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ORIGINAL ARTICLE

Subtle Myocardial Dysfunction and Fibrosis in Children with Rheumatic Heart Disease: Insight from 3D Echocardiography, 3D Speckle Tracking and Cardiac Magnetic Resonance Imaging

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Abstract
Rheumatic heart disease (RHD) is a major cause of morbidity and mortality in developing countries, so early diagnosis and treatment can reduce morbidity and mortality resulting from subsequent valvular damage. The aim of this study was to detect subtle myocardial dysfunction among children with RHD with preserved left ventricular systolic function. This is a cross-sectional case–control study that was conducted on 30 children with RHD (who had valvular affection of any degree and were not in activity) compared to 23 healthy children. After history taking and cardiac examination, 2D echocardiography, tissue Doppler imaging, 3D-echocardiography and 3D speckle tracking echocardiography were done to both groups, whereas cardiac magnetic resonance imaging was done only to the patient group. The 3D-derived left ventricular end-diastolic volume and sphericity index among patients were significantly increased when compared to controls [131.5 (101.5 to 173.7) vs. 69 (58 to 92), $P=0.001$, and 0.46 (0.36 to 0.59) vs. 0.33 (0.29 to 0.38), $P=0.001$, respectively]. The 3D-derived ejection fraction and longitudinal strain did not differ significantly among both groups. The 3D-derived global circumferential strain was higher in patients when compared to controls [−14 (−16 to −10) vs. −11(−13 to −10), $P=0.04$]. None of the examined patients demonstrated late enhancement myocardial fibrosis. In children with RHD and preserved systolic function, subtle systolic dysfunction could not be detected using conventional and novel non-conventional methods. This may indicate that the myocardial affection during the acute stage of rheumatic carditis is minimal with almost complete resolution.

Keyword Rheumatic heart disease · 3D-STE. · Cardiac MRI.

Introduction

Rheumatic heart disease (RHD) remains one of the major causes of morbidity and mortality in developing countries, so prevention, either primary or secondary; early diagnosis; and management are of paramount importance [1].

Conventional echocardiography can be used for evaluations of valvular morphology, grading of severity, and functional assessments through M-mode or 2D-derived ejection fractions (EFs), but unfortunately, these methods are based on mathematical assumptions. The foreshortening that may accompany the 2D measurement may even lead to inappropriate measurements of the EFs; moreover, the left ventricular (LV) ejection fraction (LVEF) measured by 3D echocardiography is more accurate than that measured by cardiac MRI [2, 3]. Tissue Doppler imaging (TDI) is a new technique that allows the measurement of myocardial velocity. TDI can help in the assessment of diastolic cardiac function and in the evaluation of cardiac deformation. The main limitations of this technique are its angle dependence and ability to be affected by the translational movement of the heart [4]. 2D-speckle tracking echocardiography (2D-STE) has evolved for the evaluation of cardiac deformation through the tracking of myocardial speckles throughout the cardiac cycle, and its main advantages are that it is not angle dependent or affected by the translational movement of the heart. On the other hand, the main disadvantages of 2D-STE are its inability to perform deformation in one cardiac cycle

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and its low temporal resolution [5]. Unlike 2D-STE, 3D-STE can measure deformation three dimensionally in the same cardiac cycle [6]. The aim of this study was to detect subtle myocardial dysfunction in children with RHD with preserved LV systolic function using 3D echocardiography, 3D-STE and TDI.

Patients and Methods

Study Design and Setting

This cross-sectional case–control study was carried out at the Pediatric Cardiology Unit, Cairo University Paediatric Hospital, Egypt. An informed consent form was signed by the parents/legal guardians of each participant before enrolment in the study.

Participants

The study included 30 patients with RHD, aged 8–18 years, from both sexes and 23 age-matched normal controls. Patients with valvular affection and normal EFs were included, while patients with acute rheumatic fever or rheumatic activity, those with associated congenital heart disease (CHD) or systemic diseases that could affect cardiac functions (e.g. collagen vascular disease, hypertension, renal failure, or diabetes), and patients who had non-sinus rhythms were excluded from the study.

Data Collection

A full history and cardiac examination were respectively obtained from and performed for each patient, and the data included age, sex, clinical presentation of rheumatic fever, duration since diagnosis, and the New York Heart Association (NYHA) score as well as weight, height and heart rate (HR) determinations.

