

Familial Mediterranean Fever is associated with abnormal ventricular repolarization indices

ELBIS AHBAP¹, TAMER SAKACI¹, EKREM KARA¹,
TUNCAY SAHUTOGLU¹, SEMI OZTURK²,
TANER BASTURK¹, YENER KOC¹, MUSTAFA SEVINC¹,
CUNEYT AKGOL¹, ZUHAL ATAN UCAR¹,
ARZU OZDEMIR KAYALAR¹, FEYZA BAYRAKTAR CAGLAYAN¹,
SEYFETTIN GURBUZ³, ABDULKADIR UNSAL¹

¹Department of Nephrology, Sisli Hamidiye Etfal Educational and Research Hospital, Istanbul, Turkey.

²Department of Cardiology, Haseki Educational and Research Hospital, Istanbul, Turkey.

³Department of Cardiology, Dr. Siyami Ersek Thoracic and Cardiac Surgery Educational and Research Hospital, Turkey.

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Address all correspondence to: Tuncay Sahutoglu, MD
Fellow in nephrology
Sisli Hamidiye Etfal Educational and Research Hospital
Halaskargazi Cad. EtfalSok. 34371, Sisli, Istanbul, Turkey.
tu_cay83@yahoo.com

ABSTRACT

Background: Cardiac arrhythmias can be a part of cardiovascular involvement in some rheumatic diseases, but data about familial Mediterranean fever (FMF) are conflicting. **Aim:** To search for abnormalities in ventricular repolarization indices in FMF patients. **Patients and Methods:** Seventy seven FMF patients and 30 age/gender comparable healthy controls were included. All patients were attack free and subjects with disease or drugs that are known to alter cardiac electrophysiology were excluded. Electrocardiographic data were obtained and analyzed. **Results:** Twelve FMF patients had amyloidosis. QT and QTc intervals were within the normal ranges and similar between FMF patients and healthy controls. QT dispersion, peak to end interval of T wave (Tpe), Tpe/QT and Tpe/QTc ratios were significantly higher in FMF patients than in healthy controls. Patients with amyloidosis had significantly higher QT dispersion, Tpe, Tpe/QT and Tpe/QTc than their counterparts without FMF. Levels of proteinuria were moderately correlated with QT dispersion, Tpe, Tpe/QT and Tpe/QTc. **Conclusions:** FMF patients may have an increased risk for arrhythmias.

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Key words: Arrhythmias, cardiac; Familial Mediterranean fever; Rheumatic diseases.

La fiebre mediterránea familiar se asocia a anomalías en la repolarización ventricular

Antecedentes: Las arritmias cardíacas pueden ser parte del compromiso cardíaco en enfermedades reumáticas, sin embargo, no se sabe con certeza si esto ocurre en la fiebre mediterránea familiar (FMF). **Objetivo:** Buscar anomalías en la repolarización ventricular en pacientes con FMF. **Pacientes y Métodos:** Sesenta y siete pacientes como FMF y 30 controles sanos pareados por edad y género fueron estudiados. Todos los pacientes estaban en período intercrítico y no usaban medicamentos o tenían enfermedades concomitantes que pudieran causar anomalías electrocardiográficas. Se analizaron los electrocardiogramas de estos participantes. **Resultados:** Veinte pacientes con FMF tenían amiloidosis. Los intervalos QT y QTc eran normales y similares entre pacientes y controles. La dispersión del intervalo QT, el intervalo desde el peak al final de la onda T (Tpe),

las razones Tpe/QT y Tpe/QTc fueron significativamente más altos en los pacientes que en los controles. Los pacientes con amiloidosis tenían una dispersión de QT , Tpe , Tpe/QT y Tpe/QTc mayores que sus pares sin la condición. Los niveles de proteinuria se correlacionaron moderadamente con los parámetros antes mencionados. **Conclusiones:** Los pacientes con FMF tienen mayor riesgo de arritmias.

