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Original Article

Assessment of cardiac functions using tissue Doppler imaging in children with familial Mediterranean fever

Osman Ozdemir,[1] Pinar Isik Agras,[2] Yusuf Aydin,[3] Ayhan Abaci,[3] Samil Hizli,[3] Halil Ibrahim Akkus,[3] Cihan Fidan[3]

[1]*Department of Paediatric Cardiology;* [2]*Department of Paediatric Nephrology;* [3]*Department of Paediatrics, Kecioren Training and Research Hospital, Ankara, Turkey*

Abstract *Objective:* Familial Mediterranean fever may carry a potential for cardiovascular disorders because of sustained inflammation during its course; however, there has been a limited number of studies investigating the cardiac functions in children. The aim of this study was to assess both ventricular diastolic functions using conventional echocardiography and tissue Doppler imaging in children with familial Mediterranean fever. *Patients and methods:* The study population included 25 patients with familial Mediterranean fever – mean age was 11.8 plus or minus 5.30 years – and 23 healthy patients as controls – mean age was 9.88 plus or minus 3.69 years. Both ventricular functions were measured using echocardiography comprising standard M-mode and conventional Doppler and tissue Doppler imaging during an attack-free period. *Results:* The conventional echocardiographic parameters with myocardial performance index were in normal ranges and similar in patients with familial Mediterranean fever and controls, with a p-value more than 0.05. However, right ventricular diastolic dysfunction was observed in patients with familial Mediterranean fever documented by tissue Doppler imaging, with a p-value less than 0.05 for E't and A't wave ratio. *Conclusion:* Using tissue Doppler imaging, we have demonstrated that although left ventricular functions were comparable in the patients and healthy children, right ventricular diastolic function indices were impaired in patients with familial Mediterranean fever during childhood. Impaired right ventricular diastolic function may be an early manifestation of cardiac involvement in children with familial Mediterranean fever.

Keywords: Cardiac function; children; echocardiography; familial Mediterranean fever; tissue Doppler imaging

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Familial Mediterranean fever is an autosomal recessive disorder of unknown pathogenesis, which exclusively affects people of Mediterranean ancestry, especially the Sephardic Jewish, Turkish, and Arabic population. The auto-inflammatory disease is characterised by periodic self-limiting attacks of fever and serositis caused by mutations in familial Mediterranean fever gene.[1] Although patients with familial Mediterranean fever are symptom free between the attacks, subclinical inflammation continues during the attack-free period. The main complication of not treating patients is the development of amyloidosis. In most patients with familial Mediterranean fever, colchicine treatment prevents febrile attacks and development of amyloidosis.[2] However, clinical and subclinical cardiovascular involvements have been reported in patients with familial Mediterranean fever.[3–6]

Echocardiography is a reliable, cost-effective, non-invasive, and reproducible diagnostic tool to evaluate cardiac function and structures. Cardiac functions in patients with familial Mediterranean fever have been studied extensively using conventional echocardiography. This method evaluates hydrodynamic responses, and therefore it is load-dependent and only allows semi-quantitative and partially subjective measurements. Conventional

Correspondence to: Dr O. Ozdemir, Pinarbasi Mahallesi, Sanatoryum Caddesi, Ardahan Sokak, Kecioren Egitim ve Arastirma Hastanesi (Kecioren Training and Research Hospital), Kecioren, Ankara 06380, Turkey. Tel: +90 312 356 90 00; Fax: +90 312 356 90 02; E-mail: pedkard@gmail.com

echocardiography has been shown to be too intensive to distinguish between physiological and pathological cardiac changes and to demonstrate diastolic dysfunction in patients with normal ejection fraction.[7]