Transthoracic Echo-Doppler examinations were performed in all cases in the supine or left lateral position using a General Electric (GE, Vivid-7) system with 3- or 5-MHz probes (multi-frequency transducers) according to the age of the patient. The ECG cable was connected to the ultrasound machine. The beginning of the QRS complex was used as a reference point, and the following parameters were measured: *Doppler velocities* for the mitral valve (peak E and A wave velocities, E/A ratio). *M-mode for left ventricle* was viewed using the parasternal long axis view with the cursor line at mitral valve tips [LV end-diastolic (LVED) dimension (LVEDD), LV end-systolic (LVES) dimension (LVESD), fractional shortening (FS), and EF]. *Pulsed wave tissue Doppler imaging (PW-TDI)* was performed at the basal segments of the LV lateral and septal walls [systolic (S′) and diastolic (E′, A′, E′/A′ ratio) myocardial velocities were measured]. IVA (isovolumic acceleration) at the lateral mitral annulus was also measured in the apical 4-chamber views as follows: IVA = peak S′1/acceleration time of S′1 (time from the start of S′1 to the peak of S′1 wave) [7]. *2D* automated EF measurements were made in the two-chamber and 4-chamber view. *Real-time 3D echocardiography (RT3DE)* was performed from an apical four-chamber view using a 3D matrix array transducer (GE Vingmed Ultrasound AS, Horten, Norway). A wide-angle acquisition (full volume) mode was used, in which 6 wedge-shaped sub-volumes were acquired from 6 consecutive cardiac cycles during a single breath hold for as long as possible, resulting in a study of the temporal resolution of 6 frames per cardiac cycle with a minimum frame rate of 42/s. Special care was taken to include the entire ventricular and atrial cavity in the 3D pyramidal volume. Acquisitions were stored in a DICOM format and transferred to a separate workstation for offline data analysis. 3D wall motion tracking software 4D Auto LVQ and Tom Tec Imaging Systems were used to analyse the left ventricle. The LVEF was calculated according to the formula LVEF = (LVED volume − LVES volume)/LVED volume. Global longitudinal, circumferential and radial strains were automatically calculated by the software. In addition to these standard parameters, the area strain, which integrates longitudinal and circumferential deformations, was calculated automatically. Clearly, a sphericity index derived from 3D LV volumes rather than 2D areas reflect ventricular shape more accurately. A 3D-derived sphericity index was calculated by dividing the LV end-diastolic volume (calculated from a 3D dataset) by the volume of a sphere, the diameter of which is the LV major end-diastolic long axis. This sphericity index has been shown to be an earlier and more accurate predictor of remodelling in patients following acute myocardial infarction than other clinical, electrocardiographic, or echocardiographic variables [8]. Offline 3D analysis software now permits rapid calculation of a 3D sphericity index using 3D LV volume data.

All patients then underwent cardiac MRI using the Philips Achieva and Intera 1.5 T 4 channels machine. Body and cardiac coils with ECG and respiratory (usually a breath hold) gating were used. If the child was unable to hold his breath, the signal-to-noise ratio was increased. The contrast used was intravenous gadolinium chelate (GAD-DTPA), 0.3 ml/kg. Cardiac volumes and functions were measured. If the history triggered suspicion of recent acute rheumatic myocarditis or rheumatic activity, oedema sequence and hyperaemia sequence pre- and early post-contrast (1st pass) images were obtained. Cardiac viability (fibrosis detection) was determined using post-contrast (GAD-DTPA) imaging. The average scan time was 40–45 min.

Statistical Analysis

Numerical data are described in terms of the median and interquartile range (for non-normally distributed data) or the mean ± SD (for normally distributed data), and categorical data are described as the number and percentage. Comparisons of numerical variables between the study groups were performed using Student's *t* test for independent samples in comparing 2 groups when normally distributed and the Mann–Whitney *U* test for independent samples when not normally distributed. For comparisons of categorical data, the Chi-square (χ^2) test was performed. Correlations between various variables were performed using the Pearson moment correlation equation. The Bland–Altman method was used to assess the agreement between LV volumes and EFs measured by 3D echocardiography and cardiac MRI. P values less than 0.05 were considered statistically significant. Statistical analysis was performed using SPSS (Statistical Package for the Social Science; SPSS Inc., Chicago, IL, USA) version 16 for Microsoft Windows and MedCalc for Windows, version 15.0 (MedCalc Software, Ostend, Belgium).

