The use of left atrial strain to predict left ventricular functions in asymptomatic children with mitral valve regurgitation.

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Abstract

Left atrial (LA) dilatation is a powerful predictor of cardiovascular morbidity and mortality. LA longitudinal strain parameters evaluating reservoir, conduit and contractile strain can represent LA functions. We investigated the association between LA strain and left ventricular (LV) functions using speckle-tracking echocardiography in 45 asymptomatic mitral regurgitation patients graded as mild, moderate and severe. LV strain was lower in the moderate group (–17.8±3.7%) and further reduced in the severe regurgitation group (-16±2.14%) in comparison with the reference group (-20.5±6.2%). Regarding LA functions, reservoir strain was higher in the severe and moderate mitral regurgitation groups (38±12.9% and 40.7±9.5%, respectively) in comparison with the controls (40.0±7.2%; p<0.0001). A milder depression of contraction was observed in the severe group (12.2%) than in the moderate group (13±7.2%). In the moderate and severe groups, LV strain correlated significantly with the vena contracta (r=–0.858; p=0.04). Vena contracta was the only independent association for LV longitudinal strain. ROC curve analysis predicted LV longitudinal strain as shown by vena contracta, with a cut-off value >5.65 mm. Vena contracta had a positive predictive value of 75% for predicting LV function. We propose the use of LA and ventricular strain during the follow-up of asymptomatic children with mitral regurgitation. Also, a vena contracta diameter of >5.6 mm can be used as a threshold for LV function impairment.

Introduction

Mitral regurgitation results in volume load on the left ventricle but is asymptomatic while the compensatory mechanisms work. When these mechanisms fail, cardiac functions deteriorate and the patient becomes symptomatic [1]. In adult studies, asymptomatic patients with marked left ventricular (LV) dilation and systolic dysfunction emerged as class I indications for mitral valve (MV) surgery [2]. However, a recent study suggested that remodelling the left ventricle in children differs from adults, and LV function may recover regardless of preoperative LV size or systolic function [3]. In fact, the intervention indications for chronic mitral regurgitation among children are unclear; the determinants identifying children’s high-risk asymptomatic mitral regurgitation subgroups are uncertain, and their clinical outcome and progress in regurgitation are inadequately defined [4].

Volume overload in mitral regurgitation leads to left atrial (LA) dilatation to compensate for increased LA pressure [5]. An increased LA volume is a powerful predictor of cardiovascular morbidity and mortality [6,7]. Atrial deformation analysis with speckle tracking echocardiography allows a perfect assessment of the entire cardiac cycle, closely following the LA physiology. Also, LA mechanical function can be evaluated with the longitudinal reservoir, conduit and contractile phases [8]. LA longitudinal strain parameters considering reservoir, conduit and contraction are the most valuable indexes that represent LA functional analysis [9,10]. LA reservoir function, measured using speckle-tracking echocardiography, is an important prognostic marker
in patients with heart failure involving reduced left ventricular ejection fraction (LVEF) and shows incremental predictive value over LA volume [11]. Previous studies have shown the predictive value of the reservoir in primary mitral regurgitation [12-14]. However, the prognostic implications of LA reservoir function in children with mitral regurgitation have not been evaluated.

The present study thus investigates the association between LA strain, measured using speckle-tracking echocardiography, and LV functions in a cohort of children with moderate-to-severe mitral regurgitation.