Familial Mediterranean Fever (FMF) is the most common form of periodic fever syndromes, which is caused by mutations in the MEFV gene. It is characterized by sporadic unpredictable attacks of fever, arthritis and serositis¹. The prevalence is particularly higher in certain ethnic groups within the Mediterranean basin, such as Sephardic Jews, Armenians, Turks, Arabs and Druze². The diagnosis is usually made on clinical basis and the genetic tests for MEFV gene are supportive.

Aside from symptoms and signs of episodic attacks of inflammation, FMF is a major cause of accumulation of amyloid A amyloidosis (AAA). AAA secondary to FMF can involve many different organs, but most frequently the kidneys, spleen, liver and gut. One of the earliest targets of AAA in FMF is the kidney, which can be manifested initially with isolated proteinuria and later with increased creatinine levels.

Cardiovascular system is an important target of AAA, with significant morbidity and mortality at advanced stages. FMF may cause pericarditis due to serositis and/or cardiac amyloidosis as a part of the systemic disease³. Recent studies investigated repolarization abnormalities using markers such as QT dispersion, transmural dispersion of repolarization and P-wave dispersion in FMF patients with and without AAA⁴⁻⁶. Peak to end interval of T wave is newer marker of cardiac repolarization abnormality, which has been suggested as a better predictor of sudden cardiac death or ventricular tachycardia⁷. We aimed to evaluate cardiac repolarization indices and their correlates in patients with FMF with and without AAA.

Materials and Methods

Study population

Patients who had been followed up between June 2004 and June 2014 in the outpatient clinic of Nephrology of Sisli Hamidiye Etfal Educational and Research Hospital and who were diagnosed

with FMF according to Tel Hashomer criteria were included. Diagnosis of amyloidosis was confirmed by renal biopsy in all amyloidosis positive FMF patients. Past medical history and the medications of the patients were recorded. Exclusion criteria were history of congenital or acquired heart diseases, inflammatory attack within the previous month, drug ingestion that may have an effect on ECG, chronic diseases (such diabetes, hypertension, hypothyroidism, organ failure, etc.). Age and gender comparable healthy subjects were recruited as the control group.

This is a cross-sectional study in design and variables were obtained between September 2014 and December 2014. The following clinical and laboratory variables were recorded and used for analysis: age, gender, body-mass index (BMI), serum glucose, urea, creatinine levels, electrolytes (Na, K), albumin, lipids, fibrinogen, C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), urine analysis, daily proteinuria, blood pressure, electrocardiography (ECG) and echocardiography (ECHO) parameters.

BMI was calculated by dividing weight (kilograms) by height squared (meters). Plasma level of CRP was measured by nephelometric method and ESR was determined by the Westergreen method.

Procedure

All ECG recordings were obtained using the same 12-lead commercial device (Nihon Kohden, Cardiofax M, Tokyo, Japan) while the patients were resting in supine position for 10 minutes at a room temperature of 20-23°C between 09:00 and 14:00. The device was set at a 50 mm/s paper speed and 2mV/cm. All participants were asked to avoid smoking, intake of caffeinated, alcoholic beverages and other stimulants within 3 hours and strenuous exercise 24 hours prior to study.

QT intervals were corrected according to the Bazett's formula (QTc) and the difference between maximum and minimum QTc intervals in each electrocardiogram was calculated as QT dispersion (QTd).

The Tpe interval was measured as the distance between the peak and the end of T wave in the precordial lead V5 (or in leads V4 and V6 if not measurable in V5), and was corrected according to heart rate (Figures 1a and 1b show samples of QT and Tpe measurements). Tpe/QTc ratio was calculated from these measurements. Subjects with U waves on their ECGs were excluded from the study. All ECG measurements were performed by a single blinded observer.

