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ORIGINAL ARTICLE

Effects of Familial Mediterranean Fever on Cardiac Functions in Adults: A Cross-Sectional Study Based on Speckle Tracking Echocardiography

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ABSTRACT

Objectives: This study aims to evaluate the right ventricular (RV) and left ventricular (LV) systolic and diastolic functions with speckle tracking echocardiography in addition to routine echocardiographic measurements in adult familial Mediterranean fever (FMF) patients in order to detect cardiac functions.

Patients and methods: Sixty FMF patients (23 males, 37 females; median age 35 years; interquartile range, 26 to 38 years) and 20 healthy subjects (10 males, 10 females; median age 31 years; interquartile range, 25 to 35 years) were included in the study. The diagnosis was established according to the Tel-Hashomer criteria. All patients were using regular colchicine and they were in the attack-free period. Laboratory examinations included complete blood count, creatinine, and inflammatory markers. In addition to routine echocardiographic examination, RV and LV global longitudinal strains were measured and compared.

Results: Erythrocyte sedimentation rate and C-reactive protein values were higher in FMF group. LV global longitudinal strain was similar among the groups. FMF patients had slightly lower early diastolic trans-mitral flow (E) values than controls. As similar as the mitral E flow, tricuspid E flow was slightly lower in FMF groups than controls. RV ejection fraction was similar and in normal ranges among the groups. RV global longitudinal strain was lower in FMF group than controls. RV Myocardial Performance Index (or Tei index) was higher in FMF group.

Conclusion: The present study indicates low values of mean RV global longitudinal strain and higher Tei index in FMF patients. These results suggest that FMF may cause subclinical RV deterioration.

Keywords: Familial Mediterranean fever, speckle tracking, strain echocardiography, Tei index.

Familial Mediterranean fever (FMF) is an autosomal recessive hereditary autoinflammatory disorder which is characterized by recurrent fever attacks and serosal inflammation.[1] FMF was originally described among individuals of the Mediterranean basin.[2] However, the disease was reported in other ethnicities at a lower prevalence.[3-5] Inflammation in pleura and pericardium or joints can also occur. Kees et al.[6] reported that the coexistence of pericarditis is 0.7%. FMF can cause long-term complications such as secondary amyloidosis, which decrease with the regular use of colchicine. Moreover, some studies claim that FMF can cause atherosclerosis.[7]

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Endothelial dysfunction has been demonstrated with ultrasound in FMF patients.[8] There are some studies that claim FMF is in association with diastolic dysfunction.[9,10] However, myocardial function has been investigated in FMF patients and diverse results were obtained from different studies. In a study, FMF was found to be in relation with reduced left ventricular (LV) strain in children,[11] but there is lack of research that shows the relationship between FMF and systolic function in adults.

In this study, we aimed to evaluate the right ventricular (RV) and LV systolic and diastolic functions with speckle tracking echocardiography (STE) in addition to routine echocardiographic measurements in adult FMF patients in order to detect cardiac functions.

PATIENTS AND METHODS

This single-center, cross-sectional study was conducted in the central region of Turkey, at University of Health Sciences, Dışkapı Yıldırım Beyazıt Training and Research Hospital between March 2018 and April 2018. Sixty FMF patients (23 males, 37 females; median age 35 years; interquartile range [IQR], 26 to 38 years) and 20 healthy subjects (10 males, 10 females; median age 31 years; IQR, 25 to 35 years) were included. Control group consisted of healthy individuals who were free of chronic diseases, diabetes mellitus, hypertension, and alcohol abuse, etc. They were selected from the hospital staff who are examined periodically. The study protocol was approved by the University of Health Sciences, Diskapi Yildirim Beyazit Training and Research Hospital Ethics Committee (19/3/2018-47/26). A written informed consent was obtained from each participant. The study was conducted in accordance with the principles of the Declaration of Helsinki.