Results

The baseline parameters of the study subjects are shown in Table 1. All patients were diagnosed according to the modified Jones criteria. The initial presentation was arthritis in 18 patients (60%), polyarthralgia in 7 patients (23%), clinical carditis in 5 patients (16.6%), and chorea in one patient (3%) (Table 1).

All patients were on long-acting penicillin (LAP); 23 patients showed good compliance (76.7%), and 7 patients showed poor compliance (23.3%). Mild mitral regurgitation was found in 22 (73%) patients, while mild aortic insufficiency was evident in 19 (63%) patients (Table 1).

Left Ventricular Systolic Function

Regarding M-mode data, patients showed significant LV dilatation with normal or even super-normal function (Table 2). Moreover, the LVED Z-score was significantly correlated with mitral E/E′ (Table 3).

Table 1 Characteristics of the studied groups

	Cases ($n=30$)	Control ($n=23$)	*P* value
Age (years)	13 (10 to 16)	10 (10 to 13)	0.093
Weight (kg)	49.5 (39.5 to 64.25)	34 (27 to 53)	0.065
Body surface area (m^2)	1.35 (1.11 to 1.60)	1.1 (0.94 to 1.46)	0.094
HR (BPM)	79 (75 to 90)	86 (72 to 92)	0.902
Duration since diagnosis (years)	6 (3.7 to 10)		
Sex			
Male, *n* (%)	22 (73.4%)	17 (74%)	0.794
Female, *n* (%)	8 (26.6%)	6 (26%)	
Initial presentations			
Clinical carditis, *n* (%)	5 (16.6%)		
Arthritis, *n* (%)	8 (60%)		
Poly arthralgia, *n* (%)	7 (23%)		
Chorea, *n* (%)	1 (3%)		
Compliance to long acting penicillin			
Good compliance, *n* (%)	23 (76.7%)		
Poor compliance, *n* (%)	7 (23.3%)		
NYHA score			
NYHA I, *n* (%)	22 (73%)		
NYHA II, *n* (%)	7 (23%)		
NYHA III, *n* (%)	1 (4%)		
Mitral regurge			
Mild, *n* (%)	23 (76%)		
Moderate, *n* (%)	7 (24%)		
Aortic regurge			
Mild, *n* (%)	19 (63%)		
Moderate, *n* (%)	4 (13%)		
Severe, *n* (%)	1 (3%)		

Kg kilogram, *BPM* beat per minute, *NYHA* New York heart association

Table 2 LV systolic and diastolic parameters of the studied groups

	Cases ($n=30$)	Control ($n=23$)	P value
LV systolic function			
M-mode			
LVDD (mm)	48 (41 to 53)	39 (36 to 43)	0.001*
LVDS (mm)	29 (24 to 32)	24 (23 to 27)	0.008*
FS (%)	40 (38 to 43)	38 (36 to 42)	0.145
EF (%)	71 (68 to 74)	69 (66 to 72)	0.293
Semi-automated 2D EF			
2Ch. EF (%)	60 (53 to 64)	59 (55 to 62)	0.666
4Ch .EF (%)	55 (52.7 to 57)	55 (52 to 61)	0.284
Biplane EF	57 (54 to 59)	58 (55 to 60)	0.456
PW-TDI			
S′ septal (cm/s)	8.5 (8 to 10)	8 (8 to 9)	0.076
S′ lateral (cm/s)	9.5 (9 to 11)	8 (7 to 9)	0.03*
IVA (m/s^2)	2.6 (1.3 to 3.5)	2.4 (1.7 to 3)	0.921
4D echocardiography			
EDV (ml)	131.5 (101.5 to 173.7)	69 (58 to 92)	0.001*
ESV (ml)	52 (38.5 to 79.5)	28 (26 to 39)	0.001*
SV (ml)	75.5 (64 to 102.5)	40 (32 to 50)	0.001*
LV 4DEF (%)	59 (54 to 61)	57 (54 to 62)	0.147
SPI	0.46 (0.36 to 0.59)	0.33 (0.29 to 0.38)	0.001*
4D-STE			
4D GLS (%)	−20 (−22 to −17)	−18 (−20 to −17)	0.156
4D GCS (%)	−14 (−16 to −10)	−11 (−13 to −10)	0.04*
4D GRS (%)	42.5 (33.5 to 53.25)	42 (35 to 45)	0.345
4D GAS (%)	−29.5 (−32 to −23.7)	−27 (−29 to −25)	0.0890
LV diastolic function			
Diastolic parameters			
Mitral E (cm/s)	90 (83 to 108)	50 (40 to 65)	0.001*
Mitral E/A	1.6 ± 0.2	2 ± 0.5	0.008*
Mitral A (cm/s)	60 (53 to 70)	25 (16 to 42)	0.001*
Septal E′ (cm/s)	14 (12 to 15)	15 (13 to 17)	0.07
Septal A′ (cm/s)	8 (7.7 to 9)	6 (5 to 7)	0.001*
E/E′	6.8 (5.9 to 7.5)	3.4 (2.6 to 4.7)	0.001*
Lateral E′ (cm/s)	16.23 ± 2.89	18.26 ± 2.24	0.014*
Lateral A′ (cm/s)	8.30 ± 1.44	6.48 ± 2.10	0.000*