Tissue Doppler imaging, which is a recently developed non-invasive echocardiographic diagnostic technique, has provided an objective means to quantify global and regional both ventricular functions with improved accuracy and greater reproducibility than conventional echocardiography.[8] As it can provide measurements of regional systolic and diastolic myocardial velocities with a high temporal and spatial resolution, this new modality may be more sensitive for detecting subclinical abnormalities.[9] However, the use of tissue Doppler imaging in children with familial Mediterranean fever has not been studied extensively, with one recent study evaluating only left ventricular diastolic function in this population.[3] Therefore, we aimed to investigate both ventricular functions in patients with familial Mediterranean fever using conventional echocardiography and pulse-wave tissue Doppler imaging, as well as show the usefulness of tissue Doppler imaging for detecting subclinical abnormalities. This is the first study in children with familial Mediterranean fever that used tissue Doppler imaging to assess both ventricular functions.

Materials and methods

Study population

We studied 25 patients with familial Mediterranean fever – with a mean age of 11.8 plus or minus 5.30 years – and 23 healthy controls – with a mean age of 9.88 plus or minus 3.69 years. All the patients enrolled in the study fulfilled the clinical criteria for familial Mediterranean fever[10] and they were all homozygous for one of the familial Mediterranean fever mutations. The patients included 48 ethnic Turks living in the central region of Turkey, in an area served by Ankara. Patients with other inflammatory or pulmonary diseases, moderate or severe valve abnormalities, proteinuria, and those unresponsive to colchicine therapy[11] were excluded. Clinical and laboratory assessments of patients with familial Mediterranean fever were performed during an attack-free period, lasting at least 7 days. The clinical data including age, gender, age at onset, age at diagnosis, number and duration of attacks, and dosage of colchicine were obtained. Laboratory examinations included complete blood count, erythrocyte sedimentation rate, C-reactive protein, and fibrinogen. The local ethics committee approved this study and the parents of children gave written informed consents.

Echocardiographic method

The echocardiographic examination was performed with a ViVid 3 Expert (General Electric Medical Systems, Milwaukee, WI, United States) using 7- and 3-megahertz transducers equipped with tissue Doppler imaging technology. An electrocardiogram was simultaneously recorded in all patients. All patients were studied without sedation while lying in the supine position. A single experienced paediatric cardiologist recorded all echocardiographic measurements throughout the whole study using the same device blinded to the study groups. The measurements of at least three cardiac cycles were averaged in sinus rhythm.

The left atrial, the aortic, and the left ventricular diameters with the ejection fraction and the fractional shortening of the left ventricle were also determined from M-mode traces recorded from the parasternal long-axis view according to the recommendations of the American Society of Echocardiography.[12] The left ventricular mass was calculated using the standard formulas from the M-mode echocardiogram.[13]

The mitral and tricuspid inflow velocities were recorded from the apical four-chamber view, with the pulse-wave Doppler sample volume placed at the tip of its leaflets during diastole.[14] The peak early trans-valvular filling velocity during early diastole (E), peak trans-valvular atrial filling velocity during late diastole (A), and deceleration time of E velocity were used as both ventricular diastolic function parameters. The ratios of peak velocities of E to A waves were calculated for mitral and tricuspid inflows. The isovolumic contraction time, isovolumic relaxation time, and left ventricular ejection time were measured as the interval from the end of the mitral flow to the onset of the aortic flow, the end of the aortic flow to the onset of the mitral flow, and the onset of the aortic flow to the end of the aortic flow, respectively. Then, the Doppler-derived myocardial performance index was calculated as the sum of isovolumic contraction time and isovolumic relaxation time divided by the left ventricular ejection time.[15]

Diastolic function was also evaluated by tissue Doppler indices. For left ventricular diastolic function, peak early (E'm) and atrial (A'm) velocities were measured using the sample volume that was placed at the lateral annulus of the mitral leaflets in the apical four-chamber view. Right ventricular diastolic function (E't, A't) was measured by the method that is described as left ventricle regarding the sample volume of Doppler that was symmetrically set at the tricuspid valve instead of the mitral valve. The ratios of peak velocities of E' to A' waves (E'm/A'm and E't/A't) were calculated.[9]

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Statistical analysis

Categorical and numeric variables were tested by χ^2 and Mann–Whitney U test, respectively. Data were expressed as the mean and standard deviation. The relationship between parameters was assessed using the Spearman correlation analysis. p-values less than 0.05 were considered significant.

