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Assessment of Myocardial Mechanics in Acute Rheumatic Fever Using Speckle-Tracking Echocardiography

ABSTRACT

Background: This study aims to evaluate the role of speckle-tracking echocardiography to identify myocardial deformation in acute rheumatic fever.

Methods: Twenty-seven patients and 27 healthy children were prospectively evaluated. The patient group was divided into 2 subgroups based on echocardiographic findings, with or without carditis. The left ventricular global longitudinal strain and strain rate, left ventricular global circumferential strain and strain rate, and right ventricular global longitudinal strain and strain rate were assessed by speckle-tracking echocardiography.

Results: In the acute phase of the disease, all values except the right ventricular global longitudinal strain were found to be significantly below the control group in the patient cohort. No significant difference was found between the patients grouped as carditis and non-carditis in the acute period. Comparison of the acute period with the post-treatment period revealed a significant increase in all strain values of the patients with carditis and significant increases observed in all values except left ventricular global longitudinal strain rate, left ventricular global circumferential strain rate, and right ventricular global longitudinal strain rate values in patients without carditis. Apart from the right ventricular global longitudinal strain rate, which was significantly lower in the non-carditis group compared to the control group, there was no significant difference in strain values between the patient and control groups following treatment.

Conclusion: In the present study, we found that all patients, including patients in whom no valvular involvement was detected by echocardiography in the acute phase of acute rheumatic fever, had a lower right and left ventricular strain and strain rate measurements and that these findings improved after treatment, suggesting that strain echocardiography may be a helpful diagnostic method, especially in patients without valvular involvement.

Keywords: Rheumatic heart disease, strain, speckle-tracking echocardiography, children

ORIGINAL INVESTIGATION

INTRODUCTION

Rheumatic heart disease (RHD) is endemic in developing countries specifically among school-age children. Joint, skin, and central nervous systems might be involved but heart involvement, which can cause mortality and morbidity, is the most important clinical outcome. Heart involvement is thought to start from the endocardium and progress through the pericardium.[1] Another opinion that has been put forward is that patients diagnosed with RHD can have some degree of myocardial involvement in general.[2] In patients with cardiac involvement, the degree and severity of valve involvement can be diagnosed easily; however, it is difficult to identify myocardial involvement and its severity. When there is pericardial involvement, the assumption is that there is myocardial involvement as well. In the absence of pericardial involvement, it is difficult to diagnose myocardial involvement even with endomyocardial biopsy.[3] To identify such involvement, more advanced diagnostic techniques such as speckle-tracking echocardiography (STE) need to be utilized.

Speckle-tracking echocardiography has been shown to be more effective than the conventional measures of ejection fraction (EF) and shortening fraction (FS)

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in evaluating heart functions.[4] Many patients having heart failure, hypertension, systemic lupus eythematosus, and Duchenne-type muscular dystrophy who have been evaluated as normal with conventional techniques were identified to have abnormalities in strain values.[5-8]

In this study, we tried to demonstrate that during the acute stages of rheumatic fever, there might be abnormalities due to myocardial involvement that can be diagnosed with myocardial strain and that these abnormalities might differ in patients having mild and moderate-to-severe carditis and that such abnormalities might disappear after the treatment period has ended.

METHODS

Study Population

Twenty-nine patients (mean age 12.3 ± 3.2 years, range 6-18 years; 14 male/15 female) diagnosed with acute rheumatic fever from January 2016 to January 2017 were prospectively enrolled in this study. Two patients who were diagnosed with juvenile idiopathic arthritis and systemic lupus erythematosus upon enrollment in the study were excluded afterward. According to the revised Jones criteria, the study cohort was grouped into carditis and non-carditis groups.[9] Carditis group was made up of 17 patients and the non-carditis group consisted of 10. All data were compared with those of 27 healthy children of similar sex and age (mean age 11.7 ± 3.1 years, range 7-17 years; 16 male/11 female, $P = .781$ for age, $P = .722$ for sex).

The patients were included in the study according to previously defined revised Jones criteria for acute rheumatic fever.[9] Patients with recurrent RHD were not included in the study. Erythrocyte sedimentation rate and C-reactive protein values were measured in all patients before and after the treatment. After a single dose of benzathine penicillin, patients were either treated with corticosteroids or nonsteroidal anti-inflammatory drugs depending on the involvement of the valve and the severity of the valve involvement. Standard transthoracic echocardiographic examination and STE were performed in both patients and the control group.

The study complied with the Declaration of Helsinki, and the Clinical Research Ethical Committee approved the study (Decree no: 2017-027). The families of the patients provided their informed consent.

HIGHLIGHTS

- Acute rheumatic fever is generally accepted as a disease of endocardium, and it rarely involves the myocardium.
- Speckle-tracking echocardiography provides a more sensitive assessment of myocardial functions as compared to conventional echocardiography.
- In the present study, myocardial strain and strain rates were demonstrated to be significantly reduced in all patients, including patients without valvular involvement, during the acute phase of the disease compared to the controls.