LV left ventricle, *LVDD* left ventricle diastolic dimension, *LVDS* left ventricle systolic dimension, *FS* fractional of shortening, *EF* Ejection fraction, *2ch* 2 chamber view, *4ch* 4 chamber view, *IVA* isovolumic acceleration, *EDV* end-diastolic volume, *ESV* end-systolic volume, *SV* stroke volume, *SPI* sphericity index, *GLS* global longitudinal strain, *GCS* global circumferential strain, *GRS* global radial strain, *GAS* global area strain, *PW-TDI* pulsed wave tissue Doppler imaging, *STE* speckle tracking echocardiography

*Statistically significant

The LVEF was obtained using several methods. The LVEF was calculated from M-mode, semi-automated from two- and four-chamber views and finally directly measured using 3D echocardiography, using all modalities; the LVEF did not differ significantly between patients and controls, although the loading conditions were significantly different (Table 2).

The systolic function of the LV was further assessed using TDI. With this tool, systolic function was reflected by two parameters, namely, the systolic excursion velocity (S′) and the IVA index. The TDI parameters were obtained from the basal portion of the IVS and the lateral wall of the left ventricle. The S′ velocity was higher in the patients than in the controls, reaching a statistically significant value in the basal portion of the left ventricle (Table 2). The IVA index did not differ between the groups (Table 2).

Finally, the LV systolic function was evaluated using novel 3D echocardiography and 3D speckle tracking

Table 3 Correlation between LVED z-score and LV diastolic parameters

Parameters	Correlation coefficient (r)	P value
LVED Z-score		
Mitral E	0.367	0.04*
Mitral A	0.338	0.06
Septal E′	−0.276	0.14
Septal A′	−0.411	0.02*
E/E′	0.478	0.008*
3D-LVEDV		
MRI-LVEDV	0.998	< 0.0001*
3D-LVESV		
MRI-LVESV	0.996	< 0.0001*
3D-LVEF		
MRI-LVEF	0.994	< 0.0001*

LVED left ventricle diastolic dimension, *MRI* magnetic resonance imaging, *LVED* left ventricle end-diastolic dimension, *LVEDV* left ventricle end-diastolic volume, *LVESV* left ventricle end-systolic volume, *LVEF* left ventricle ejection fraction

*Statistically significant

echocardiography. Using this novel modality, we were able to confirm that the left ventricle was significantly loaded with a significantly larger LVED in the patients than in the controls (Table 2).

The sphericity index was significantly higher in the patients than in the controls (Table 2), whereas the measured LVEF did not significantly differ between the patients and controls (Table 2). With 3D-STE, the deformation was assessed mainly in two directions: the longitudinal and circumferential directions. The longitudinal deformation was higher in the patients, although this difference was not statistically significant. On the other hand, the circumferential deformation was significantly higher in the patients than in the controls, while the area strain did not show a significant difference (Table 2).