Results

Clinical characteristics of the study groups are presented in Table 1. There were no significant differences between groups with regard to age, sex, weight, height, and body mass index – p more than 0.05. There was a significant difference between the groups regarding the level of C-reactive protein and fibrinogen – p less than 0.05. Erythrocyte sedimentation rate, haemoglobin, and white blood cell counts did not differ significantly among the patients in both groups – p more than 0.05. Data of genetic analysis were available in all patients who were homozygous for mutations. The mutations were M694V (56%), M680I (28%), and V726A (16%). All the patients were receiving colchicine at a mean dosage of 0.81 milligrams per day depending on body weight. Whereas mean treatment duration was 1.94 years, mean duration of the disease was 5.90 years, suggesting approximately a 4-year delay between the onset of symptoms and treatment. Before the onset of colchicine treatment, the patients had a mean of 16 attacks in a year, but they had 2.72 attacks during colchicine therapy, with a p-value less than 0.05. Similarly, the mean duration of attacks was significantly decreased in the patients with familial Mediterranean fever after the onset of colchicine therapy, with a p-value less than 0.05.

The data obtained from the M-mode and standard Doppler echocardiography are summarised in Table 2. Cardiac dimensions, left ventricular mass, fractional shortening, and ejection fraction of left ventricle values were in normal ranges and similar in patients with familial Mediterranean fever and controls, with a p-value more than 0.05. The myocardial performance index, peak mitral and tricuspid wave velocities with E and A wave ratios did not differ in both groups, with a p-value more than 0.05.

The tissue Doppler imaging examination results are given in Table 3. There was a statistically significant difference regarding the parameter observed by tissue Doppler imaging such as E't and A't wave ratio, with a p-value less than 0.05; Figure 1. The other velocities and ratios of both groups were not significantly different, with a p-value more than 0.05.

The analysis of data revealed no correlation between the echocardiographic measurements and age at diagnosis, disease duration, C-reactive protein, erythrocyte sedimentation rate, and fibrinogen levels.

Table 1. Clinical and laboratory characteristics of the subjects: mean plus or minus standard deviation.

Parameters	FMF patients (n = 25)	Controls (n = 23)	p-value* for difference
Age (years)	11.8 ± 5.30	9.88 ± 3.69	0.32
Sex (M/F)	13/12	10/13	0.56**
Weight (kg)	47.5 ± 29.0	34.6 ± 14.0	0.70
Height (cm)	144 ± 38.2	136 ± 19.7	0.88
BMI (kg/m^2)	21.5 ± 2.50	17.8 ± 2.92	0.27
Age at diagnosis (years)	8.20 ± 3.90	–	
Disease duration (years)	5.90 ± 3.75	–	
Dosage of colchicine (mg/day)	0.81 ± 0.28	–	
Treatment duration (years)	1.94 ± 1.70	–	
Number of attacks in one year	16.0 ± 8.90***	–	0.01
	2.72 ± 3.27****		
Duration of attacks (days)	2.40 ± 0.76***	–	0.01
	0.68 ± 0.58****		
ESR (mm/h)	22.4 ± 20.7	13.1 ± 8.79	0.11
CRP (mg/dl)	1.06 ± 1.32	0.18 ± 0.15	0.01
Fibrinogen (mg/dl)	394 ± 88.3	321 ± 118	0.01
Haemoglobin (g/dl)	12.6 ± 1.43	13.0 ± 1.05	0.09
WBC (10^9/l)	8.43 ± 2.57	7.63 ± 1.48	0.29

BMI = body mass index; CRP = C-reactive protein; ESR = erythrocyte sedimentation rate; F = female; FMF = familial Mediterranean fever; M = male; WBC = white blood cell

*For the comparison of continuous variables, the Mann–Whitney U test was used

**For the comparison of proportions, the χ^2 test was used

***Before the onset of colchicine treatment

****During the colchicine treatment

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Table 2. M-mode and standard Doppler echocardiographic data: mean plus or minus standard deviation.