Familial Mediterranean fever diagnosis was established according to the Tel-Hashomer criteria.[12] All FMF patients were under regular colchicine treatment at a dose of 1-1.5 mg/day and all of them were in the attack-free period during echocardiographic evaluation. None of the FMF patients had experienced pericarditis before. The clinical data including age, sex, age at onset and dosage of colchicine were obtained. Laboratory examinations included complete blood count, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), and fibrinogen.

Patients who experienced less than three FMF attacks per year were included. Patients on biologic drugs were excluded. None of the patients had subclinical inflammation at one-year follow-up. ESR, CRP, and fibrinogen levels were within normal ranges during attack-free phase. According to genetic mutations, 20 patients were homozygous (MEFV 694 V), 11 patients were heterozygous, and 29 patients were compound heterozygotes.

Patients with other inflammatory diseases, moderate or severe heart valve abnormalities, proteinuria, hypertension, renal failure, diabetes mellitus, cardiomyopathy, coronary artery disease, chronic obstructive pulmonary disease, or those who were smokers, chronic alcohol users or pregnant were excluded. Amyloidosis was excluded from the absence of proteinuria in complete urine analysis and in 24 hours urine test. Transthoracic echocardiographic examination was performed using the Philips Epic 5 (Philips Healthcare, Andover, Massachusetts, USA) instrument with a 1-5 MHz transducer. Standard parasternal long and short-axis views, and apical two and four-chamber views were obtained for all patients. LV and left atrial diameter were measured from the M-mode images in parasternal long axis view.[13] Peak tricuspid regurgitant velocities were recorded by the continuous wave Doppler technique and a modified Bernoulli equation was used to estimate pulmonary artery systolic pressure (PASP). The modified Simpson's method was used for calculating the LV ejection fraction (LVEF) using the apical four-chamber views.[13] From the apical window, a 2 mm pulsed Doppler sample volume was placed at the mitral valve tip and mitral flow velocities of three cardiac cycles were recorded by obtaining peak velocities of the early diastolic trans-mitral flow (E) and late diastolic trans-mitral flow (A). Additionally, early diastolic lateral mitral annulus velocity ($E'_{lateral}$), velocity during atrial contraction ($A'_{lateral}$) and lateral systolic (S) myocardial velocity were measured by tissue Doppler imaging (TDI) using the pulsed wave Doppler.[14]

Right ventricle free wall TDI allows quantitative assessment of both RV systolic and diastolic

function. Myocardial systolic velocity (S) correlates with the RV systolic function. From the apical window, a 2 mm pulsed Doppler sample volume was obtained from lateral tricuspid annulus and early diastolic annulus velocity ($E'_{tricuspid}$) during atrial contraction ($A'_{tricuspid}$) and lateral systolic myocardial velocity was measured by TDI using the pulsed wave Doppler.[14]

The Tei index (also known as myocardial performance index), described by Tei et al.,[15] is a Doppler-derived time interval index that combines both systolic and diastolic cardiac performance. The Tei index was calculated by the following formula: (isovolumic contraction time + isovolumic relaxation time)/ejection time. RV Tei index was measured by using pulsed tissue Doppler imaging of the RV free wall.[14]

Two-dimensional (2D) global longitudinal strain (GLS) echocardiography images were obtained from standard apical four-chamber, three-chamber, and two-chamber views of the LV from the apex. Three stable cardiac cycles were stored for each view and all data were collected and studied on the echocardiography machine's own program (QLAB 10.1, Philips Healthcare, Andover, Massachusetts, USA) as to offline analysis. Frame rates used for GLS analysis were 40-80 frames/s.[16] Conventional 2D grayscale echocardiographic images were used by the system and activity of the speckles was tracked throughout the myocardial tissue. The regions of interest (ROIs) were manually outlined by marking the endocardial borders at the mitral annulus level as well as at the apex of each digital loop; the epicardial surface was automatically generated by the software system. After any required manual adjustment, the ROIs were divided into six segments. Each segment was then scored automatically by the software according to the image quality. The peak systolic strain values in an 18-segment LV model were used.[16] The results for all three planes were then combined in a single bulls-eye summary that provided the GLS. Measurements were repeated at least three times and the average of these measurements was determined. GLS rate was measured by the same technique.