Echocardiographic Examination

Echocardiography was performed by using the Philips iE33 ultrasound system (Philips, The Netherlands) and a 5 MHz transducer. Conventional echocardiography and STE were performed before and after treatment (4-6 weeks after when acute phase reactants decrease). Systolic function was assessed by M-mode-derived FS and EF. Left ventricular EF >54% and FS >28% were accepted as normal left ventricular systolic function.[10]

For STE, 2-dimensional 4-chamber images together with short-axis mid-circumferential images of the left ventricular were obtained. Three cardiac cycles were recorded as cine loop clips. Strain and strain rate measurements were performed using the software package QLAB Advanced Quantification Software (version 6.0, Philips, The Netherlands). The main measures were left ventricular global longitudinal strain (LVGLS) and left ventricular global longitudinal strain rate (LVGLSR), left ventricular global circumferential strain (LVGCS) and left ventricular global circumferential strain rate (LVGCSR), and right ventricular global longitudinal strain (RVGLS) and right ventricular global longitudinal strain rate (RVGLSR). All the images were obtained in the left lateral decubitus position under ECG monitoring. All echocardiographic parameters were analyzed by 1 researcher at 2 different time points.

Statistical Analysis

Study data were analyzed with the Statistical Package for Social Sciences (SPSS) for Windows 17.0 package program (SPSS Inc., Chicago, Ill, USA). For descriptive measures, mean and SD were used. The variables were considered to be distributed regularly by Shapiro–Wilk test, and comparisons between groups were made by independent samples *t*-test, one-way analysis of variance (ANOVA). The differences in each group before and after the treatment were identified by paired samples *t*-test. A *P*-value of <.05 was considered as being statistically significant.

RESULTS

Patient Characteristics

Fourteen of the patients enrolled in the study were male (51.9%), while 13 were female (48.1%). The mean age of the patients was 12.3 ± 3.2 (6-18) years. The hospitalization period of the patients was a median of 7 days. Polyarthralgia was the most common complaint (17 patients), followed by arthritis (10 patients) and fever (5 patients). We only had 1 patient with subcutaneous nodules. There was no patient with the diagnosis of erythema marginatum.

M-mode Derived Echocardiographic Findings

All patients (carditis group EF 69.6 ± 2.29%, FS 38.9 ± 1.8%; mild/no carditis group EF 69.6 ± 3.7%, FS 38.99 ± 3.2%) and healthy controls (EF 69 ± 2.72%, FS 38.2 ± 1.98%) had normal systolic functions and there was no statistically significant difference between the 2 groups (Table 1).

Furthermore, there were no statistically significant differences for EF and FS between pre-treatment (mean EF 69.3 ± 3%, FS 38.6 ± 2.4%) and post-treatment (mean EF 69.6 ± 2.8%, FS 38.8 ± 2.3%) measurements in the study group ($P = .768$ for

Table 1. Ejection Fraction, Fractional Shortening of the Patient, and Control Groups before Treatment

	Mean EF (%)	*P*
Carditis	70.2 ± 3.5	.297
No carditis	68.5 ± 2.5	
Control	69 ± 2.7	
	Mean FS (%)	
Carditis	39.5 ± 3.0	.168
No carditis	38.2 ± 2.0	
Control	38.2 ± 1.9	

EF, ejection fraction; FS, fractional shortening.

EF, $P = .698$ for FS), in moderate/severe carditis group ($P = .59$ for EF, $P = .29$ for FS), and in mild/no carditis group ($P = .922$ for EF, $P = .748$ for FS).

Speckle-Tracking Echocardiographic Findings

Left ventricular global longitudinal strain, LVGLSR, LVGCS, LVGCSR, RVGLS, and RVGLSR were significantly lower in all the patients and the controls before the treatment. Besides, no statistically significant difference was found between groups with and without carditis in terms of strain parameters (Table 2).

Regardless of the presence or absence of carditis, when the patient group was analyzed as a whole, a statistically significant difference was obtained between all parameters before and after treatment ($P < .05$). After treatment, a paired samples *t*-test showed a statistically significant increase in all strain values of all patients except LVGLSR, LVGCSR, and RVGLSR values of the patients without carditis (Table 3). Comparing the post-treatment strain parameters of the patients with those of the control group, no significant difference was observed in the parameters except for the RVGLSR in the non-carditis and control groups. When we compared the strain parameters of the patients with those of the controls after the treatment, there were not any significant differences (Table 4).

DISCUSSION

Rheumatic heart disease is one of the major causes of cardiac mortality and morbidity in school-age children specifically in developing countries. The estimates show 15 million cases worldwide, 233 000 of them dying every year.[11] Hence, the diagnosis, the treatment, and the pathophysiology of the disease assume utmost importance.

