Correlation between 2D Speckle Tracking Echocardiography and Exercise Stress Echocardiography in Asymptomatic Patients with Severe Rheumatic Mitral Regurgitation

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Abstract

Background: Mitral regurgitation (MR) is a common valvular heart disease. Data available about the proper diagnosis and management of asymptomatic patients with severe rheumatic MR with good systolic function are still controversial. Our objective was to assess the role of Two D-Speckle Tracking Echocardiography (2DSTE) in patients with severe rheumatic MR with correlation to exercise stress echocardiography.

Patients and methods: The present study was conducted on 187 participants (90 patients and 97 healthy controls). Patients were asymptomatic and had severe rheumatic MR. 2DSTE was done to all participants and correlated with the results of exercise stress echocardiography.

Results: Global longitudinal strain (GLS) of the left ventricle (LV) by 2DSTE was significantly lower in rheumatic patients (-16.95 ± 2.12%) than in controls (-23.01 ± 0.71%) (P=0.001). Controversially, global circumferential and radial strain of LV (GCS, GRS) showed no statistically significant difference between the two groups. GLS had a significant negative correlation with exercise duration and percentage of age-gender predicted METs. Interestingly, GLS ≤ -17 had better exercise parameters, longer exercise duration and better percentage of age-gender predicted METs.

Conclusion: 2DSTE has incremental value beyond conventional measures of LV function. Patients with GLS ≤ -17 have a good functional capacity and better exercise parameters than those with GLS > -17. A cut off value of GLS > -17 could identify patients at high risk of cardiovascular morbidity.

Keywords: Correlation; 2D speckle tracking echocardiography; exercise stress echocardiography; rheumatic; mitral regurgitation

Introduction

Valvular heart disease (VHD) is a one of the most common causes of morbidity and mortality...
worldwide. Rheumatic heart disease is considered one of the most important causes of VHD in developing countries. Mitral regurgitation (MR) is a common type of rheumatic VHD [1]. Left ventricular dysfunction is frequently subclinical despite normal LV ejection fraction (LVEF) and may precede the onset of symptoms. Current guidelines [2] recommend valve replacement/repair in cases of severe MR that cause symptoms or reduced LVEF, as surgery before development of irreversible myocardial damage prevents progressive postoperative LV dysfunction and improves clinical outcome [3].

Echocardiography and cardiac magnetic resonance are the best available current modalities for assessment of LV function; they allow dynamic imaging of the heart and assess regional and global LV function. But cardiac magnetic resonance is costly, not easily available in developing countries, and cannot be used for routine clinical application in all patients [4]. Routine echocardiographic parameters such as volume and LVEF are often unable to disclose initial LV dysfunction; LV function may remain compensated despite the changes in myocardial deformation properties. Tissue Doppler imaging (TDI) allows measurement of tissue velocities within the myocardium and assessment of LV function and filling pressures [5]. However, TDI depends on the angle and measures only a single component of regional velocity vector along the scan line [5, 6]. 2D Speckle tracking echocardiography (2DSTE) is a newer technique that provides non-Doppler, relatively angle independent measurement of myocardial deformation [6]. 2DSTE evaluates LV mechanics, rotation, and torsion and allows for semi-automated quantification of myocardial deformation (strain and strain rate) in the three spatial directions (longitudinal, radial, and circumferential), which is useful to assess LV long and short axis function as the chronic LV remodeling process may have a different effect on LV short and long axis function [7-9]. Although strain parameters are all partially load-dependent, the strain rate is relatively load-independent [10].

Exercise testing plays an important role in primary asymptomatic MR; it allows better assessment of symptoms and its relation to valve disease severity, and safe deferral of surgery in patients with preserved exercise capacity and helps in individual risk stratification. The objective of the present study was to assess the role of 2DSTE and its incremental value beyond conventional measures of LV function in patients with severe rheumatic MR with correlation to exercise stress echocardiography. Results suggest that the application of this new modality for identification of early abnormalities in LV function, particularly in the case of preserved LVEF and before the onset of clinical symptoms.

