ± 6.0	20.8 ± 4.4	0.04	20.9 ± 5.8	25.2 ± 6.2*,†	0.01

A = late mitral inflow; E = early mitral inflow (E); E/A = mitral E/A ratio; E' = average peak early diastolic longitudinal mitral annular velocity; EF = ejection fraction; DT = mitral deceleration time; IVSd = end-diastolic interventricular septum; IVRT = isovolumic relaxation time; LAd = left atrial diameter; LVIDd = end-diastolic left ventricular internal diameter; LVIDs = end-systolic left ventricular internal diameter; LVMI = left ventricular mass index; LVPWd = end-diastolic left ventricular posterior wall.

Values are expressed as mean ± standard deviation.

* p = 0.05: vs control.

† p = 0.05: vs mild.

Table 3
Comparison of left ventricular global strain and strain rate values of groups and subgroups according to mitral regurgitation severity

				MR severity		
Global deformation	MVP (n = 72)	Control (n = 40)	p	Mild (n = 34)	Moderate (n = 38)	p
GLS (%)	−21.45 ± 3.92	−22.10 ± 3.94	0.34	−21.04 ± 2.96	−22.15 ± 3.32	0.21
GLS (four-chamber) (%)	−20.54 ± 2.05	−21.12 ± 2.57	0.18	−20.23 ± 2.02	−21.57 ± 3.15	0.54
GLS (three-chamber) (%)	−21.02 ± 2.12	−21.57 ± 3.52	0.12	−20.84 ± 2.22	−21.52 ± 2.89	0.64
GLS (two-chamber) (%)	−22.32 ± 3.09	−22.45 ± 3.13	0.84	−22.06 ± 2.89	−22.65 ± 3.14	0.34
GS (circumferential) (%)	−17.05 ± 3.8	−17.64 ± 4.58	0.56	−17.01 ± 2.9	−17.09 ± 4.12	0.40
GS (Radial) (%)	54.1 ± 11.4	55.4 ± 11.8	0.53	53.6 ± 10.9	54.5 ± 11.9	0.41
SRs (s^{-1})	−1.26 ± 0.40	−1.29 ± 0.42	0.10	−1.25 ± 0.31	−1.27 ± 0.38	0.38
SRe (s^{-1})	1.40 ± 0.25	1.62 ± 0.54	<0.001	1.49 ± 0.38*	1.32 ± 0.31*,†	<0.001
SRa (s^{-1})	1.21 ± 0.37	1.16 ± 0.25	0.32	1.19 ± 0.34	1.23 ± 0.37	0.51
Mitral E/SRe Ratio(cm)	72.7 ± 5.6	62.1 ± 4.9	<0.001	69.4 ± 5.1*	75.1 ± 6.4*,†	<0.001

E = early mitral inflow; GS = global strain; GLS = global longitudinal strain; SRa = late diastolic strain rate; SRe = global early diastolic strain rate; SRs = global systolic strain rate.

Values are expressed as mean ± standard deviation.

* p = 0.05: vs control.

† p = 0.05: vs mild.

of the mitral leaflets, LV twist and torsion showed no statistically significant difference.

Discussion

According to standard echocardiography and Doppler parameters, there was no difference between the pediatric patients with mild MR and control groups. However, we demonstrated decreases in SRe in mild and moderate MR groups compared to controls. Although there was no significant difference in E/SRe ratio between mild MR and controls, as the degree of valvular regurgitation increases mild to moderate, we found increases in E/SRe in patients with moderate MR.

