

Echocardiographic and Laboratory Findings of Turkish Children during the First Attack of Acute Rheumatic Fever

Erman Çilsal¹, Ayhan Pektaş², Bilgehan M. Pektaş³, Buğra H. Koca⁴

¹Clinic of Pediatric Cardiology, Adana City Training and Research Hospital, Adana, Turkey

²Department of Pediatric Cardiology, Afyon Health Sciences University School of Medicine Hospital, Afyon, Turkey

³Department of Pharmacology, Afyon Health Science University School of Medicine, Afyon, Turkey

⁴Department of Medical Biochemistry, Afyon Health Science University School of Medicine, Afyon, Turkey

ABSTRACT

Objective: In this study, we aim to determine demographic features and laboratory data of Turkish children who are diagnosed with acute rheumatic carditis and to evaluate echocardiographic indices of the left ventricle (LV) and right ventricle (RV) systolic-diastolic functions at the time of diagnosis.

Methods: This is a retrospective review of 100 children who were hospitalized because of the diagnosis of acute rheumatic fever (ARF)-related acute-stage carditis and 100 healthy children who were matched with respect to age and body mass index. All subjects initially underwent detailed two-dimensional (2D), pulsed Doppler, and tissue Doppler for assessment of ventricular functions.

Results: Internal diameter of LV, measured during end-systole, was significantly increased and the mitral annular plane systolic excursion was decreased in patients compared with those in controls ($p=0.005$). Although E' velocity derived from septal mitral annulus were significantly lower, isovolumetric contraction time and myocardial performance index were increased in the carditis group compared with that in the control group. Peak early diastolic (E'), late diastolic (A'), and systolic (S') myocardial velocities; isovolumetric contraction time; and myocardial performance index measured from the tricuspid annulus were similar in the carditis and control groups, although isovolumetric relaxation time was significantly prolonged. The carditis group had significantly lower mean corpuscular and platelet volume than the control group, although erythrocyte sedimentation rate and serum C-reactive protein levels were higher.

Conclusion: We detected a subclinical reduction in the systolic and diastolic function of both ventricles in children with the first attack of ARF. "Pulsed" and tissue Doppler techniques in pediatric patients with ARF have an important role in assessing cardiac functions.

Keywords: Acute rheumatic fever, carditis, children, Doppler echocardiography

INTRODUCTION

Acute rheumatic fever (ARF) is an inflammatory disease caused by a delayed autoimmune response to a preceding Group A streptococcal infection of the throat. It is still an endemic disease, particularly observed among school-aged children in developing countries, and the incidence of an ARF episode following streptococcal pharyngitis is 0.5%-3% (1-3).

Being a multisystem disease, ARF can affect different tissues and cause a wide spectrum of clinical features, including carditis, arthritis, chorea, subcutaneous nodules, and erythema marginatum. The most clinical presentation of ARF is migratory arthritis with severe pain, observed in approximately 80% of patients. Major joints, like the knees, ankles, elbows, or shoulders, are often affected. Sydenham chorea, a neurologic expression of ARF, is the most common cause of acute chorea in pediatric population despite declining incidence of ARF (4-6).

Carditis is the most important manifestation of rheumatic fever, affecting 30%-50% of ARF patients. In fact, ARF is the leading cause of acquired heart diseases in children and adolescents worldwide. Because rheumatic fever can involve the pericardium, myocardium, and free borders of cardiac valve cups, it may develop into chronic and progressive valvular lesions because of immune-mediated damage and thus, result in significant morbidity and mortality. The mitral valve is the most affected valve, which is followed by the aortic and tricuspid valves, respectively. Moreover, carditis with progressive congestive heart failure, a new murmur, or pericarditis may indicate unrecognized previous ARF episodes (4, 7). This disease is more frequent in developing countries where low living standards and poor public health conditions are observed (8, 9).