**Methods**

**Study Design and Patients**

A total of 45 patients with primary degenerative asymptomatic mitral regurgitation referred to our outpatient echocardiographic laboratory in the paediatric department of . . . . . University Medical Faculty, Istanbul, Turkey between January 2021 and February 2022 were included in the study. All the patients were younger than 18 years old. We excluded patients whose images were of poor quality or whose image loops did not depict all cardiac segments and did not allow speckle tracking of atrial and LV boundaries. Patients without sinus rhythm, clinical symptoms of heart failure and those who underwent cardiac surgery were also excluded. We performed complete two-dimensional (2-D) transthoracic echocardiography to evaluate all patients’ diastolic and systolic functions. The Colour Doppler quantitative technique was used to grade the mitral disease according to the American Society of Echocardiography (ASE) criteria. We imaged vena contracta in a view perpendicular to the commissural line and we used the frame with the largest VC width for measurement. The Nyquist limit was ≥50 cm/s, we increased gain to a point just under the threshold at which color noise occurs for optimizing color Doppler resolution to accurate measure of the VC width A vena contracta of up to 3 mm indicates mild mitral regurgitation, moderate regurgitation is between 3 and 7 mm, and a width of ≥7 mm defines severe mitral regurgitation. All the patients’ legal guardians gave their written informed consent for the study, which complied with the declaration of Helsinki and was performed with the approval of the local ethics committee.

Echocardiographic studies were performed using a high-quality machine (EPIQ CVx Philips, Netherlands) equipped with a matrix transducer. The patients were examined in the left lateral recumbent position. The LV and LA size measurements were taken, along with the LVEF (using Simpson’s method) and diastolic LV filling velocities, all per the current ASE recommendations. We used the ratio between peak early (E) and late (A) filling velocities as standard indexes of LV diastolic function. We used the area-length method from the apical four and two-chamber views for measuring LA volumes and subsequently indexed these by body surface area to produce the LA volume index maximum and minimum.

**Strain measurements**

Echocardiographic images were obtained in the apical four-chamber view. We used offline speckle tracking echocardiographic analysis to measure the LA longitudinal reservoir conduit and contractile functions in the four-chamber view (Fig. 1). The LV strain package (QLAB 9; Philips Medical Systems, Andover, MA) was used for the analysis of LV longitudinal strain as defined elsewhere according to recent guidelines; the interatrial septum was included, while the atrial appendages were excluded. We placed basic markers (lateral and septal mitral/tricuspid annulus and septal roof) manually in the end-diastole; the software automatically generated atrial contours and performed speckle tracking echocardiographic analysis through the cardiac cycle. We manually adjusted the tracking as necessary. Three consecutive measurements were obtained for each parameter, and the mean of these was used. We used the QRS complex (R-R gating) as the initiation of the strain calculation. End-systolic strain values were calculated, with end-systole automatically calculated at aortic valve closure (Fig. 1). An experienced paediatric cardiologist (HB) acquired the images, and another (SD) performed the measurements.

**Statistics**

Continuous variables were expressed as mean±standard deviation, while categorical variables were expressed as percentages. The normality of data distribution for continuous variables was assessed upon histogram
observation and using the Kolmogorov–Smirnov test. Group comparisons were made using the Student’s t-test, ANOVA and the Mann-Whitney U and Kruskal-Wallis tests according to the normal distribution of the data and the number of independent groups. For each variable with non-normal distribution, the homogeneity of variance was assessed using Levene’s test. The distribution of continuous variables was assessed using skewness, kurtosis, visual inspection of the histogram, Q–Q plot and Shapiro–Wilk test. Receiver operating characteristic (ROC) curves were performed to estimate the performance of each potential predictor for predicting late LV dysfunction presented by LV longitudinal strain. Area under the curve (AUC) was calculated with a 95% confidence interval (CI). The value maximizing sensitivity and specificity was identified. Combinations of the most discriminatory values were used to determine the predictors of late LV dysfunction and sensitivity, specificity, positive predictive value and negative predictive value.

Results

Study population characteristics

No significant difference was observed between the control and patient groups regarding age, sex, heart-rate or body mass index (BMI). LVEF was in the normal range and not significantly different among all mitral regurgitation patients and controls. In order to observe the relationship between the longitudinal atrial strain parameters and mitral regurgitation, the atrial and ventricular strain parameters of the control group and three patient groups were compared (Table 1; Fig. 1).