Statistical analysis

SPSS 20.0 software (SPSS Inc, Chicago, USA) was used for statistical analysis. Parametric data were presented as mean \pm SD. Normality test was performed to all variables. Student t-test was used for parametric variables and Mann Whitney U test was used for non-parametric distribution of variables. Spearman and Pearson tests were used for correlation analysis. Yates correction, chi-square test and Fisher's exact test were used for comparison of categorical data. One-way ANOVA with Tukey post-hoc analysis correction was used for intergroup analysis. Multivariate analyses were performed by logistic regression. P value < 0.05 was considered as significant.

The study was approved by local Ethics Committee, and informed consent was obtained from each participant.

Results

General characteristics

Clinical characteristics, laboratory and echocardiographic parameters and repolarization indices of the FMF patients and the controls are shown in Table 1. There were 67 FMF patients and 30 healthy controls eligible to study. The mean disease duration was 9.1 ± 8.2 years and all FMF patients were receiving 1 to 1.5 mg/day colchicine, orally.

All of the general characteristics were similar between FMF patients and the controls, except for mildly lower diastolic blood pressure and higher proteinuria, LV ejection fraction and LV mass index in the FMF group. Notably, inflammatory markers (ferritin, CRP, ESR and fibrinogen) were also similar between the two groups (Tables 1 and 2). However, patients with amyloidosis had higher levels of proteinuria, LV mass index, ESR and fibrinogen when compared to patients without amyloidosis (Table 3).

Cardiac repolarization

QT and QTc intervals were within the normal ranges and similar between the patients and controls ($p > 0.05$), whereas Tpe interval, Tpe/QT ratio and Tpe/QTc ratio were significantly increased in patients with FMF as compared to the healthy controls ($p < 0.001$) (Table 2).

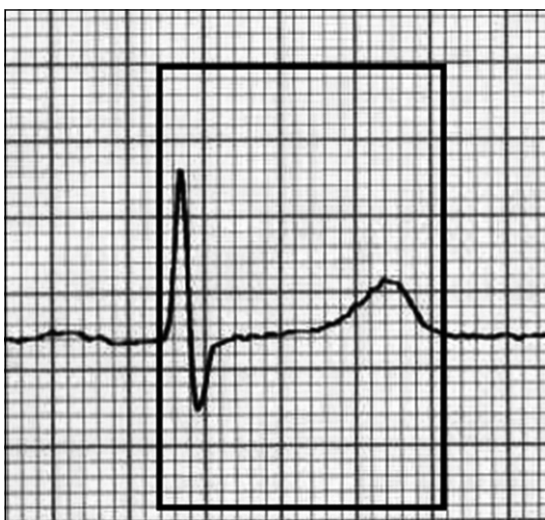


Figure 1a. Measurement of QT interval in an FMF patient without amyloidosis.



Figure 1b. Measurement of T peak to T end interval in an FMF patient without amyloidosis.

Table 1. Comparison of demographic and laboratory parameters between healthy controls and FMF patients

	Control (n = 30)	FMF (n = 67)	p
Demographics			
Age (years)	37.9 ± 15.2	36.1 ± 11.8	NS
Sex (male/female)	13/17	30/37	NS
FMF disease duration (years)			
Weight (kg)	71.9 ± 15.6	69.9 ± 16.1	NS
Body mass index (kg/m ²)	25.3 ± 4.7	25.6 ± 5.3	NS
Systolic BP (mmHg)	115.5 ± 6.9	113.7 ± 13.0	NS
Diastolic BP (mmHg)	74.5 ± 5.6	71.0 ± 7.4	0.009
Laboratory			
Urea (mg/dL)	27.0 ± 9.0	30.7 ± 17.1	NS
Creatinine (mg/dL)	0.8 ± 0.1	0.9 ± 0.4	NS
Uric acid (mmol/L)	4.8 ± 1.1	4.7 ± 1.5	NS
Sodium (mmol/L)	140.9 ± 2.4	139.8 ± 2.1	NS
Potassium (meq/L)	4.5 ± 0.4	4.4 ± 0.4	NS
Hemoglobin (g/dL)	13.7 ± 1.7	13.3 ± 1.6	NS
Total cholesterol (mmol/L)	193.3 ± 29.3	179.9 ± 40.7	NS
Triglyceride (mmol/L)	140.1 ± 103.6	119.0 ± 80.8	NS
LDL (mmol/L)	114.3 ± 22.1	106.5 ± 37.4	NS
HDL (mg/dL)	52.4 ± 15.9	49.5 ± 12.7	NS
Albumin (g/dl)	4.7 ± 0.3	4.5 ± 0.5	NS
Ferritin (ng/mL)	68.1 ± 51.4	61.0 ± 72.5	NS
Proteinuria (mg/24 h)	69.3 ± 34.6	605.8 ± 1834.8	< 0.001
CRP (mg/L)	4.5 ± 2.2	7.1 ± 11.5	NS
ESR (mm/h)	12.3 ± 6.4	15.5 ± 16.0	NS
Fibrinogen (mg/dL)	269.8 ± 57.6	281.6 ± 75.2	NS