Patients and Methods

The present study was conducted in the Cardiology Department, Faculty of Medicine, Tanta University, during the period from October 2017 to March 2019 on 90 asymptomatic patients with severe rheumatic mitral incompetence (group I) who were selected randomly during this period and 97 age- and sex-matched healthy controls (group II). The mean age of group I was 33.02 ± 6.12 years with 51 male patients (56.7%), while the mean age of group II was 33.94 ± 6.18 years with 45 male patients (46.4%). All participants gave written informed consent to participate in this study and the study was approved by the local ethics committee.

Inclusion and Exclusion Criteria

Patients were asymptomatic with severe rheumatic mitral incompetence, LV systolic function ≥ 60%, LVEDD < 4.5 cm, while patients with evidence of double mitral valve lesion (N = 205), multivalvular affection (N = 350), ischemic heart disease (N = 20), LV function <60% (N = 150), atrial or ventricular arrhythmia (N = 88), renal disorders, hepatic disorders, diabetes mellitus, hypertension, congenital heart diseases, hematological and neoplastic diseases (N = 185) were excluded.

All patients and healthy controls were subjected to history taking and general and local cardiac examination. Routine 12-lead ECG was performed for the studied populations to detect changes suggestive of coronary artery disease and exclude arrhythmia and conduction abnormalities.

Data were collected by a case record form, which included routine laboratory investigations including
kidney function tests, random blood sugar and liver function tests. All participants were subjected to 2D, Doppler, and color Doppler echocardiography for the assessment of the mitral valve. Echocardiographic examinations were carried out with the Vivid E9 dimension (General Electric Medical Systems, Horten, Norway) equipped with a 2.5-MHz variable-frequency transducer S probe for 2D imaging. Standard views (parasternal long and short axis, apical four, five and two chamber, subcostal and suprasternal views) with ECG tracing were obtained in 2D modes, with assessment of LV diameter in end diastole, and end systole by M mode with estimation automatically of LVEF, assessment of LA diameter in parasternal long axis view by M mode at end systole [11] and assessment of other cardiac valves to exclude any associated valvular lesion. Assessment of the mitral valve was done first by 2D, then assessment by color flow mapping to assess origin and direction of jet, width of jet at the level of the orifice averaged from all views (vena contracta) [12]; continuous wave signal and dense forward flow ascertained the degree of mitral incompetence [13]. The right side of the heart and right ventricular systolic pressure (RVSP) were assessed by estimating maximum velocity of tricuspid incompetence by continuous Doppler flow [14]. In all patients, RVSP was < 50mmHg. In apical 4 chamber view pulsed wave TDI sample volumes were placed at the level of the lateral mitral annulus and at the level of the septal mitral annulus, with proper alignment to minimize the incident angle. Peak myocardial velocities during systole (s’) were measured in 3 consecutive cycles and averaged [15].

Two D-Speckle Tracking Echocardiography and Exercise Stress Echocardiography

Gated images with high quality are obtained during end expiratory breath hold with stable ECG tracing. Three consecutive heart cycles were recorded and averaged at frame rate adjusted at 60 - 80 frames/second. Three, four and two apical chambers are necessary for estimation of global longitudinal strain; however for circumferential and radial strain, parasternal views were obtained at basal, papillary muscle and apical levels [16, 17]. Measurement of the aortic valve closure was performed by acquiring a clear M-Mode signal where the valve closure was clearly visible or from a proper Doppler signal including both mitral and aortic valves. Recordings were processed by software (Echo Pac, GE Vivid E9 echocardiography system version 113) for off-line measurements of speckle-based strain [16, 17]. The region of interest was outlined manually by tracing the endocardium and then the epicardium and automatically outlined; the peak systolic global longitudinal, circumferential and radial strain were calculated [16, 17]. All strain measurements were performed independently by two separate investigators experienced in analysis and blinded to clinical and other echocardiographic patient’s data. Exercise stress echocardiography was performed for all patients (group I) using a treadmill with a modified Bruce protocol in which an expected exercise level for each gender and age group was expressed as a functional aerobic capacity, and also expected maximum heart rate achieved. Rapid image acquisition was performed at peak stress to estimate LV systolic function and RVSP by estimating maximal velocity of tricuspid incompetence for correlation with the results of 2DSTE. The patients were followed-up for 6 months for cardiovascular symptom development in the form of dyspnea and palpitation, signs of heart failure and cardiac hospitalization.