The present study was designed to evaluate demographic features and laboratory data of patients with acute rheumatic car-

Corresponding Author: Erman Çilsal E-mail: ermancilsal@gmail.com

Received: 26.09.2017 • **Accepted:** 29.12.2017

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ditis. We also aimed to compare echocardiographic indices of LV and RV systolic and diastolic function in newly diagnosed patients with those of controls.

METHODS

This study was approved by the institutional review board and ethical committee of Afyon Kocatepe University Hospital where it was conducted at the department of pediatric cardiology between January 2015 and December 2015. Written informed consent was obtained from each participant and their parents.

Study Population

We retrospectively studied 100 patients presenting with their first attack of rheumatic carditis to our clinic over 12 months. All subjects had evidence of ongoing rheumatic activity, including elevated acute phase reactants. We also recruited 100 healthy subjects who were referred for evaluation of an innocent murmur over the same period.

Diagnosis of ARF was based on the revised Jones criteria, whereas acute rheumatic carditis was defined as the presence of a new murmur, tachycardia, gallop rhythm, cardiomegaly, or congestive heart failure and is diagnosed by echocardiography. The World Health Organization Expert Committee specified four criteria of mitral and aortic regurgitant jets to distinguish between normal and pathological regurgitation on echocardiography and between normal and pathological mitral and aortic regurgitation. Accordingly, the regurgitant jet should be at least 1 cm in length, seen in at least two planes, have a peak velocity of 2.5 m/s, and should persist throughout the systole or diastole (10, 11).

The patients who had previously been diagnosed with congenital or rheumatic heart disease were excluded from this study. In addition, patients who had abnormal hepatic or renal functions, those with myeloproliferative disorders and malignancies, and those who used any medications (such as aspirin) that might have caused platelet or coagulation abnormalities during the last 2 months before blood sampling were excluded from the study.

Echocardiography Examination

Echocardiography examination was performed using equipment with 3- and 5-MHz transducers (Vivid S6, GE Healthcare, UK). All subjects underwent echocardiographic examination within 24–48 h after the diagnosis of ARF and before starting anti-inflammatory treatment.

Standard Echocardiographic Assessment

Parasternal long-axis views provided two-dimensional M-mode images. All children's interventricular septal wall thickness left ventricular internal diameters and left ventricular posterior wall thickness measurements were determined. Using the shortening fraction, we evaluated systolic functions of the left ventricle (LV). The Teichholz method was utilized for calculating the ejection fraction (12).

Mitral and tricuspid annular plane systolic excursion (MAPSE and TAPSE, respectively) were measured using the standard M-mode

technique. TAPSE and MAPSE were measured in an M-mode examination in the apical four-chamber view during systole, at the junction of the right ventricle (RV) and LV with the tricuspid and mitral valve, and expressed in mm.

"Pulsed" Doppler measurements were performed with the transducer from the apical 4-chamber view. The LV and RV-inflow pattern at the tips of the mitral valve and tricuspid provided peak early filling velocity (E) and peak late filling velocity (A) and E/A ratio.

Measurements of "pulsed" tissue Doppler were attained with the transducer from the apical 4-chamber view by aligning the Doppler beam perpendicular to the plane of the lateral tricuspid and lateral and septal mitral annulus. The off-line analysis used the average measurements of the peak systolic (S'), early diastolic (E'), and late diastolic (A') myocardial velocities in 2–3 cardiac cycles.

The isovolumic contraction time (IVCT: interval between the end of the A' wave and the beginning of the S' wave) and the isovolumic relaxation time (IVRT: interval between the end of the S' wave and the beginning of the E' wave) were measured for both sides of the mitral annulus and lateral side of the tricuspid annulus on the tissue Doppler. The following formula was used for calculating the myocardial performance index [MPI: isovolumic relaxation time + isovolumic contraction time/LV ejection time (defined as the duration of the S' wave)] (13).