Mann-Whitney U test. BP, blood pressure; LDL, low density cholesterol; HDL, high density cholesterol; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate.

Table 2. Comparison of echocardiographic and ventricular repolarization parameters between healthy controls and FMF patients

	Control (n = 30)	FMF (n = 67)	p
Echocardiography findings			
EF (%)	61.8 ± 2.2	63.5 ± 3.5	0.008
LAD (cm)	3.2 ± 0.3	3.3 ± 0.3	NS
LVESD (cm)	2.85 ± 0.34	2.91 ± 0.33	NS
LVEDD (cm)	4.42 ± 0.30	4.47 ± 0.33	NS
IVST (cm)	0.98 ± 0.15	1.04 ± 0.15	NS
PWT (cm)	0.93 ± 0.14	1.01 ± 0.13	NS
LV mass	166.3 ± 50.9	186.5 ± 49.5	NS
LV massindex	91.2 ± 27.1	104.4 ± 22.9	0.008
Repolarization indices			
QT interval (msec)	367.1 ± 28.9	366.4 ± 24.5	NS
QTc interval (msec)	396.9 ± 17.2	400.5 ± 20.3	NS
QT dispersion (msec)	22.6 ± 6.9	35.4 ± 16.0	< 0.001
QT dispersion variance	24.5 ± 7.0	39.8 ± 17.7	< 0.001
Tpeinterval (msec)	72.3 ± 6.1	79.8 ± 8.3	< 0.001
Tpe/QT ratio	0.191 ± 0.026	0.218 ± 0.024	< 0.001
Tpe/QTc ratio	0.182 ± 0.016	0.199 ± 0.021	< 0.001

Mann-Whitney U test. EF, ejection fraction; LAD, left atrium diameter; LVESD, left ventricular end systolic diameter; LVEDD, left ventricular end diastolic diameter; IVST, interventricular septum thickness; PWT, posterior wall thickness.

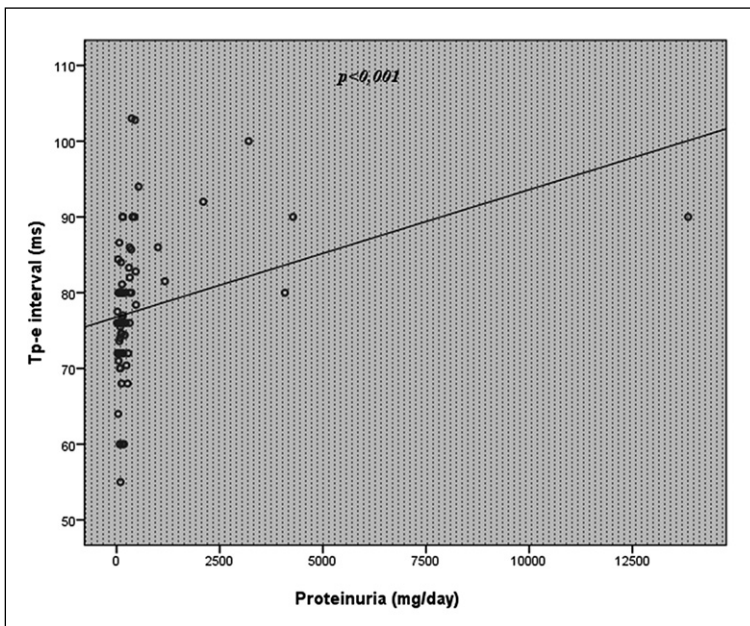


Figure 2. Spearman correlation between levels of proteinuria and Tpe intervals.