Variables	FMF patients (n = 25)	Controls (n = 23)	p-value* for difference
Aorta (mm)	21.4 ± 3.05	20.4 ± 3.04	0.16
Left atrium (mm)	25.5 ± 3.34	24.8 ± 3.47	0.19
Aorta/left atrium	0.85 ± 0.11	0.83 ± 0.09	0.63
IVSd (mm)	7.19 ± 1.20	7.40 ± 1.27	0.82
LVEdD (mm)	36.1 ± 5.68	34.5 ± 5.25	0.26
LVPWd (mm)	7.41 ± 1.14	6.97 ± 1.05	0.10
IVSs (mm)	10.1 ± 1.38	9.71 ± 1.44	0.21
LVEsD (mm)	21.8 ± 2.97	20.6 ± 3.11	0.09
LVPWs (mm)	11.6 ± 1.87	10.8 ± 2.22	0.11
LVM (g)	70.9 ± 31.6	59.3 ± 25.1	0.13
EF (%)	70.8 ± 4.43	71.7 ± 4.81	0.32
FS (%)	39.5 ± 3.98	40.2 ± 4.19	0.35
Mitral inflow			
E (cm/s)	104 ± 18.0	102 ± 19.8	0.76
A (cm/s)	53.0 ± 12.7	59.4 ± 20.5	0.48
E/A	2.03 ± 0.45	1.85 ± 0.50	0.16
E wave DT (ms)	130 ± 22.7	119 ± 25.7	0.11
MPI (%)	0.45 ± 0.06	0.47 ± 0.07	0.10
Tricuspid inflow			
E (cm/s)	69.3 ± 15.5	77.3 ± 15.6	0.10
A (cm/s)	42.4 ± 13.9	48.3 ± 15.1	0.17
E/A	1.71 ± 0.39	1.66 ± 0.27	0.83

A = late diastolic peak velocity; DT = deceleration time; E = early diastolic peak velocity; E/A = ratio of early to late diastolic peak velocity; EF = ejection fraction of the left ventricle; FMF = familial Mediterranean fever; FS = fractional shortening of the left ventricle; IVSd = interventricular septum diastolic thickness; IVSs = interventricular septum systolic thickness; LVEdD = left ventricular end-diastolic dimension; LVEsD = left ventricular end-systolic dimension; LVM = left ventricular mass; LVPWd = left ventricular posterior wall diastolic thickness; LVPWs = left ventricular posterior wall systolic thickness; MPI = myocardial performance index
*For the comparison of continuous variables, the Mann–Whitney U test was used

Table 3. Pulsed wave tissue Doppler imaging measurements: mean plus or minus standard deviation.

Variables	FMF patients (n = 25)	Controls (n = 23)	p-value* for difference
Mitral lateral annulus			
E'm peak velocity (cm/s)	16.2 ± 2.56	15.6 ± 3.45	0.44
A'm peak velocity (cm/s)	5.51 ± 1.31	6.22 ± 2.20	0.38
E'm/A'm ratio	3.04 ± 0.68	2.66 ± 0.68	0.15
E'm wave DT (ms)	84.1 ± 13.3	83.7 ± 12.8	0.67
IVRT (ms)	49.7 ± 4.47	54.3 ± 6.38	0.08
Tricuspid annulus			
E't peak velocity (cm/s)	15.8 ± 2.49	16.1 ± 2.52	0.27
A't peak velocity (cm/s)	9.23 ± 3.56	7.86 ± 2.42	0.40
E't/A't ratio	1.94 ± 0.81	2.19 ± 0.59	0.03