Laboratory Studies

Complete blood count, including hemoglobin level, mean corpuscular volume (MCV), red cell distribution width (RDW), leukocyte count, neutrophil/lymphocyte ratio, platelet count, and mean platelet volume (MPV), was calculated using an automated counter (Coulter analyzer, Max Instruments Laboratory, Milan, Italy). Erythrocyte sedimentation rate (ESR) was determined by the Westergren method. Serum C-reactive protein (CRP) and mannan-binding lectin (MBL) levels were measured by enzyme-linked immunosorbent assay, whereas serum 25-hydroxy-vitamin D levels were recorded by radioimmunoassay (DSL Diagnostic Systems Laboratories, USA).

Statistical Analysis

Data are presented as mean±SD. Comparisons between the groups were calculated using nonparametric tests (Mann-Whitney U test) for non-normally distributed data and parametric tests (Student's t-test) for normally distributed data. Kolmogorov-Smirnov test was used for checking the distribution of the variables. A $p < 0.05$ was considered to be significant. All statistical analyses were performed using SPSS (Statistical Package for Social Sciences) version 18.0 (IBM Corp.; Armonk, NY, USA).

RESULTS

Clinical Features

A hundred children with rheumatic carditis (41 male; 59 female) and 100 healthy controls (33 male; 67 female) were recruited. The mean age of the patients and controls were 13.2 ± 3.0 and 13.9 ± 2.3 years, respectively. Table 1 summarizes the demographic characteristics of the children enrolled in the study. Both the

Table 1. Demographic Characteristics of the Study Population

	Carditis Group (n=100)	Control Group (n=100)	p
Age (years)	13.2±3.0	13.9±2.3	0.133
Male/Female (%)	(41/59)	(33/67)	0.115
Body weight (kg)	48.9±12.7	48.6±12.2	0.196
Body height (cm)	157.7±15.0	157.2±11.2	0.214
Body mass index (kg/m ²)	19.3±3.3	19.4±3.2	0.157

Data are presented as mean±SD; *p<0.05 was accepted to be statistically significant.

Table 2. Echocardiography Findings of the Study Population

	Carditis Group (n=100)	Control Group (n=100)	p
Ejection fraction (%)	74.1±10.6	72.2±10.6	0.127
Fractional shortening (%)	43.2±10.1	42.2±9.0	0.177
Systolic volume	55.0±19.0	50.7±16.8	0.146
End-diastolic volume	73.0±22.1	70.2±21.9	0.230
Left ventricle internal diameter end-systole (cm)	2.3±0.5	2.1±0.5	0.005*
Left ventricle internal diameter end-diastole (cm)	3.6±1.2	3.9±0.6	0.248
Left ventricle posterior wall diameter-systole (cm)	1.5±0.3	1.5±0.3	0.214
Left ventricle posterior wall diameter-diastole (cm)	1.1±0.5	1.1±0.2	0.219
Interventricular septum systole (cm)	1.8±1.1	1.4±0.3	0.484
Interventricular septum diastole (cm)	1.0±0.2	1.1±0.8	0.092

Data are presented as mean±SD; *: p<0.05 was accepted to be statistically significant.

carditis and control groups were statistically similar with respect to age, body weight, body height, body mass index, and gender distribution (p>0.05 for all). Of the 100 patients, 68 had mild mitral, 24 had moderate mitral, and 8 had mild mitral and aortic regurgitation.