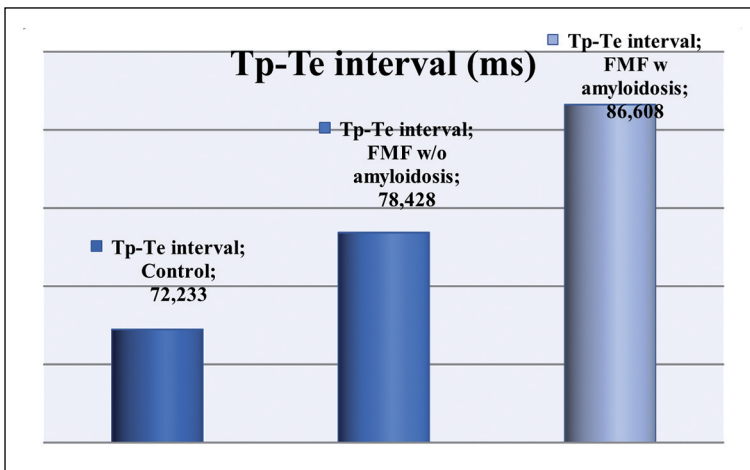


Figure 3. Comparison of mean Tpe intervals between the control group, amyloidosis negative and positive FMF patients.

When repolarization indices were compared between FMF patients with and without amyloidosis, we found that QT and QTc intervals were within the normal ranges and similar between the two groups, whereas Tpe interval, Tpe/QT and Tpe/QTc ratios were higher in patients who had amyloidosis as compared to those without amyloidosis (Table 4 and Figure 3). Tpe interval, Tpe/QT and Tpe/QTc ratios still remained higher in FMF patients as compared to healthy controls,

even after the patients with amyloidosis were excluded from the analysis.

Correlation analysis

Proteinuria and the presence of amyloidosis showed moderate correlations with Tpe interval, Tpe/QT and Tpe/QTc ratios, but not with QT or QTc intervals (Table 5). Tpe interval was weakly correlated with male gender, serum albumin, left atrial diameter, LVEDD and moderately with

Table 3. Comparison of demographic and laboratory parameters between FMF patients with and without amyloidosis

	Amyloidosis (-) (n = 55)	Amyloidosis (+) (n = 12)	p
Demographics			
Age (years)	36.0 ± 12.4	36.9 ± 8.7	NS
Sex (male/female)	23/32	7/5	NS
Duration of amyloidosis (years)			
Weight (kg)	71.1 ± 15.7	64.4 ± 17.2	NS
Body mass index (kg/m ²)	26.0 ± 5.5	23.5 ± 4.1	NS
Systolic BP (mmHg)	114.1 ± 12.8	111.6 ± 14.0	NS
Diastolic BP (mmHg)	71.2 ± 6.9	70.0 ± 9.5	NS
Laboratory			
Urea (mg/dL)	28.1 ± 13.4	42.6 ± 26.0	0.034
Creatinine (mg/dL)	0.85 ± 0.32	1.19 ± 0.74	NS
Uric acid (mmol/L)	4.5 ± 1.3	5.7 ± 1.9	0.002
Sodium (mmol/L)	139.7 ± 2.0	140.3 ± 2.4	NS
Potassium (meq/L)	4.3 ± 0.3	4.6 ± 0.5	NS
Hemoglobin (g/dL)	13.3 ± 1.7	13.3 ± 1.3	NS
Total cholesterol (mmol/L)	176.2 ± 34.6	197.1 ± 60.4	NS
Triglyceride (mmol/L)	116.4 ± 83.9	130.5 ± 66.0	NS
LDL (mmol/L)	103.8 ± 30.1	118.6 ± 61.2	NS
HDL (mg/dL)	49.6 ± 11.4	48.7 ± 18.3	NS
Albumin (g/dl)	4.6 ± 0.3	4.0 ± 0.9	0.006
Ferritin (ng/mL)	54.2 ± 56.3	92.2 ± 121.1	NS
Proteinuria (mg/24 h)	166.5 ± 121.6	2619 ± 3839	< 0.001
CRP (mg/L)	7.2 ± 12.6	7.0 ± 5.1	NS
ESR (mm/h)	11.8 ± 8.0	32.0 ± 29.2	0.003
Fibrinogen (mg/dL)	264.6 ± 57.7	359.3 ± 97.8	0.002