A'm = late diastolic myocardial peak velocity of mitral lateral annulus; A't = late diastolic myocardial peak velocity of tricuspid annulus; DT = deceleration time; E'm = early diastolic myocardial peak velocity of mitral lateral annulus; E'm/A'm = ratio of early to late diastolic myocardial peak velocity of mitral lateral annulus; E't = early diastolic myocardial peak velocity of tricuspid annulus; E't/A't = ratio of early to late diastolic myocardial peak velocity of tricuspid annulus; FMF = familial Mediterranean fever; IVRT = isovolumic relaxation time
*For the comparison of continuous variables, the Mann–Whitney U test was used

Discussion

In this study, we have investigated cardiac functions in children with familial Mediterranean fever using conventional echocardiography and tissue Doppler imaging. We have demonstrated that although left ventricular dysfunction and pericardial effusion were not found, indices of right ventricular diastolic function were impaired in children with familial Mediterranean fever during the attack-free period.

Subclinical inflammation occurs widely and over prolonged periods in patients with familial Mediterranean fever.[16] In the present study, we found that markers of acute phase reaction, that is, C-reactive protein and fibrinogen, were significantly higher in the patients even in the attack-free period when

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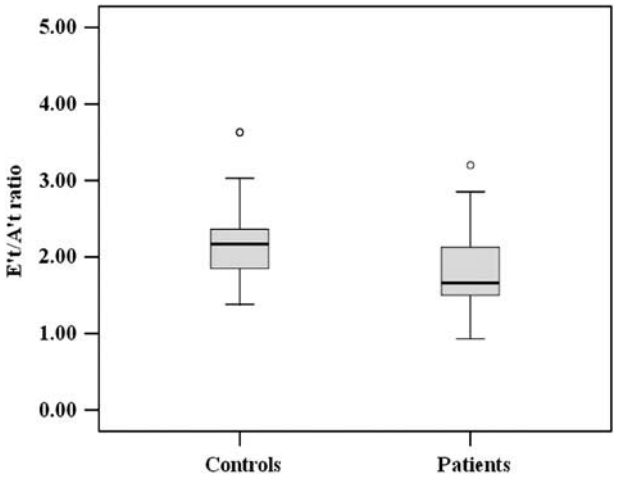

Figure 1.
Distribution of the ratio of early-to-late diastolic peak velocity of tricuspid annulus.

compared with those in the healthy children. These findings were compatible with ongoing subclinical inflammation, although there were no apparent clinical familial Mediterranean fever attacks.

The pericardium may be involved in familial Mediterranean fever. Although pericardium is a double-layered serous membrane, pericarditis is a rare manifestation of familial Mediterranean fever. The incidence of pericardial effusion was 3.6% during attacks of familial Mediterranean fever.[16,17] In addition, there are several reports regarding other cardiac involvement in patients with familial Mediterranean fever.[3–6] The mechanisms have been suggested as a cause of cardiac dysfunction in inflammatory disorders such as the fibrous scarring of the heart muscle, abnormal myocardial collagen deposition, myocardial infarcts, focal inflammation, vasculitis, myocarditis, arteritis, and amyloidosis.[3–6,18,19]

Systemic inflammation is an important factor for the development of amyloidosis in familial Mediterranean fever.[20] Some authors demonstrated statistically elevated serum amyloid A and C-reactive protein for patients in the attack-free period. They concluded that chronic subclinical inflammation during attack-free periods might be found in patients with familial Mediterranean fever.[20,21] In this study, we have also demonstrated that, during asymptomatic periods, children with familial Mediterranean fever had significantly higher serum C-reactive protein and fibrinogen levels than the controls. The data have reflected that there was a chronic systemic inflammation for patients with familial Mediterranean fever, compatible with previous investigations.[20,21]