Right ventricular strain was measured by 2D STE on the RV-focused apical four-chamber view using QLAB package program (QLAB 10.1; Philips Healthcare, Andover, Massachusetts, USA). After any required manual adjustment, the ROIs were divided into six segments. The software automatically divided the RV free wall and the interventricular septum into three segments each (basal, mid, and apical), resulting in a six-segment model.

Statistical analysis

Statistical analyses were performed using the IBM SPSS version 20.0 software (IBM Corp., Armonk, NY, USA). Kolmogorov-Smirnov test was used to determine whether the data distribution was normal or not. Descriptive statistics were expressed as median (interquartile ranges) for

Table 1. Demographic and biochemical features of FMF and control groups

	FMF patients (n=60)			Controls (n=20)			
	%	Median	IQR	%	Median	IQR	*p*
Age (year)		35	26-38		31	25-35	NS
Gender Female	61.7			50			NS
Hemoglobin (g/dL)		14	12.8-15.2		13.3	12.2-14.8	0.05
WBC (10^9/L)		6.8	5.8-8.1		6.7	5.9-7.4	NS
Neutrophils (10^9/L)		4.2	31-4.8		4.2	4-5.2	NS
Lymphocyte (10^9/L)		2.1	1.76-2.8		1.6	1.4-1.8	<0.001*
Creatinine (mg/dL)		0.89	0.7-0.9		0.9	0.8-0.9	NS
ESR (mm/h)		10	7-20		6	4-8.5	<0.002*
CRP (mg/L)		5.7	2.9-10		5	4-6	NS
Fibrinogen (mg/dL)		311	250-354		311	250-354	<0.02*

FMF: Familial Mediterranean fever; IQR: Interquartile range; NS: Not significant; WBC: White blood cells; ESR: Erythrocyte sedimentation rate; CRP: C-reactive protein; * Statistically significant.

non-normally distributed data. Categorical and ordinal variables were given as percentages. Mann-Whitney U test was performed to analyze the significance of the differences of medians, and the differences were studied using post hoc tests. A *p* value <0.05 was considered statistically significant.

RESULTS

Characteristics of FMF and control groups are given in Table 1. Mean disease duration was 15.1±9.3 years and mean colchicine dosage was 1.42±0.2 mg/day. There was no statistically significant difference between groups in terms of age, sex, white blood cells and creatinine levels. However, hemoglobin 14 (IQR: 12.8-15.2; p=0.05) vs. 13.3 (IQR: 12.2-14.8; p=0.05), lymphocyte 2.1 (IQR: 1.76-2.8; p<0.001) vs. 1.6 (IQR: 1.4-1.8; p<0.001), ESR 10 (IQR: 7-20; p<0.002*) vs. 6 (IQR: 4-8.5; p<0.002*) and fibrinogen 311 (IQR: 250-354; p<0.02) vs. 311 (IQR: 250-354; p<0.02) levels were higher in the FMF group than controls (Table 1).