Left Ventricular Diastolic Function

With pulsed Doppler, the early and late diastolic filling of the left ventricle were significantly increased in the studied patients. The E/A ratio was significantly reduced in the patients compared to the controls (Table 2). The diastolic function of the left ventricle was further assessed using TDI. The TDI parameters were obtained from the basal portion of the IVS and from the lateral wall of the left ventricle. The patients showed a significantly increased E/E′ ratio. Moreover, the E/E′ ratio significantly correlated with the LVEDD Z-score ($r = 0.48$, $P = 0.008$) (Table 3).

Cardiac MRI

MRI revealed no evidence of myocardial oedema, myocardial hyperaemia, myocardial fibrosis or pericardial thickening. Only 2 patients had minimal pericardial effusion (Table 4). The limits for agreement between LV end-diastolic volume measurements by 3D echocardiography and cardiac MRI were −2.9 to +2 ml, and the correlation curve had an r value of 0.998. The limits for agreement for LV end-systolic volumes were −2.3 to +2.5 ml, and the correlation curve had an r value of 0.996. Furthermore, the limits for agreement for the LVEFs were −1.6 to +2.2%, and the correlation curve had an r value of 0.994.

Discussion

Acute rheumatic fever and RHD continue to be widely prevalent in the developing world, which raises concerns about the efficiency of the control programmes [9]. Despite advances in diagnosis and management, RHD remains one of the major causes of mortality and morbidity in developing countries [10].

Table 4 cardiac MRI results for patient group

	Cardiac MRI, $n = 30$	3D-echocardiography, $n = 30$	P value
LV volumes			
LVEDV	131 (102 to 167)	131 (102 to 165)	0.952
LVESV	51 (39 to 74)	52 (39 to 75)	0.947
EF	60 (54 to 61)	59 (54 to 61)	0.801
MRI cardiac tissues			
Myocardial fibrosis (n)	0		
Pericardial fibrosis (n)	0		
Myocardial oedema (n)	0		
Myocardial hyperemia (n)	0		
Pericardial effusion (n)	2 (trivial effusion)		

EF ejection fraction, *MRI* magnetic resonance imaging, *LV* left ventricle, *LVEDV* left ventricle end-diastolic volume, *LVESV* left ventricle end-systolic volume, *LVEF* left ventricle ejection fraction

The aim of the present study was to evaluate LV function in a group of RHD children (without active carditis), diagnosed according to the modified Jones criteria with variable degrees of valve affection and normal systolic function assessed by conventional echocardiography. This cohort was compared to a group of healthy age-matched controls. LV systolic and diastolic function were assessed using conventional and non-conventional echocardiographic modalities in addition to cardiac MRI to detect myocardial involvement in the form of myocardial fibrosis, oedema or hyperaemia. In clinical settings, early identification of subtle myocardial dysfunction before the occurrence of irreversible myocardial dysfunction is challenging. Therefore, there are continuous efforts in this field to develop an inexpensive, bedside, accurate and reproducible technique that is able to detect patients with early subclinical LV dysfunction. Non-conventional echocardiographic studies should be performed for patients with RHD as a part of their medical care for early identification of subclinical LV myocardial dysfunction, optimization of therapeutic strategies, correct risk stratification as well as, prognostic stratification of RHD. These patients might benefit from early therapeutic measures before irreversible myocardial damage occurs.

Regarding systolic function, the LV systolic function was assessed using the gold standard LVEF obtained using different modalities, such as M-mode and 3D echocardiography. The major advantage of the 3D-derived EF over the conventional M-Mode-derived EF is its direct measurement without the need for a mathematical assumption. In addition, 3D echocardiography allows the foreshortening observed with 2D measurements to be avoided [11]. Another advantage of using 3D echocardiography for measuring LVEF is the fact that the assessment occurs during the same cardiac cycle, thus avoiding the bias of HR variability. Therefore, several studies in the literature have shown that the 3D-derived LVEF is as accurate as MRI-derived values [3]. In the present study, the LVEFs did not differ significantly between patients and controls (Table 2), even though the loading conditions were significantly different, as evidenced by RHD patients having an increased indexed LVED volume. Furthermore, the sphericity index was significantly higher in the patients than in the controls (Table 2), signifying an altered LV shape (from almond to a rather spherical shape). In accordance with previous studies, our results did not show any systolic dysfunction when interpreting the LV systolic function using the gold standard EF [12].