Although some investigators suggest that RHD always presents as pancarditis, it is generally accepted as a disease

Table 2. Strain Parameters before Treatment

	No Carditis (n = 10)	Carditis (n = 17)	Control (n = 27)	*P1*	*P2*	*P3*	*P4*
LVGLS	17.7 ± 2.2	19.2 ± 2.4	22.1 ± 3.5	.001	.001	.015	.241
LVGLSR	0.39 ± 0.14	0.33 ± 0.21	0.64 ± 0.40	.009	.047	.014	.648
LVGCS	18.3 ± 2.2	18.4 ± 3.1	21.1 ± 3.2	.013	.025	.037	.985
LVGCSR	0.32 ± 0.26	0.40 ± 0.22	0.68 ± 0.35	.002	.011	.012	.707
RVGLS	19.9 ± 3.1	18.8 ± 3.1	23.9 ± 6.8	.010	.079	.013	.663
RVGLSR	0.33 ± 0.15	0.30 ± 0.19	0.70 ± 0.42	.001	.004	.003	.981

P1: NC/Ca/C, P2: NC/Co, P3: Ca/Co, P4: NC/Ca.
C, control; Ca, carditis; NC, no carditis.
LVGLS, left ventricular global longitudinal strain; LVGLSR, left ventricular global longitudinal strain rate; LVGCS, left ventricular global circumferential strain; LVGCSR, left ventricular global circumferential strain rate; RVGLS, right ventricular global longitudinal strain; RVGLSR, right ventricular global longitudinal strain rate.

Table 3. Strain Parameters of the Patients before and after the Treatment

		Pre-treatment (mean ± SD)	Post-treatment (mean ± SD)	*P*
Carditis	LVGLS	19.2 ± 2.5	22.0 ± 2.2	.001
	LVGLSR	0.33 ± 0.21	0.62 ± 0.34	.002
	LVGCS	18.5 ± 3.1	22.6 ± 3.3	.001
	LVGCSR	0.40 ± 0.22	0.62 ± 0.34	.036
	RVGLS	18.8 ± 3.1	21.8 ± 4.4	.009
	RVGLSR	0.32 ± 0.19	0.53 ± 0.26	.002
No carditis	LVGLS	17.7 ± 2.2	21.6 ± 3.4	.009
	LVGLSR	0.39 ± 0.14	0.43 ± 0.34	.753
	LVGCS	18.3 ± 2.3	21.9 ± 3.8	.040
	LVGCSR	0.32 ± 0.26	0.61 ± 0.37	.116
	RVGLS	19.9 ± 3.0	23.3 ± 4.2	.015
	RVGLSR	0.33 ± 0.15	0.41 ± 0.13	.210

LVGLS, left ventricular global longitudinal strain; LVGLSR, left ventricular global longitudinal strain rate; LVGCS, left ventricular global circumferential strain; LVGCSR, left ventricular global circumferential strain rate; RVGLS, right ventricular global longitudinal strain; RVGLSR, right ventricular global longitudinal strain rate.

Table 4. Strain Parameters after the Treatment

	No carditis (n = 10)	Carditis (n = 17)	Control (n = 27)	*P1*	*P2*	*P3*	*P4*
LVGLS	21.6 ± 3.4	22.0 ± 2.2	22.8 ± 3.2	.902	.914	.987	.941
LVGLSR	0.43 ± 0.34	0.62 ± 0.34	0.61 ± 0.37	.322	.319	.992	.354
LVGCS	21.9 ± 3.8	22.6 ± 3.3	21.8 ± 3.5	.435	.853	.384	.884
LVGCSR	0.61 ± 0.37	0.62 ± 0.34	0.61 ± 0.32	.788	.853	.821	.998
RVGLS	23.3 ± 4.2	21.8 ± 4.4	23.9 ± 6.8	.517	.951	.669	.496
RVGLSR	0.41 ± 0.13	0.53 ± 0.26	0.78 ± 0.40	.059	.020	.281	.271

P1: NC/Ca/C, P2: NC/Co, P3: Ca/Co, P4: NC/Ca
C, control; Ca, carditis; NC, no carditis.
LVGLS, left ventricular global longitudinal strain; LVGLSR, left ventricular global longitudinal strain rate; LVGCS, left ventricular global circumferential strain; LVGCSR, left ventricular global circumferential strain rate; RVGLS, right ventricular global longitudinal strain; RVGLSR, right ventricular global longitudinal strain rate.