Caliskan et al[6] demonstrated that the Doppler parameters of ventricular diastolic function and coronary flow reserve were impaired in patients with familial Mediterranean fever. In addition, they found that the severity of these impairments was correlated with high sensitive C-reactive protein. We did not investigate coronary flow in our study; however, coronary vascular involvement might be a possible mechanism of ventricular diastolic dysfunction. In that, the possible pathophysiological link of diastolic dysfunction is elevated levels of circulating cytokines, which may cause endothelial dysfunction that inversely affects arterial vasculature to accommodate the increased afterload. Those cytokines remain elevated in patients with familial Mediterranean fever, even in the attack-free periods.[18] Moreover, reduced nitric oxide production in familial Mediterranean fever may have a contributory effect on impaired endothelial function.[19]

Another possible mechanism developing diastolic dysfunction in familial Mediterranean fever might be atherosclerosis. Previous studies demonstrated that elevated levels of C-reactive protein and serum amyloid A were strongly associated with the development of atherosclerosis and its complications.[4,5,22] Finally, subclinical chronic-sustained inflammation, the main underlying mechanism, may be responsible for ventricular diastolic dysfunction in the patients with familial Mediterranean fever.[3–6,18,19]

Diastolic dysfunction can be identified by standard echocardiography and/or recently introduced methods such as tissue Doppler imaging. Standard echocardiography has several limitations.[7] Measurements of right ventricular functions are difficult because of the complex three-dimensional structure and non-concentric contraction of this ventricle.[23] Therefore, the tissue Doppler imaging is a new technique that offers useful information about ventricular functions.[9] Baysal et al[3] studied left ventricular functions in children with familial Mediterranean fever using conventional echocardiography and tissue Doppler imaging. They found significant differences between patients with familial Mediterranean fever and healthy controls with respect to values of left ventricle such as A wave, E and A wave ratio, E'm, A'm, and E'm and A'm ratio. The authors concluded that left ventricular diastolic dysfunction might be a result of impaired active left ventricular relaxation or reduced left ventricular compliance. They suggested that although systolic functions were in normal range, some of the diastolic function parameters were impaired in patients with familial Mediterranean fever during childhood.[3]

In our study, there are no differences between groups with values of left ventricular functions estimated by conventional echocardiography and tissue Doppler imaging measurements. In addition, conventional echocardiography of the right ventricle has revealed similar results for patients with familial

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Mediterranean fever and controls. However, tissue Doppler imaging indices of right ventricular diastolic function have statistically differed in patients with familial Mediterranean fever compared with healthy children. We have suggested that the right ventricle may be affected before the left ventricle with chronic inflammation of familial Mediterranean fever, because the right ventricle has non-concentric contraction and is more complex structure than the left ventricle. Diastolic function is more important in the right ventricle than the left ventricle. We have thought that the result may be early cardiac effect of inflammation in patients with familial Mediterranean fever.

There were some limitations in this study. The study population was small and quite young for the appearance of heart disease. In addition, all the patients received regular colchicine treatment, and thus we could not compare the results of colchicine responders and non-responders. Colchicine treatment probably protects patients from the harmful effects of inflammation and causes to conceal or delay any findings of inverse effects on the heart.

In conclusion, our study has revealed that tissue Doppler imaging indices of right ventricular diastolic function have statistically differed in patients with familial Mediterranean fever compared with healthy children. To our knowledge, this is the first result in children with familial Mediterranean fever for impaired right ventricular functions using tissue Doppler imaging. However, we cannot explain the exact mechanism of diastolic dysfunction. Impaired diastolic dysfunctions in echocardiography are not always associated with clinically important cardiac problem. However, subclinical myocardial involvement may be an early manifestation of the development of cardiovascular disorder in children with familial Mediterranean fever. Therefore, patients must be monitored over a life-long period, like other inflammatory diseases. For this purpose, larger longitudinal studies are still needed to clarify whether these patients have a higher risk for ventricular dysfunction than normal population. Systematic echocardiographic screening can be recommended as a non-invasive and early diagnostic method.

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