In the present study, similar to previous adult studies,[12,13] MVP was more common in female gender. There was no difference between the ages, heights, and office blood pressures of mild/moderate or classical/nonclassical MVP subgroups. Consistent with previous adult studies, we demonstrated increased LV dimensions, LA enlargement, and decreased Mitral E, and Mitral E/A ratio.[12–14]

The LV function can be evaluated using EF. However, EF does not perform wall motion dynamics, and diastolic functions. The SR correlates more closely with invasively determined variables of global function. The reduction in global longitudinal strain values has been shown to be associated with heart failure.[15] For MVP patients, a decrease in the longitudinal and circumferential GS and SR values in

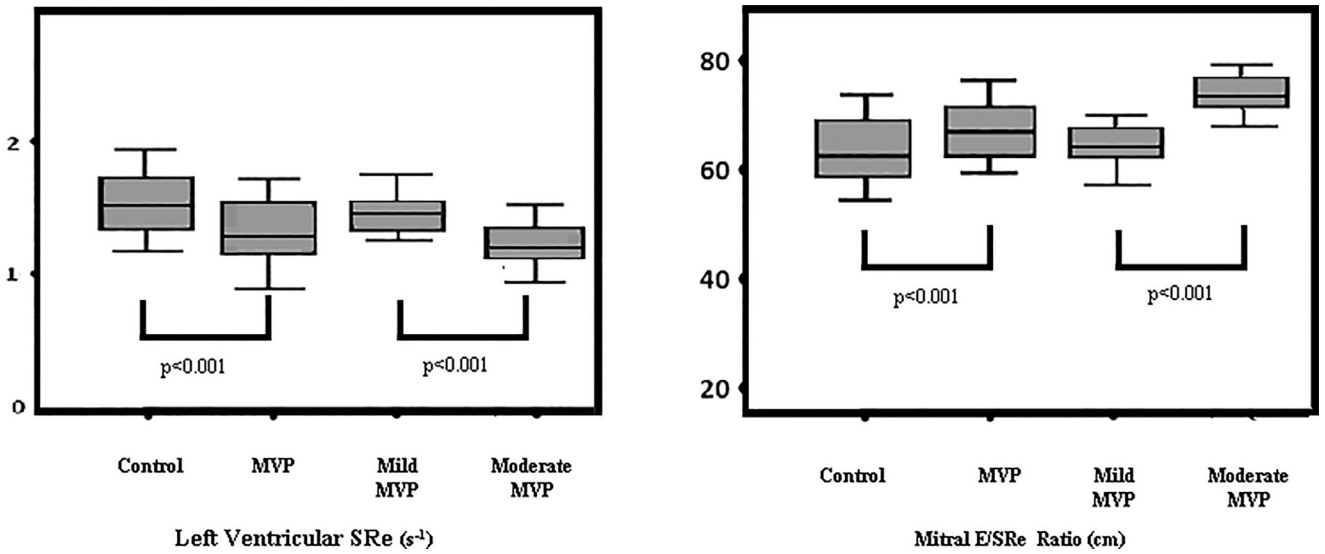

Figure 3. The evaluation of global early diastolic strain (SRe), and early mitral inflow velocity to early diastolic strain ratio (E/SRe) showed significantly impaired cardiac mechanics in MVP patients as compared to controls and each others. MVP = mitral valve prolapse.

Table 4
Comparison of echocardiographic findings according to global early diastolic strain, and early mitral inflow velocity to early diastolic strain ratio

	SRe				Mitral E/SRe			
	Univariate analysis		Multivariate analysis		Univariate analysis		Multivariate analysis	
Parameters	r	p	beta	p	r	p	Beta	p
LAd	−0.72	0.041	−0.25	0.045	0.28	<0.001	0.145	<0.001
LVIDd	−0.12	<0.01	−0.146	0.046	0.32	<0.001	0.25	<0.001
EF	0.66	0.75			−0.16	0.12		
IVRT	0.42	0.52			−0.62	0.23		
Mitral E	0.20	0.04	0.28	0.04	0.44	<0.001	0.31	<0.001
Mitral A	−0.14	0.62						
Mitral E/A	0.16	0.04	0.9	0.04	0.58	0.18		
E/E'	−0.39	<0.01	−0.28	0.041	0.36	<0.001	0.66	<0.001

A = late mitral inflow; E = early mitral inflow; E/A = mitral E/A ratio; E' = average peak early diastolic longitudinal mitral annular velocity; EF = ejection franction; SRe = global early diastolic strain rate; E/SRe = ratio of early mitral inflow velocity to global diastolic strain rate; IVRT = isovolumic relaxation time; LAd = left atrial diameter; LVIDd = end-diastolic left ventricular internal diameter.