The systolic function of the left ventricle was further assessed using S′ velocity, which is known to be a load-dependent parameter. S′ measured at the lateral annulus of the mitral valve was significantly higher in the patients than in the controls (Table 3). This can be simply explained by the length-dependent activation observed in the Frank-Starling mechanism. The abnormal values of TDI systolic excursion observed in some patients with persistent valvular involvement may be incurred by persistent LV volume overload that increases wall stress, possibly causing sub-endocardial ischaemia [13].

3D STE-derived strain is a novel echocardiographic modality to determine LV deformation and systolic function. Using this novel modality, this study demonstrated that chronic mild and moderate LV volume overload in RHD is well tolerated by the myocardial fibres and mainly resulted in dilatation of the mitral ring and overstretching of the circumferential fibres, which are mainly located in the lateral wall of the left ventricle [14], resulting in enhancement of the circumferential deformation (Table 2). On the other hand, the volume overload stretches the longitudinal fibres located mainly in the IVS [14] to a lesser extent, resulting in almost normal longitudinal deformation. The global LV ejection, which is the net result of both deformations, remains unchanged and did not apparently differ significantly when compared to normal. The discrepancy between our results and those of previous studies [15, 16] demonstrating reduced LV deformation in RHD patients can be explained by the difference in the cohort age. Our study was conducted with children and adolescents, while other studies were conducted with adults. The myocardial reserve is definitely preserved in children compared to adults. In addition, the present study used a more advanced technique for assessing myocardial deformation. GLS and GCS derived from 3D-STE are more valid techniques for detecting longitudinal and circumferential deformation than 2D-STE techniques [6]. Thus, we conclude that in the present study, subtle systolic dysfunction is not detectable using conventional or novel non-conventional methods. This may indicate that the myocardial affection in rheumatic carditis is minimal with almost complete resolution. Our findings regarding LV systolic function, assessed by 3D echocardiography, were confirmed by MRI because none of the examined patients had myocardial fibrosis. Thus, our data support previous observations that rheumatic carditis mainly affects the endocardium rather than the myocardium. The mechanism underlying cardiac dysfunction in RHD has been extensively studied, and multiple mechanisms have been proposed. Several older studies have suggested that cardiac dysfunction in RHD is mainly due to myocardial inflammation [17], whereas more recent studies have suggested that it is mainly due to an endocardial affection and valvulitis with subsequent myocardial dysfunction secondary to chronic volume overload [18]. Thus, inotropes are usually not needed as a first line therapy in patients with RHD.

Regarding diastolic function, in the present study, the diastolic function of the left ventricle was assessed using pulsed Doppler imaging and TDI. The TDI parameters were obtained from the basal portion of the IVS and the lateral wall of the left ventricle (Table 2). With pulsed Doppler

imaging, the early and late diastolic filling of the left ventricle were significantly enhanced in the patients compared to the controls (Table 2). The enhancement of the early peak velocity can be explained by an increase in the left atrial pressure secondary to mitral regurgitation. The filling pressure affects all variables of the diastole (early and late filling peak velocities and, thus, the E/A ratio) because an increase in the left atrial pressure will increase the driving pressure across the mitral valve, thus shifting the diastolic pressure–volume curve upward and to the right [19]. With increasing preload, the atrial contribution to the diastolic filling process usually decreases. In the present study, we found a paradoxical enhancement of the atrial contribution because the late diastolic peak velocity was significantly increased in the patients compared to the controls (Table 2). The amount of filling with atrial contribution is related to the underlying ventricular compliance and the intrinsic atrial contractility, as well as the LV pressure at which atrial contraction begins. In patients with high LV pressures at the onset of atrial contraction, the atrial contribution is less [20]. With diminished compliance, the contribution from atrial contraction is less [21]. The atrial muscle contraction may still be effective in these instances and result in a pronounced pressure increase and increased retrograde flow into the pulmonary veins. Accordingly, it might be possible that our patients initially had an abnormal relaxation (grade I diastolic dysfunction) with an increased atrial contribution. This was, however, masked by the increased atrial filling pressure secondary to the mitral regurgitation. In favour of this hypothesis is the reduced E/A ratio (i.e. grade I diastolic dysfunction) found in our patients compared to the controls (Table 2) and the increased E/E′ ratio observed in the patients compared to the controls, which, on the other hand, did not exceed the overall accepted cut-off point of 15 that signifies an elevated LV end-diastolic pressure.