of the endocardium and the valves, and it rarely involves the myocardium.[12] Clinical findings such as tachycardia and tachypnea indicate heart failure for which valvular regurgitation is the main reason, although myocardial involvement can also contribute to that process.[13,14] Narula et al[3] found no myocyte necrosis, but non-specific changes were frequently observed in the right ventricular biopsy specimens. Several recent studies questioned myocardial involvement contributing to myocardial dysfunction and they proposed that RHD is only a disease of the endocardium and that myocardial influences are due to valve regurgitation.[15,16] For patients with RHD, the postmortem microscopic examination of the cardiac muscle showed lymphocyte infiltration during the acute stage and fibrosis during the chronic stage, and functional disorders of the heart muscle were reported due to these changes.[17,18] Myocardial biopsies demonstrated mononuclear cells and fibrin degeneration while myocardial necrosis was not reported.[3] Cross-reactivity between cardiac myosin and group A beta-hemolytic Streptococcal M protein has also been demonstrated.[17]

Two-dimensional STE can detect myocardial contraction abnormalities long before decreases in left ventricular ejection fraction are observed.[19,20] Moreover, STE is less angle dependent than Doppler-based methods.[20] In this study, patients were analyzed before and after the treatment and compared to healthy controls by STE.

In the present study, significantly reduced left ventricular global longitudinal and circumferential strain and strain rates and RVGLS and RVGLSR were found in patients with preserved left ventricular ejection fraction and fractional shortening in the acute phase of RHD compared to healthy controls. According to our results, there were no statistically significant differences in strain and strain rates between carditis and non-carditis patients with normal cardiac functions assessed by conventional methods. Thus, we suggest that the reductions in strain parameters were associated with effects on myocardial tissue rather than valvular involvement. In line with this finding, Ozdemir et al[2] found higher troponin T levels in 28 patients with active rheumatic carditis compared to healthy controls and they speculated that most patients may have involvement in the myocardial region adjacent to the endocardium, albeit to a lesser extent. Additionally, by using paired samples *t*-test, we found improvement in left ventricular global longitudinal and circumferential and right ventricular global longitudinal strain and strain ratios after treatment. After the treatment, except for RVGLSR in the non-carditis patient group, all strain and strain rates were statistically increased.

In the literature, there are a limited number of studies analyzing RHD and myocardial strain. In one such study, in adults with rheumatic mitral stenosis, LVGCS and LVGCS were lower than those of the controls, and recovery was seen after balloon mitral valvuloplasty. This was not due to myopathic processes but due to a tethering effect caused by the secondary restriction of the basal myocardium from mitral stenosis.[21] In another study similar to this one, 60 adult patients with rheumatic mitral stenosis having preserved EF LVGLS and LVGLSR were low.[22] Beaton et al[23] one of the rare studies examining the relationship between myocardial strain and RHD in children, found that LVGLS values were lower in patients with latent RHD with normal systolic function compared to controls and they suggested that myocardial strain may play a role in understanding the pathophysiology of latent RHD.[23] In this study, similar to ours, a pediatric patient group without systolic dysfunction was analyzed and the only difference was the inclusion of patients in the study during the latent stage. Unlike this study, we found that global longitudinal strain values differed from healthy controls only in the acute phase of the disease. After treatment, LVGLS and also RVGLS increased to the same extent as healthy children in our study. In pediatric patients with latent RHD, normal heart muscle function was demonstrated with conventional methods; a new technique, 3D strain echocardiography, found normal strain values during the latent stage supporting our study.[24]

Study Limitations

While it contributes to the literature, our study has certain limitations. First of all, the number of patients is rather low to draw a meaningful conclusion. Furthermore, we measured strain parameters only globally; the radial strain was not analyzed and the 17-segment model recommended by American Heart Association was not used. Therefore, segmental strain imaging would be preferable. Moreover, we do not have long-term follow-up results.

CONCLUSION

The aim of this study is to identify subtle ventricular dysfunction by STE in children with active RHD, who are shown to have normal cardiac functions by conventional methods. In the literature, there are a very limited number of studies investigating myocardial strain in RHD. This is the first study assessing myocardial deformation during the acute phase of RHD. According to our study, myocardial strain and strain rate values were lower in patients with acute RHD compared to healthy controls, even in those without valvular involvement. Based on our data, this was thought to be due to myocardial impairment rather than valvular involvement. These findings raise the possibility that all patients with acute RHD may have some degree of myocardial involvement. We need to perform more detailed studies to understand the reason behind myocardial dysfunction; however, based on available information, this is more likely due to myocardial inflammation than myocardial necrosis. We need to identify the role of myocardial strain and strain rate on RHD pathophysiology, diagnosis, and treatment with studies conducted on larger patient groups.

Ethics Committee Approval: This study was approved by Ethics Committee of Ankara Child Health and Diseases Hematology Oncology Training and Research Hospital (Approval No: 027, Date: 2017).

Informed Consent: Written informed consent was obtained from the patients' parents who agreed to take part in the study.

Peer-review: Externally peer-reviewed.

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