Conventional and Doppler Echocardiographic Parameters (Standard Echocardiographic Evaluation)

Table 2 shows echocardiographic findings of the study population. The carditis and control groups were statistically similar with respect to echocardiographic parameters, including ejection fraction, fractional shortening, systolic volume, end-diastolic volume, LV internal diameter at end-diastole, LV posterior wall diameter at systole and diastole, and interventricular septum diameter at systole and diastole. The carditis group had significant-

Table 3. Pulsed and Tissue Doppler Echocardiography Parameters of the Study Population

	Carditis Group (n=100)	Control Group (n=100)	p
Mitral E (m/s)	1.3±0.3	1.2±0.2	0.052
Mitral A (m/s)	0.8±0.3	0.7±0.1	0.001*
Mitral E/A	1.6±0.4	1.8±0.4	0.001*
Mitral annular plane systolic excursion (cm)	3.0±0.5	3.2±0.6	0.049*
Tricuspid E (m/s)	1.0±0.2	0.9±0.2	0.019*
Tricuspid A (m/s)	0.6±0.2	0.6±0.3	0.906
Tricuspid E/A	1.6±0.4	1.6±0.5	0.085
Tricuspid annular plane systolic excursion (cm)	3.7±0.6	3.9±0.7	0.165
Lateral mitral annulus			
E' (m/s)	0.15±0.09	0.15±0.03	0.621
A' (m/s)	0.12±0.05	0.11±0.03	0.314
S' (m/s)	0.13±0.03	0.14±0.02	0.387
Isovolumetric relaxation time (ms)	61.8±14.1	65.0±15.6	0.225
Isovolumetric contraction time (ms)	58.8±15.4	61.5±15.3	0.154
Myocardial performance index	0.49±0.13	0.47±0.11	0.168
Interventricular septum			
E' (m/s)	0.18±0.03	0.19±0.04	0.036*
A' (m/s)	0.08±0.00	0.07±0.02	0.186
S' (m/s)	0.11±0.02	0.11±0.03	0.272
Isovolumetric relaxation time (ms)	57.3±12.7	60.1±14.0	0.107
Isovolumetric contraction time (ms)	65.9±12.6	62.1±12.7	0.033*
Myocardial performance index	0.52±0.11	0.47±0.13	0.021*
Lateral tricuspid annulus			
E' (m/s)	0.13±0.03	0.13±0.04	0.831
A' (m/s)	0.07±0.02	0.07±0.02	0.061
S' (m/s)	0.08±0.02	0.08±0.02	0.082
Isovolumetric relaxation time (ms)	62.6±13.0	58.3±13.3	0.011*
Isovolumetric contraction time (ms)	64.6±11.7	65.8±14.0	0.661
Myocardial performance index	0.53±0.15	0.54±0.19	0.756

Data are presented as mean±SD; *: p<0.05 was accepted to be statistically significant

ly greater LV internal diameter at end-systole than the control group. Values of MAPSE were significantly lower in the carditis

Table 4. Laboratory Findings of the Study Population

	Carditis Group (n=100)	Control Group (n=100)	p
Hemoglobin (g/dL)	13.1±1.1	13.4±1.3	0.161
Mean corpuscular volume (fl)	82.9±8.6	84.3±8.8	0.046*
Red cell distribution width	14.1±1.7	14.1±2.2	0.193
Leukocyte count (/mm ³)	7158.0±1735.6	7083.3±1513.0	0.966
Neutrophil count (/mm ³)	5567.6±1192.9	5563.9±1026.0	0.918
Lymphocyte count (/mm ³)	3306.9±1019.2	3434.8±1178.4	0.645
Neutrophil/Lymphocyte ratio	1.97±1.15	1.82±0.81	0.873
Platelet count (/mm ³)	301240±81377	278447±63433	0.058
Mean platelet volume	7.54±1.07	8.10±0.98	0.001*
Erythrocyte sedimentation rate (mm/h)	27.0±6.5	9.2±2.3	0.001*
C-reactive protein (mg/L)	3.84±1.99	0.60±0.34	0.001*
Mannan-binding lectin (ng/mL)	12.7±7.7	11.8±6.5	0.506
25-hydroxy-vitamin D (ng/mL)	17.6±4.7	16.6±3.5	0.148

Data are presented as mean±SD; *: p<0.05 was accepted to be statistically significant.

group, whereas those of TAPSE were similar between the groups. The E velocity of the mitral annulus was significantly higher in the carditis group, and the E/A ratio of the mitral annulus was significantly higher in the control group, whereas mitral E velocity was similar for both groups. The E/A ratio of the tricuspid annulus was significantly higher in the control group, whereas E and A velocity were similar between groups (Table 3).