Comparison of atrial strain parameters in control and patient groups

Among the 1,205 segments analysed, the software was able to track 1,168 (97%) segments correctly. Global LV longitudinal strain was higher in the mild mitral regurgitation group (-21.5±0.7%) than the control group (-20.0%; p<0.05); global longitudinal strain was lower in the moderate mitral regurgitation group (-17.8±3.7%) and further reduced in the severe mitral regurgitation group (16±2.14%) in comparison with the reference group (20.5±6.2%; overall p<0.05 for all pairwise comparisons).

Regarding LA function analysis, reservoir strain was higher in the severe and moderate mitral regurgitation groups (38±12.9% and 40.7±9.5%, respectively) than in the control group (40.0±7.2%; p<0.0001 for both). However, a more mild depression of contraction strain was observed in the severe mitral regurgitation group (12.2±4.1%) than in the moderate mitral regurgitation group (13±7.2%) (Table 2).

Relationships of atrial strain and ventricular indices with clinical and echocardiographic variables in patient groups

In the moderate and severe mitral regurgitation groups, total left ventricular longitudinal strain correlated significantly with the vena contracta (r=-0.858; p=0.04). In the moderate and severe mitral regurgitation groups, other clinical and echocardiographic parameters were not related to LV strain.

Linear regression results showed that for LV longitudinal strain (model r²=0.311), the only independent association was vena contracta (B=−0.858; p=0.04). Logistic regression was employed to determine whether atrial functional strains (reservoir, conduit and contraction) could predict total LV longitudinal strain in pathological mitral regurgitation. We did not find a statistically significant functional index for predicting LV function via strain analysis.

The ROC curve analysis was calculated, and the most significant overall performance for the prediction of LV longitudinal strain was found to be shown by vena contracta, with a cut-off value of >5.65 mm (AUC vena contracta: 0.841; p=0.001; (95% CI 71–97 %)). Vena contracta had a sensitivity of 75% (95% CI 70–93%), specificity of 75% (95% CI 60–98%), and positive and negative predictive values of 75% (for each) (Fig. 2)

Discussion

In our study, we analysed changes in the LA function in three groups of asymptomatic patients with mild, moderate and severe mitral regurgitation with normal LVEF. Compared with the referral values, atrial strain analysis by speckle tracking echocardiography showed an increase of the atrial longitudinal deformation in
patients with moderate and severe mitral regurgitation and, instead, a stepwise decline from the moderate mitral regurgitation group to that with severe mitral regurgitation. LV strain analysis by speckle-tracking echocardiography showed a decrease in the LV deformation among patients with moderate and severe mitral regurgitation. We found a meaningful correlation between total LV deformation and the corresponding values of vena contracta and LA strain.

LA dilation in response to mitral regurgitation is an essential factor in predicting adverse outcomes in pathological MV regurgitation [6]. Assessment of atrial function, however, has received less attention. When using volumetric methods, preoperative atrial dysfunction is masked by a regurgitation load that drives awareness of the assessment of atrial function [8]. Moustafa et al. described atrial function using volumetric data in 43 symptomatic patients who had an indication for surgical intervention with MV prolapse (MVP) [4]. Atrial emptying was preserved in the mild but reduced in the severe mitral regurgitation patients.

The reservoir phase of atrial contraction function is essential for LV filling by storing energy during ventricular systole, which is released after MV opening [16]. In our study, the reservoir function, the parameter for the functional evaluation of the reservoir phase, increased in all patients with mitral regurgitation, possibly due to enhanced atrial compliance [17]. Similar results have been obtained in a study conducted by atrial strain analysis [18]. In that case, there was a progressive impairment of global peak atrial longitudinal strain in moderate and severe mitral regurgitation groups, explained as LA ultrastructural abnormalities often associated with chronic mitral regurgitation, such as myocyte hypertrophy, interstitial fibrosis and decreased metalloproteinase expression. Here, however, we did not find a declining trend through moderate-to-severe mitral regurgitation. The three phases of atrial functions by strain analysis showed no differences attributable to regurgitation severity. Instead, our study showed a graded decline in LV function by strain analysis according to regurgitation severity as presented by vena contracta, which was consistent with the linear correlations we found between LV longitudinal strain and vena contracta.