In the present study, the findings of increased E/E′ ratio are in accordance with the results of Jane et al., [22]. We also found a positive correlation between the LV volume evaluated with the Z-score and E/E′ ratio. This observation does not necessarily mean that the LV end-diastolic pressure in our patients was significantly elevated. Interpretations of the E/E′ ratio in RHD with mitral regurgitation should be made cautiously because the elevated early peak velocity obtained from pulsed Doppler is falsely enhanced by the increased preload. To interpret the increased E/E′ ratio as a marker of increased end-diastolic pressure, the E′ obtained from TDI should be decreased, which was not observed in our patients (Table 2). Thus, this is probably due the fact that elevated early peak velocity obtained from pulsed Doppler is falsely enhanced by the increased preload rather than diastolic myocardial dysfunction. However, further studies are needed to confirm this hypothesis.

Patients with RHD who are found to have subtle LV myocardial dysfunction (systolic or diastolic) by non-conventional echocardiographic studies should be closely followed, with medical control of the volume overload resulting from valvular insufficiency, rather than using inotropes, with further assessment.

Although we did not exclude patients with mitral stenosis from our study; however, nowadays we do not see many cases with mitral stenosis due to the widespread and early use of long acting penicillin. Also mitral stenosis is more likely seen in adolescent and adult patients. It would be also of value to compare the results of this study with further studies focusing on patients with RHD who have isolated mitral stenosis to abolish the effect of chronic LV volume overload on the myocardial fibres.

Conclusion

In children with RHD and preserved systolic function, subtle systolic dysfunction could not be detected using conventional and novel non-conventional methods. This may indicate that the myocardial affection in rheumatic carditis is minimal with almost complete resolution. The volume load caused by valvular incompetence results in alterations in the E/E′ ratio, which does not necessarily signify an elevation in the LV end-diastolic pressure.

We believe that performing a similar study with a larger sample size and correlating its results with pro-BNP and cardiac MRI findings will add to the conclusions supplied by this study.

Limitations

The cross-sectional and non-longitudinal study design is a limitation of the present work. Additionally, the absence of invasive measurements of LV end-diastolic pressure limits the confirmation of our conclusions concerning diastolic function.

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Compliance with Ethical Standards

Conflict of interests The authors declare that there is no conflict of interests.

Ethical Standard All procedures that were performed were in accordance with the ethical standards of the Kasr Al Ainy Research Committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. The study protocol was approved by the institutional review board.