Tissue Doppler Echocardiography (TDI)

Table 3 demonstrates the Doppler echocardiography findings of the study population. Comparison of TDI parameters measured from the lateral mitral annulus demonstrated similar E', A', and S' velocities for the groups. Although E' velocity and IVCT time derived from the septal mitral annulus were significantly lower, MPI was prolonged in the carditis group compared with that in the control group. E', A', and S' velocities; IVCT; and MPI measured from the tricuspid annulus were found to be similar in the carditis and control groups, although IVRT was significantly lower.

Laboratory Findings

Laboratory findings of the study population are enlisted in Table 4. The carditis group had significantly lower MCV and MPV values and higher ESR and CRP levels than the control group (p=0.001). Both groups had statistically similar measurements for hemoglobin, RDW, neutrophil/lymphocyte ratio, platelet count, MBL, and 25-hydroxy-vitamin D values.

DISCUSSION

Pathogenesis of ARF is very complicated because of underlying environmental and genetic factors in the etiology. After a specific bacterial infection, the antigen initiates an adaptive immune response in a susceptible host and obviously, this clinical entity is the result of activating innate immunity (14, 15).

The present study aims to assess demographic, clinical, and biochemical features of Turkish children who were diagnosed with acute rheumatic carditis and evaluate cardiac functions using echocardiography at the time of diagnosis. The predominant manifestation of rheumatic carditis is valvular involvement, particularly mitral and aortic regurgitation. Because of mitral and aortic regurgitation, resultant volume overload occurs during the acute phase of the disease. This overload was evidenced by significantly increased end-diastolic and - the systolic volume of LV (16). Children with acute carditis had statistically similar echocardiography findings on M-mode measurements, except the LV internal diameter at the end-systole that was significantly shorter in the carditis group. In our study, the carditis group had significantly greater LV internal diameter at the end-systole, but there were no significant changes in LV internal diameter at the end-diastole. Lack of significant changes in the diameter of LV at end-diastole may be due to the small number of patients with active carditis, and these findings also suggest that reviewed patients having mild disease and cardiac functions were not severely impaired. Such discrepancy may be also attributed to the fact that most indices used in practice, such as the ejection fraction and fractional shortening as a marker of ventricular function, do not clearly reflect the contractile power of the ventricle. As reported before, the ejection fraction and internal dimensions of LV do not reliably predict systolic functions of LV after surgical correction of mitral regurgitation (17).

In our study, we also investigated changes in the function of the ventricle presented after the first attack of ARF. As for 'pulsed' Doppler echocardiography findings, the carditis group in this study had significantly higher mitral A and tricuspid E velocities and lower mitral annulus E/A ratio and MAPSE. These patterns show that there is a subclinical diastolic dysfunction of LV (18). Various pediatric and adult studies have described subclinical

impairment of systolic functions with changes in MPI, isovolumetric contraction, and relaxation time (19). In our study, increase in MPI and decrease in isovolumetric contraction and relaxation time also indicate a subclinical systolic dysfunction of both ventricles. These findings indicate that there is a subclinical systolic dysfunction of both ventricles, and Doppler echocardiography is useful for specification of mild alterations in cardiac functions of pediatric patients with ARF. In a previous Turkish study, 30 healthy children and 82 children with ARF-related carditis were compared with respect to tissue Doppler findings, and subclinical systolic dysfunction of LV was demonstrated in children with a primary episode of rheumatic carditis (20). Thus, it has been concluded that tissue Doppler imaging is a quantifiable indicator that can be used for assessing the cardiac function during clinical follow-up of the disease. In addition, assessment of systolic indices of the mitral annulus with tissue Doppler imaging has previously been shown to provide a global estimate of the left ventricular systolic function (21).