Statistical Analysis

Statistical analysis was performed using SPSS 20 (IBM, Armonk, NY, USA). Quantitative data were expressed as mean ± standard deviation (SD). Qualitative data were expressed as frequency and percentage. The Student’s t test was used for the comparison between two groups in quantitative data and the chi-square (χ²) test in proportions. A P-value <0.05 was considered to indicate statistical significance. Correlation analysis (using Spearman's method) assessed the strength of association between 2DSTE results and exercise stress echocardiography results. The correlation coefficient denoted symbolically “r” defines the strength and direction of the linear relationship between two variables.
Results

The present study included 187 participants: 90 patients with severe rheumatic mitral incompetence with preserved systolic function (group I) and 97 healthy controls with no history of any disease (group II). The patients’ ages ranged from 27-39 years with a mean of 33.02 ± 6.12 years including 51 male patients and 39 female patients with no statistically significant difference between the two groups. The heart rate was significantly higher among patients with severe rheumatic MR compared to control subjects (71.26 ± 7.77 vs. 68.74 ± 8.12 bpm, P=0.032), Table 1.

Table 1. Baseline demographic, clinical and echocardiographic data of the two groups

<table>
<thead>
<tr>
<th></th>
<th>Group I (N= 90) (patients with severe MR)</th>
<th>Group II (N= 97) (control group)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>33.02 ± 6.12</td>
<td>33.94 ± 6.18</td>
<td>0.310</td>
</tr>
<tr>
<td>Male gender, n (%)</td>
<td>51 (56.7%)</td>
<td>45 (46.4%)</td>
<td>0.160</td>
</tr>
<tr>
<td>Smoking, n (%)</td>
<td>31 (34.4%)</td>
<td>29 (29.9%)</td>
<td>0.506</td>
</tr>
<tr>
<td>Dyslipidemia, n (%)</td>
<td>16 (17.8%)</td>
<td>24 (24.7%)</td>
<td>0.246</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>166.97 ± 5.21</td>
<td>165.94 ± 11.31</td>
<td>0.431</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>69.31 ± 7.20</td>
<td>69.35 ± 7.52</td>
<td>0.971</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>24.92 ± 2.86</td>
<td>26.17 ± 12.36</td>
<td>0.348</td>
</tr>
<tr>
<td>Heart rate (bpm)</td>
<td>71.26 ± 7.77</td>
<td>68.74 ± 8.12</td>
<td>0.032*</td>
</tr>
<tr>
<td>Systolic BP, (mmHg)</td>
<td>117.39 ± 9.66</td>
<td>119.18 ± 9.23</td>
<td>0.198</td>
</tr>
<tr>
<td>Diastolic BP, (mmHg)</td>
<td>79.13 ± 4.90</td>
<td>77.65 ± 6.18</td>
<td>0.072</td>
</tr>
<tr>
<td>LVEDD, (cm)</td>
<td>6.20 ± 0.20</td>
<td>5.25 ± 0.18</td>
<td>0.001*</td>
</tr>
<tr>
<td>LVESD, (cm)</td>
<td>4.23 ± 0.14</td>
<td>3.43 ± 0.22</td>
<td>0.001*</td>
</tr>
<tr>
<td>LVEF, (%)</td>
<td>63.57 ± 2.90</td>
<td>62.95 ± 2.58</td>
<td>0.124</td>
</tr>
<tr>
<td>LA diameter, (cm)</td>
<td>4.97 ± 0.19</td>
<td>3.39 ± 0.39</td>
<td>0.001*</td>
</tr>
<tr>
<td>S' lateral, (cm/s)</td>
<td>7.96 ± 0.30</td>
<td>9.35 ± 1.10</td>
<td>0.001*</td>
</tr>
<tr>
<td>S' septal, (cm/s)</td>
<td>8.00 ± 0.31</td>
<td>9.15 ± 1.11</td>
<td>0.001*</td>
</tr>
<tr>
<td>GLS, (%)</td>
<td>-16.95 ± 2.12</td>
<td>-23.01 ± 0.71</td>
<td>0.001*</td>
</tr>
<tr>
<td>GCS, (%)</td>
<td>-22.58 ± 0.73</td>
<td>-22.67 ± 0.68</td>
<td>0.407</td>
</tr>
<tr>
<td>GRS, (%)</td>
<td>45.31 ± 0.86</td>
<td>45.37 ± 0.71</td>
<td>0.623</td>
</tr>
</tbody>
</table>