References

1. Seckeler MD, Hoke TR (2011) The worldwide epidemiology of acute rheumatic fever and rheumatic heart disease. Clin Epidemiol 3:67–84. https://doi.org/10.2147/CLEP.S12977
2. Monaghan MJ (2006) Role of real time 3D echocardiography in evaluating the left ventricle. Heart 92:131–136. https://doi.org/10.1136/hrt.2004.058388
3. Shibayama K, Watanabe H, Iguchi N et al (2013) Evaluation of automated measurement of left ventricular volume by novel real-time 3-dimensional echocardiographic system: Validation with cardiac magnetic resonance imaging and 2-dimensional echocardiography. J Cardiol 61:281–288. https://doi.org/10.1016/j.jjcc.2012.11.005
4. Ho CY, Solomon SD (2006) A clinician's guide to tissue doppler imaging. Circulation 113:396–399. https://doi.org/10.1161/CIRCULATIONAHA.105.579268
5. Mor-Avi V, Lang RM, Badano LP et al (2011) Current and evolving echocardiographic techniques for the quantitative evaluation of cardiac mechanics: ASE/EAE consensus statement on methodology and indications endorsed by the Japanese Society of Echocardiography. Eur J Echocardiogr 12:167–205. https://doi.org/10.1093/ejechocard/jer021
6. Altman M, Bergerot C, Aussoleil A et al (2014) Assessment of left ventricular systolic function by deformation imaging derived from speckle tracking: A comparison between 2D and 3D echo modalities. Eur Heart J Cardiovasc Imaging 15:316–323. https://doi.org/10.1093/ehjci/jet103
7. Vogel M (2002) Validation of myocardial acceleration during isovolumic contraction as a novel noninvasive index of right ventricular contractility: comparison with ventricular pressure-volume relations in an animal model. Circulation 105:1693–1699. https://doi.org/10.1161/01.CIR.0000013773.67850.BA
8. Vieira MLC, Oliveira WA, Cordovil A et al. 3D Echo pilot study of geometric left ventricular changes after acute myocardial infarction. Arq Bras Cardiol 101:43–51. https://doi.org/10.5935/abc.20130112
9. Karthikeyan G, Zühlke L, Engel M et al (2012) Rationale and design of a global rheumatic heart disease registry: the REMEDY study. Am Heart J 163:535–40.e1. https://doi.org/10.1016/j.ahj.2012.01.003
10. Carapetis J, Brown A, Maguire G, Walsh W (2012) The Australian guideline for prevention, diagnosis and management of acute rheumatic fever and rheumatic heart disease. Heal. https://doi.org/10.1016/j.hlc.2007.12.002
11. Otterstad JE, Froeland G, St John Sutton M, Holme I (1997) Accuracy and reproducibility of biplane two-dimensional echocardiographic measurements of left ventricular dimensions and function. Eur Heart J 18:507–513. https://doi.org/10.1093/oxfordjournals.eurheartj.a015273
12. Guven S, Sen T, Tufekcioglu O et al (2014) Evaluation of left ventricular systolic function with pulsed wave tissue doppler in rheumatic mitral stenosis. Cardiol J 21:33–38. https://doi.org/10.5603/CJ.a2013.0058
13. Lee LC, Zhihong Z, Hinson A, Guccione JM (2013) Reduction in left ventricular wall stress and improvement in function in failing hearts using algisyl-LVR. J Vis Exp. https://doi.org/10.3791/50096
14. Torrent-Guasp F, Kocica MJ, Corno A et al (2004) Systolic ventricular filling. Eur J Cardio-thoracic Surg 25:376–386. https://doi.org/10.1016/j.ejcts.2003.12.020
15. Kayıkçıoğlu M (2010) Pulmoner hipertansiyonda etiyopatogenez: inflamasyon, vasküler yeniden şekillenme. Anadolu Kardiyol Derg 10:5–8. https://doi.org/10.5152/akd.2010.113
16. Younan H (2013) Role of two dimensional strain and strain rate imaging in assessment of left ventricular systolic function in patients with rheumatic mitral stenosis and normal ejection fraction. Egypt Hear J 67:193–198. https://doi.org/10.1016/j.ehj.2014.07.003
17. Bryant PA, Robins-Browne R, Carapetis JR, Curtis N (2009) Some of the people, some of the time susceptibility to acute rheumatic fever. Circulation 119:742–753. https://doi.org/10.1161/CIRCULATIONAHA.108.792135
18. Essop MR, Wisenbaugh T, Sareli P (1993) Evidence against a myocardial factor as the cause of left ventricular dilation in active rheumatic carditis. J Am Coll Cardiol 22:826–829. https://doi.org/10.1016/0735-1097(93)90197-9
19. Nishimura RA, Abel MD, Hatle LK, Tajik AJ (1989) Assessment of diastolic function of the heart: background and current applications of Doppler echocardiography. Part II. Clinical studies. Mayo Clin Proc 64:181–204
20. Greenberg NL, Firstenberg MS, Castro PL et al (2002) Doppler-derived myocardial systolic strain rate is a strong index of left ventricular contractility. Circulation 105:99–105. https://doi.org/10.1161/hc0102.101396
21. Gaasch WH, Levine HJ, Quinones MA, Alexander JK (1976) Left ventricular compliance: mechanisms and clinical implications. Am J Cardiol 38:645–653
22. Mona S, Jain KH, Sharma ND, Jadhav, Komal H, Shah A, Konat (2015) Tissue doppler imaging in rheumatic mitral valve disease patients for the assessment of left ventricular function. Am J Adv Med Surg Res 1(1):3–8