Values are expressed as mean ± standard deviation.

septal segments had been shown by Malev et al.[14] Conversely, Huttin et al claimed that changes of deformation pattern in adult MVP patients are present during early-systolic and postsystolic phases with little or no changes in peak systolic deformation, and there are no statistically significant changes in deformation pattern according to the MR severity except for SRe.[16] Unlike the previous studies, the patients in the present study were classified according to the severity of MR. Consistent with the study of Huttin et al, we found no statistically significant difference between the 2 groups with respect to GLS and Global strain rate (GSR). Similary, Zito and et al showed no difference in GLS or radial strain in adult patients with MVP.[17]

Our findings suggest that most of strain parameters remain unchanged in the pediatric patients with MVP. However, we demonstrated decreases in SRe in MVP patients when compared with controls. Furthermore, as the degree of mitral valve insufficiency increased, the reduction in SRe was further increased. This may be due to possible stabilized poise of increased stroke volume or LV remodeling.[16] Although there are limitations of Doppler-based methods, such as angle dependency, SRe derived from 2-dimensional STE was presented as a novel parameter to demonstrate LV relaxation functions.[6,18] Our patients had good systolic functions, probably, diastolic dysfunction may begin in MVP patients before systolic dysfunction. Borg et al detected not only a reduction but also a delay of early diastolic LV untwisting peak which is a marker of LV diastolic dysfunction in patients with chronic degenerative MR.[19]

Morever, E/SRe ratios were found increased in moderate MVP subgroup when compared with controls and mild MR subgroup. Some studies have demonstrated the relation between invasive measured LV filling pressure

and E/SRe[20,21]; and E/SRe has been shown to be superior to E/E'.[22,23] Dahl et al showed that preoperative E/SRe and E/E' were correlated, however, E/SRe was superior to E/E' in estimation long-term postoperative survival than the E/E' ratio in patients with severe aortic stenosis who undergone aortic valve replacement, approximately 3-fold increase in mortality per unit.[23] Similarly, Lassen et al found that E/SRe was a superior prognosticator to E/E' to predict long-term risk of cardiovascular morbidity and mortality in the general population, especially like our patients with good systolic function as assessed by GS.[22]

The actin-myosin separation in diastole, and the slow progressive disorder of active myocardial relaxation in which ATP hydrolysis is needed for calcium decomposition from troponin-C, and the resulting inappropriate ADP/ATP ratio are subtle changes by which diastolic function is possibly affected before systolic function. Thus, SRe and E/SRe may be sensitive markers of early cardiac dysfunction, especially for diastolic dysfunction. The compensatory lengthening of myocardial fibers could be responsible for a decreased diastolic SR value. Although most of LV function parameters which are evaluated by standard echocardiography, tissue Doppler imaging, and STE have been preserved, after a while they will be disrupted when compensating mechanisms are exceeded.

Despite our results, the findings may be explained by our younger patient population, and the exclusion criteria for the patients with severe MR. STE analysis of patients with severe MR were not performed due to the small number. We did not perform a 24-hour ECG Holter monitoring, so we cannot claim a link between cardiac strain parameters and arrhythmia, which is a well-known factor to affect cardiac functions.

Global early diastolic strain and E/SRe may be more sensitive markers of early subtle myocardial injury in pediatric patients with MVP, and are associated with the degree of MR between mild and moderate MVP. The assessment of LV function by 2-dimensional STE can improve pathophysiologic understanding of MR. However, it is too early to claim the predictive values of STE to identify patients at risk who could need early surgery or more aggressive cardio-protective treatment program and further studies and longer follow-up periods are required.

Disclosures

The author has no conflicts of interest to disclose.

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