MR: mitral regurgitation; BMI: body mass index; BP: blood pressure; LVEDD: left ventricular end diastolic dimension; LVESD: left ventricular end systolic dimension; LVEF: left ventricular ejection fraction; LA: left atrium; S' lateral: peak systolic lateral mitral annular velocity; S' septal: peak systolic septal mitral annular velocity; GLS: global longitudinal strain; GCS: global circumferential strain; GRS: global radial strain.

All included participants’ LVEF was more than 60% with no significant difference between the two groups, but left ventricular dimensions in diastole and systole (LVEDD, LVESD) showed statistically significant differences with more dilatation in the rheumatic group (6.20 ± 0.20 cm and 4.23 ± 0.14 cm, respectively than in the control group (5.25 ± 0.18 cm and 3.43 ± 0.22 cm, respectively) (P = 0.001). The left atrium (LA) was also significantly dilated in group I (4.97 ± 0.19 vs. 3.39 ± 0.39 cm in the control group) (P = 0.001). Despite LVEF being higher than 60% in all participants, peak systolic S’ wave of LV at septal and lateral mitral annulus was significantly lower in rheumatic patients (8.00 ± 0.31, 7.96 ± 0.30 cm/s, respectively) as compared to the control group (9.15 ± 1.11, 9.35 ± 1.10 cm/s, respectively) (P=0.001). Global longitudinal strain (GLS) of LV by two-dimensional strain was significantly lower in rheumatic patients (-16.95 ± 2.12%) than in the control group (-23.01 ± 0.71%) (P=0.001). Controversially, global circumferential and radial strain of LV (GCS, GRS) showed no statistically significant difference between the two groups.

Furthermore, group I was subjected to exercise stress echocardiography to assess functional capacity of the patients with severe rheumatic mitral regurgitation. Correlation between 2DSTE parameters and exercise stress echocardiographic parameters showed that GLS had a significant negative correlation with exercise duration and percentage of
age-gender predicted METs (P=0.001). GCS correlated negatively with peak stress LVEF (P=0.002). GRS did not correlate with exercise stress echocardiographic parameters, as shown in Table 2 and Figures 1 and 2.

Figure 1. The correlation between global longitudinal strain and exercise duration.

Figure 2. The correlation between global longitudinal strain and age-gender predicted METs.
Table 2. The correlation between 2D speckle tracking echocardiographic results and exercise stress echocardiographic results

<table>
<thead>
<tr>
<th>Exercise duration (minutes)</th>
<th>Maximum predicted HR, (%)</th>
<th>% Age-gender predicted METs</th>
<th>Peak stress RVSP, (mm Hg)</th>
<th>Peak stress LVEF, (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>GLS, (%)</td>
<td>-0.791</td>
<td>0.001*</td>
<td>-0.085</td>
<td>0.427</td>
</tr>
<tr>
<td>GCS, (%)</td>
<td>-0.107</td>
<td>0.317</td>
<td>0.082</td>
<td>0.443</td>
</tr>
<tr>
<td>GRS, (%)</td>
<td>-0.201</td>
<td>0.057</td>
<td>0.165</td>
<td>0.121</td>
</tr>
</tbody>
</table>

HR: heart rate; METs: metabolic equivalents; RVSP: right ventricular systolic pressure; LVEF: left ventricular ejection fraction; GLS: global longitudinal strain; GCS: global circumferential strain; GRS: global radial strain.