Mean platelet volume is a good sign of the platelet size and rate of platelet production in the bone marrow. Thus, MPV may be used as an indicator of platelet activation and multiplicity of inflammation. Recently, increased MPV values have been used as a simple marker for the severity of inflammatory disorders, such as familial Mediterranean fever, rheumatoid arthritis, asthma, hypertension, diabetes mellitus, myocardial infarction, and secondary pulmonary hypertension (22). It has been hypothesized that decreased MPV values may indicate the intensity of the inflammatory process in conditions with elevated inflammatory markers. Excessive production of cytokines, such as IL-6 and acute phase reactants, may affect the platelet production and suppress the size of the platelets released from the bone marrow. Moreover, IL-6 release and/or intensive consumption of larger platelets in the areas of inflammation may contribute to the low MPV during acute ARF attacks (23). The results of this study can further support this suggestion that inflammatory markers ESR and CRP were significantly elevated in children with ARF-related carditis. In contrast, Özdemir et al. (24) were unable to detect a significant alteration in MPV values in children with acute rheumatic carditis. Likewise, Sert et al. (25) found lower MPV values in patients with ARF. This study also pointed out significantly lower MPV values in patients with ARF-related carditis.

It has been well established that ARF attacks may lead to an increase in acute phase reactants, including leukocyte count, ESR, CRP, and IL-6, and neutrophil-lymphocyte ratio. These reactants can be normalized because of suppression of cytokines by anti-rheumatic treatment (26). Only ESR and CRP values were found to be significantly increased in patients with rheumatic carditis in our study. This finding may be a result of the relatively small cohort size and presumably high prevalence of mild disease.

Mannan-binding lectin is an acute phase inflammatory protein that is involved in primary defense against microorganisms. Circulating MBL binds to the surface of numerous pathogens, including Group A streptococci. MBL deficiency is associated with an increased risk of infectious and autoimmune diseases (27,28).

The power of the present study is limited by its retrospective design in the absence of longitudinal data and lack of subgroup analysis with respect to the severity of the disease. Large-scale longitudinal studies should be conducted for clarifying the demographic, clinical, and biochemical characteristics of Turkish children with ARF-related carditis.

CONCLUSION

This study showed that assessment of both ventricular functions using tissue Doppler imaging demonstrated significant differences in cardiac parameters measured by echocardiography in patients with ARF-related carditis. The ultimate future goal will be to accurately identify these patients with speckle-tracking echocardiography using a more sensitive imaging method. Adequately powered, well-designed clinical trials are necessary for clearly defining echocardiographic indices of the valvular involvement of the disease.

Ethics Committee Approval: Ethics committee approval was received for this study from institutional review board and ethical committee of Afyon Kocatepe University (Approval Date: 17.04.2014; Approval No: 2014/06-118)

Informed Consent: Written informed consent was obtained from all patients who participated in this study.

Peer-review: Externally peer-reviewed.

Author contributions: Concept - E.Ç., A.P.; Design - E.Ç., A.P.; Supervision - B.M.P., B.H.K.; Resource - E.Ç., B.M.P., B.H.K.; Materials - A.P., B.M.P., B.H.K.; Data Collection and/or Processing - A.P., B.H.K.; Analysis and/or Interpretation - E.Ç., A.P., B.H.K.; Literature Search - E.Ç., B.H.K.; Writing - E.Ç.; Critical Reviews - B.M.P., B.H.K.

Conflict of Interest: The authors have no conflicts of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

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How to cite:

Çilsal E, Pektaş A, Pektaş BM, Koca BH. Echocardiographic and Laboratory Findings of Turkish Children during the First Attack of Acute Rheumatic Fever. *Eur J Ther* 2018; 24(2): 77–82.