Table 2. Echocardiographic findings of FMF and control groups

	FMF group (n=60)		Control group (n=20)		
	Median	IQR	Median	IQR	p
Groups					
LVEF (%)	60	58.7-62	62	60-63	0.003*
LVEdD (cm)	4.2	3.8-4.4	4.1	3.9-4.1	NS
LVEsD (cm)	2.9	2.7-3	2.9	2.7-3	NS
LA (cm)	2.9	2.8-3.2	2.9	2.8-3.2	NS
Mitral inflow					
E (m/s)	0.7	0.6-0.8	0.8	0.7-0.9	0.02*
A (m/s)	0.6	0.5-0.7	0.6	0.5-0.7	NS
Deceleration time (ms)	175	164.2-185	177.5	165-185.5	NS
IVRT (ms)	68	65-70.5	65	64.2-70	NS
Mitral lateral annulus					
E'm peak velocity (cm/s)	12.9	9.3-16	12.1	11.7-13.2	NS
A'm peak velocity (cm/s)	9.2	8-12	9.5	7.8-12.2	NS
S m peak velocity (cm/s) (>6)	9	7-10	10	9-10.5	0.03*
Tricuspid inflow					
Tricuspid E (m/s)	0.5	0.5-0.6	0.5	0.5-0.6	0.04*
Tricuspid A (m/s)	0.4	0.3-0.6	0.4	0.3-0.6	NS
Tricuspid annulus					
E't peak velocity (cm/s)	11.5	8-14	10	8-14	NS
A't peak velocity (cm/s)	14	10.3-16.1	14	11-15.3	NS
S t peak velocity (cm/s)	12.5	11-13.2	11.4	10.9-14.2	NS
TAPSE (cm)	2.4	2.3-2.5	2.5	2.2-2.6	NS
PASP (mmHg) <25	25	20-25.2	22	20-25	NS
RVEF (%)	54.9	53.2-57.4	55	53.8-57.6	NS
Tei index	0.32	0.3-0.36	0.23	0.21-0.25	<0.001*
LV GLS (%)	-23.5	-23- -25	-28	-27- -29	<0.001*
RV GLS (%)	-23.9	-22.5- -25	-28.1	-26.5- -30.4	<0.001*

FMF: Familial Mediterranean fever; IQR: Interquartile range; LVEF: Left ventricle ejection fraction; LVEdD: Left ventricle end-diastolic diameter; LVEsD: Left ventricle end-systolic diameter; LA: Left atrium; E: Early diastolic peak velocity; A: Late diastolic peak velocity; IVRT: Isovolumic relaxation time; E'm: Early diastolic myocardial peak velocity of mitral lateral annulus; A'm: Late diastolic myocardial peak velocity of mitral lateral annulus; S m: Peak systolic velocity of mitral lateral annulus; E't: Early diastolic myocardial peak velocity of tricuspid annulus; A't: Late diastolic myocardial peak velocity of tricuspid annulus; S t: Peak systolic velocity of tricuspid annulus; TAPSE: Tricuspid annular plane systolic excursion; PASP: Pulmonary artery systolic pressure; RVEF: Right ventricle ejection fraction; LV: Left ventricle; GLS: Global longitudinal strain; NS: Not significant * Statistically significant.

Left ventricular ejection fraction was slightly lower in the FMF group (60% IQR: 58.7-62) than controls (62% IQR: 60-63; p=0.003) but all values were within normal ranges. LV diameters or left atrium size were not statistically significantly different between groups. Moreover, LV deceleration time, isovolumetric relaxation time, early diastolic myocardial peak velocity of the mitral lateral annulus (E' m), late diastolic myocardial peak velocity of the mitral lateral annulus (A' m) and lateral systolic (S) myocardial velocity were similar for both groups. Although late diastolic trans-mitral flow (A) was not different among groups, FMF patients had slightly lower early diastolic trans-mitral flow (E) values 0.7 (IQR: 0.5-0.6) vs. 0.8 (IQR: 0.7-0.9), p=0.02, respectively, Table 2.

Right ventricular ejection fraction was similar for both groups. Similarly, tricuspid annular plane systolic excursion, PASP, or late diastolic trans-tricuspid flow (A) were not statistically significantly different among FMF and control groups. As well as the mitral E flow, early diastolic trans-tricuspid flow was slightly lower in FMF groups than controls (0.5 [IQR: 0.5-0.6] vs. 0.5 [IQR: 0.5-0.6], respectively, p=0.04). Tei index was higher in the FMF group than controls (0.32 [IQR: 0.3-0.36] vs. 0.23 [IQR: 0.21-0.25], respectively, p<0.001). 2D GLS and 2D GLS rate were statistically significantly different among the groups. Mean RV strain was measured as -23.9% (IQR: -22.5-[-25]) in FMF group and this value was significantly lower than the control group (-28.1% IQR: -26.5-[-30.4], p<0.001).