Table 3. Comparison between the two subgroups of global longitudinal strain

<table>
<thead>
<tr>
<th></th>
<th>Group IA GLS &gt; -17 (N = 50)</th>
<th>Group IB GLS ≤ -17 (N = 40)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exercise duration (minutes)</td>
<td>10.46 ± 1.01</td>
<td>14.25 ± 1.15</td>
<td>0.001*</td>
</tr>
<tr>
<td>Maximum predicted heart rate, (%)</td>
<td>92.82 ± 6.06</td>
<td>94.27 ± 7.37</td>
<td>0.307</td>
</tr>
<tr>
<td>% Age-gender predicted METs</td>
<td>94.64 ± 4.49</td>
<td>109.90 ± 3.32</td>
<td>0.001*</td>
</tr>
<tr>
<td>Peak stress RVSP, (mm Hg)</td>
<td>34.66 ± 6.05</td>
<td>32.37 ± 3.42</td>
<td>0.036*</td>
</tr>
<tr>
<td>Peak stress LVEF, (%)</td>
<td>66.72 ± 3.36</td>
<td>67.05 ± 2.82</td>
<td>0.621</td>
</tr>
</tbody>
</table>

METs: metabolic equivalents; RVSP: right ventricular systolic pressure; LVEF: left ventricular ejection fraction; GLS: global longitudinal strain.

Furthermore, group I was divided into two subgroups according to the median value of GLS, which was -17; Group IA had GLS > -17 (N = 50) and Group IB had GLS ≤ -17 (N = 40). As compared to patients with GLS > -17, patients with GLS ≤ -17 had better exercise parameters, longer exercise duration, more percentage of age-gender predicted METs and lower peak stress RVSP, Table 3. During follow-up of the patients for 6 months, we noticed that 4 patients of Group IA (GLS > -17) developed symptoms in the form of dyspnea and palpitation and one patient was admitted to hospital with atrial fibrillation.

Discussion

The present study emphasized the role of 2DSTE and its incremental value beyond other conventional measures of LV function. Moreover, we correlated it to exercise stress echocardiography and to the best of our knowledge we were the first to put a cut-off value of GLS > -17 to determine the patients with severe MR at high risk of cardiovascular morbidity. Severe MR is associated with increased risk of morbidity and mortality; recent guidelines recommend surgery in symptomatic patients with severe MR and in asymptomatic patients with signs of LV dysfunction to confer a better outcome [18, 19]. The LVEF is often overestimated in the presence of MR and may remain in the normal or supernormal range for a long time, even if alterations in contractility develop. Thus, it is important to detect LV contractile dysfunction very early to favor better surgical outcome and life expectancy after surgery for severe MR [20, 21]. Conventional echocardiographic parameters cannot detect subclinical LV dysfunction; recently 2DSTE is used for quantitative assessment of global and segmental LV function [22, 23]. In the present study GLS of LV by two-dimension strain was significantly lower in rheumatic patients with severe MR in comparison with the control group, while GCS and GRS were similar in two groups. In agreement with the present study, Kim et al. [24] studied 59 patients with severe MR and LVEF ≥50% and 34 healthy controls. Speckle tracking imaging was performed to measure peak systolic radial, circumferential and longitudinal strain rates. In all patients, GLS was significantly depressed when compared with a control group. Preoperative speckle tracking–derived GLS and longitudinal strain and strain rate values strongly
predicted a postoperative LVEF decrease of >10%. The authors reported that long axis function (longitudinal strain) becomes depressed earlier than short axis function (circumferential and radial strain) in remodeling process [24]. Lee et al. and Agricola et al. also showed previously that the deterioration in LV GLS is a predictor of latent LV dysfunction and a predictor of postoperative LV dysfunction [25, 26]. In disagreement to our study, Marciniak et al. [8] showed that circumferential strain has a biphasic pattern, being enhanced in moderate MR and then significantly reduced with severe MR in comparison with a control group, but this was studied in a small group of patients [8].