During the atrial reservoir phase, the LA myocardium obeys Starling’s law in the same way as the left ventricle, showing an enhanced contractile function in response to an increased preload, such as in mitral regurgitation. In our study, the reservoir function contribution to the LV filling phase was higher in the moderate than severe mitral regurgitation group, showing a good response of LA myocardial tissue to the increase of preload. The slight reduction of reservoir strain observed in the severe mitral regurgitation group is potentially attributable to the high LV filling pressures and increased LA afterload, resulting in an overwhelmed Frank-Starling mechanism.

One study has looked at the relationship between LA strain and LV diastolic function in order to determine whether LA strain might indicate diastolic dysfunction [19]. There, the authors reported that LA strain measurements are feasible and allow accurate categorization of diastolic dysfunction because, unlike the traditional parameters, this changes progressively with the severity of diastolic dysfunction. Thus, left atrial strain may become a valuable tool for LV diastolic assessment in future clinical practice for patients with MV disease, defined as regurgitation that is less than mild because a more significant level of regurgitation can lead to complexity in grading diastolic dysfunction according to Doppler measurements.

In another multicentre study of 382 patients, the diastolic function of the left ventricle was found to be significantly linked to the myocardial function of the left atrium [20]. In agreement with those authors, we think that LA myocardial function presented by strain measurement can be used to detect LV dysfunction. Although it is significantly different from normal strain parameters, we could not show statistically that LA strain parameters directly affect LV longitudinal strain, which we think is probably due to the small number of patients in the study. Instead, we found that vena contracta, the most straightforward tool for grading Mitral regurgitation severity, is associated with LV dysfunction when it is greater than 5.65 mm and with a sensitivity and specificity of 75%.

A broad spectrum of pathology and a high incidence of co-existing cardiac anomalies lead to reservations to surgical management of even MV repair in cases of MV disease in children. In this study, we aimed to describe the importance of a high-volume load on the left atrium; disturbing atrial and LV functions may
be overlooked if only conventional echocardiography methods are used.

According to the European and American guidelines [21,22], patients with severe primary mitral regurgitation are to be referred to surgical treatment in the presence of either symptoms or overt LV dilatation and dysfunction in order to reduce the risks of cardiac surgery. Using these parameters, however, there is the risk of treating patients only when cardiac chambers are irreversibly damaged. Children with chronic mitral regurgitation are asymptomatic for long periods due to the adaptive LV and LA remodelling, even in severe degrees of regurgitation [23]. For asymptomatic children with primary mitral regurgitation, current indications for surgical treatment have not been entirely determined.

**Limitations**

This study had three main limitations. First, we only included 45 mitral regurgitation patients, so the statistical power of the analysis was not high. Second, this was not an outcome-based study, so we could not infer any conclusions about the prognostic value of LA strain in this population. Third, our study only aimed to clarify the LA deformation mechanics in moderate-to-severe MV disease. Future studies with a large sample size are thus warranted to clarify the prognostic value of LA strain rate in MV disease in children.

We propose that LA and LV strain with volumetric study be used during follow-up of asymptomatic children with MVP. In addition, vena contracta of diameters over 5.6 mm can be used as a threshold for LV function impairment. Our findings support the utility of the quantitative assessment of atrial function by speckle tracking echocardiography as an additional tool to guide the accurate evaluation of LV functions for further decisions.

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Authors’ Contributions: Both authors contributed to the design and data analysis and critically read the final manuscript.