DISCUSSION

In the present study, we have investigated cardiac functions in adult FMF patients with echocardiography. Our results have shown that FMF patients have a higher Tei index and lower RV strain than controls. Moreover, LVEF, early diastolic trans-mitral and trans-tricuspid flows were found to be slightly lower in the FMF group. A majority of the previous studies on FMF have been conducted on the child population, so this study may provide promising information about adult patients.

Diastolic dysfunction in FMF patients was shown in some studies.[9,10,17] In our study, there was no clear finding for diastolic impairment. However, a slight but statistically significant decrease in early diastolic trans-mitral and trans-tricuspid E wave may indicate an early sign of diastolic dysfunction. Several mechanisms have been suggested to explain diastolic dysfunction. One of the most accepted theories is systemic inflammation which causes early atherosclerosis.[17] This was supported by studies that have shown an increased intima-media thickness of carotid arteries and decreased endothelium-dependent flow-mediated dilation of the brachial artery.[8] According to our results, elevated ESR, lymphocyte and fibrinogen levels are concordant with relative systemic inflammation increase. Other possible causes of diastolic impairment are impaired active LV relaxation or reduced LV compliance, reduced passive LV filling, decrease in ventricular preload and vasculitis.[9,18]

Tei index is an independent marker of LV and RV dysfunction. This index provides information about systolic and diastolic functions of ventricles. It has shown that various cardiovascular diseases are associated with increased Tei index such as pulmonary hypertension,[19,20] coronary artery disease,[21] congestive heart failure,[15] chronic pulmonary obstructive disease[22] and cardiac amyloidosis.[23] Amyloidosis is one of the most fatal consequences of FMF. Kim et al.[23] have previously reported that cardiac amyloidosis is associated with increased RV Tei index.[24] In our study population, RV Tei index of FMF patients was increased. To the best of our knowledge, this is the first report describing the association between FMF and increased RV Tei index in adult population.

The LV systolic and diastolic functions were analyzed using conventional echocardiography techniques (2D, Doppler, and tissue Doppler), and systolic functions were also studied using 2D STE. GLS is an advanced echocardiography technique and can determine the possible systolic dysfunction in the initial phase before the decline of the LVEF and the occurrence of apparent heart failure. GLS can also be used to determine RV systolic function in many diseases. Previously published studies have demonstrated that RV strain analysis provides important diagnostic and prognostic benefits in pulmonary hypertension,[24,25] congenital heart diseases[26] and arrhythmogenic RV dysplasia.[27] The latest guidelines of American Society of

Echocardiography and the European Association of Cardiovascular Imaging have recommended RV strain for clinical use as a sensitive and reproducible index of RV performance.[13,28] The current guideline recommends the normal value of RV strain -29±4.5, which was close to the value of our control group. However, RV strain of FMF patients was significantly lower. The reduction of the RV GLS in FMF patients is a novel finding to the best our knowledge. In the light of these findings, beyond the conventional RV assessment, novel RV function evaluation techniques such as Tei index and RV strain may provide useful information about RV clinical and subclinical functions, particularly in systemic diseases.

The most important limitation of our study was the relatively small number of patients. Moreover, when conducting an echocardiographic study, intra- and inter-observer variability is high. Adding cardiac magnetic resonance imaging would have added more precise data when comparing RV function assessment. Larger-size multicenter studies are needed to clarify the exact estimation of RV functions in FMF patients.

In conclusion, we have investigated the left and right ventricular systolic functions using STE in addition to conventional echocardiographic evaluation in adult FMF patients and demonstrated that RV Tei index and GLS were impaired in adults with FMF during the attack-free period.

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