When assessing patients with severe rheumatic MR, there is a diagnostic and management dilemma. Exercise testing plays an important role in the assessment of the clinical status of those patients and in sorting out some of these clinical challenges. In asymptomatic patients with severe MR, exercise testing allows symptom assessment and determines the link of symptoms to valve disease severity, deferral of surgery in patients with preserved exercise capacity and helps in individual risk stratification [27]. In the current study, rheumatic patients with severe MR were subjected to exercise stress echocardiography to assess functional capacity, RVSP and LVEF at peak stress and correlation between 2DSTE parameters and exercise parameters was performed. GLS had a significant negative correlation with exercise duration and percentage of age-gender predicted METs. In agreement with the present study Supino et al. [28] prospectively followed 38 patients with chronic severe non ischemic MR who underwent modified Bruce exercise Treadmill testing; all patients lacked surgical indications at study entry. Their baseline exercise parameters were also compared with those from 46 patients with severe MR who, at entry, had already reached surgical indications. Their results from univariate analysis showed that exercise duration (p = 0.004) predicted peak heart rate (p = 0.01) and heart rate recovery (p < 0.02). In multivariate analysis, only exercise duration was predictive (p < 0.02). Average annual event risk was 5-fold lower (4.62%) with exercise duration ≥15 minutes vs. <15 minutes (average annual risk=23.48%, P=0.004). The authors concluded that among asymptomatic patients with chronic severe non-ischemic MR and no objective criteria for operation, progression to surgical indications is rapid. However, those patients with excellent exercise tolerance had a relatively benign course. Mentias et al. [29] studied a group of patients to determine whether resting LV GLS and exercise test provide incremental prognostic utility in asymptomatic patients with severe MR and preserved ejection fraction. The conclusion was that reduced exercise capacity and worsening resting LV GLS were associated with increased mortality and providing additive prognostic utility. In the same issue Mentias et al. [30] sought to evaluate the incremental impact of LV GLS on exercise capacity and studied 660 patients who underwent rest-stress echocardiography, Standard strain data were obtained and their conclusion was that in asymptomatic patients with ≥3+ primary MR, non-dilated LV and preserved LVEF, worsening resting LV GLS is significantly associated with reduced functional capacity, independently and incrementally to other known predictors [30].

In the current study, group I was divided into two subgroups according to the median value of GLS. Patients with GLS ≤ -17 were found to have better exercise parameters, longer exercise duration, more percentage of age-gender predicted METs and lower peak stress RVSP.

**Conclusion**

The role of 2DSTE and its incremental value beyond conventional measures of LV function was studied herein with correlation to exercise stress echocardiography. The application of this new modality for identification of early abnormalities in LV function, particularly in the case of preserved LVEF and before the onset of clinical symptoms, rheumatic patients with severe MR (with GLS ≤-17) had a good functional capacity and better exercise parameters than those with GLS>-17. Using GLS>-17 as a cut-off value could be an important criterion in the future to identify such high risk group of patients at high risk of cardiovascular morbidity.
Conflict of interest

None.

Acknowledgment

We acknowledge the assistance of all doctors, nurses, technicians and hospital staff who cared for our patients. With special acknowledgment for Prof Dr, Ram Singh and Prof Dr, Galal Eldin Nagib Elkilany for their valuable advices and expert revision of the manuscript.

References


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