**References**


Table 1. Clinical Characteristics and Reference Value of Echocardiographic Parameters of Patients

<table>
<thead>
<tr>
<th>Sex</th>
<th>Controls</th>
<th>Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>34</td>
<td>13 (11-14)</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>153.9±12 (140.2-162.4)</td>
<td>149±18.9 (106-174)</td>
</tr>
<tr>
<td>BSA (m²)</td>
<td>1.3±0.3</td>
<td>1.32±0.27 (0.60-1.72)</td>
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Echocardiographic Parameters

LVEF (%) | 79.2±5.1 | 68.4±6.2 (58-76) |

Mitral valve Doppler E/A | 1.8±0.4** |

Mitral valve tissue Doppler e’ wave (m/sc) | 0.15±0.03 (0.1-0.23) |

Mitral valve E/e’ | 5.7±1.3 |

Total GLS % | -20.0 (19.1-20.8)** |

Left atrial strain indexes

Reservoir strain (reservoir) % | 31.3±7.5* |

Conduit strain (conduit) % | 23.7±7.1* |

Contractile strain (contraction) % | -7.6±2.6** |

LAVmax (mL/m²) | 25.4±3.9** |

LAVmin Left ventricle ejection fraction | 9.8±2.6** |

Vena Contracta (mm) | - |

BSA: Body surface area; LV: left ventricular; LVEF: left ventricle ejection fraction; E: early transmural velocity; A: late transmural velocity; e’: early diastolic mitral myocardium velocity; LAVmax: left atrial indexed volume maximum; LAVmin: left atrial indexed volume minimum.

* p<0.05 patients vs. controls.

** p<0.001 patients vs. controls.

Table 2 Clinical characteristics and echocardiographic parameters of patients grouped by mitral valve regurgitation severity
Sex (Female/male)
Age 14.9152± 10 2 (13-17)
BSA (m2) 1.27± 0.28 (0.7-1.6)
Left ventricle ejection fraction (%) EF 68.5 ±6.9 (58-75)
Left ventricle shortness fractionCF 38.5±5.6 (30-51)
Mitral Valve E/e’ 5.28± 1.64 (2.69-9.9)
End diastolic volum 97.6 ±41 (43-217)
End diastolic volume index 76±21 (52-136)
End systolic volume 37.9±15.4 (17-.73)
End systolic volume index 25.8 12.5 (9-47)
Total GLS -22.8 ±6.74 (10-35)
Total GCS) 29.3 ±4.95 (14-36)
Twist 8.75±5 (0.2-19)
Torsion 1.21±0.7 (0.1-3.1)
Vena Contracta (mm) 6.59±1.4(4.1-9.1)

** BSA: Body surface area; mitral regurgitation: mitral regurgitation; LV: left ventricular; E: early transmitral velocity; A: late transmitral velocity; e’ = early diastolic mitral myocardial velocity; lleft ventricular longitudinal strain : Total global left ventricular longitudinal strain; LAVmax: Left atrial indexed volume max (mL/m²); LAV min: Left atrial indexed volume min (mL/m²)

*P < 0.05 moderate vs. severe mitral regurgitation groups by the Mann-Whithney U test.

**P < 0.001 moderate vs. severe mitral regurgitation groups by the Mann-Whithney U test.

§ Since the patient number was small in patients with mild regurgitation group comparisons could not be made in this group

**Figure legends**

**Fig. 1a** Atrial strain analysis from the apical 4-chamber view. Typical image depicting the analysis of atrial strain using speckle tracking imaging. The region of interest is manually identified and optimized before the software produces a time-deformation graph for six segments (solid traces) with an average. The three phases of atrial strain are reservoir, conduit, and contractile (annotated). HR: heart rate; b . Left ventricular (LV) strain analysis

**Fig. 2** ROC curves for the analysis of diagnostic accuracy in predicting LV function by strain analysis in the study population. LAVmax: indexed left atrial (LA) volume maximum; LAVmin: indexed LA volume minimum