Mann-Whitney U test. BP, blood pressure; LDL, low density cholesterol; HDL, high density cholesterol; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate.

Table 4. Comparison of echocardiographic and ventricular repolarization parameters between healthy controls and FMF patients with and without amyloidosis

	Control (n = 30)	Amyloidosis (-) (n = 55)	Amyloidosis (+) (n = 12)	p
Echocardiography findings				
EF (%)	61.8 ± 2.2	63.6 ± 3.7	63.0 ± 2.2	0.007
LAD (cm)	3.2 ± 0.3	3.3 ± 0.3	3.5 ± 0.3	NS
LVESD (cm)	2.85 ± 0.34	2.88 ± 0.30	3.03 ± 0.45	NS
LVEDD (cm)	4.42 ± 0.30	4.45 ± 0.31	4.60 ± 0.40	NS
IVST (cm)	0.98 ± 0.15	1.05 ± 0.15	1.01 ± 0.11	NS
PWT (cm)	0.93 ± 0.14	1.01 ± 0.14	1.00 ± 0.09	NS
LV mass	166.3 ± 50.9	185.6 ± 49.0	190.6 ± 53.8	NS
LV mass index	91.2 ± 27.1	102.9 ± 22.5	111.3 ± 24.6	0.014
Repolarization indices				
QT interval (msec)	367.1 ± 28.9	366.2 ± 23.1	366.9 ± 31.3	NS
QTc interval (msec)	396.9 ± 17.2	400.6 ± 19.8	400.4 ± 23.2	NS
QT dispersion (msec)	22.6 ± 6.9	32.6 ± 14.7	48.3 ± 15.8	< 0.001
QT dispersion variance	24.5 ± 7.0	36.9 ± 16.9	52.9 ± 15.9	< 0.001
Tpe interval (msec)	72.3 ± 6.1	78.4 ± 8.1	86.6 ± 5.6	< 0.001
Tpe/QT ratio	0.191 ± 0.026	0.214 ± 0.025	0.234 ± 0.015	< 0.001
Tpe/QTc ratio	0.182 ± 0.016	0.196 ± 0.020	0.216 ± 0.015	< 0.001

Mann-Whitney U test. EF, ejection fraction; LAD, left atrium diameter; LVESD, left ventricular end systolic diameter; LVEDD, left ventricular end diastolic diameter; IVST, interventricular septum thickness; PWT, posterior wall thickness.

Table 5. Correlation analysis of ventricular repolarization indices with proteinuria and amyloidosis

Repolarization indices	Proteinuria		Amyloidosis	
	r	p	r	p
QT interval (msec)	-0.142	NS	-0.037	NS
QTc interval (msec)	-0.031	NS	+0.008	NS
QT dispersion (msec)	+0.538	< 0.001	+0.393	< 0.001
QT dispersion variance	+0.580	< 0.001	+0.384	< 0.001
Tpe interval (msec)	+0.500	< 0.001	+0.463	< 0.001
Tpe/QT ratio	+0.537	< 0.001	+0.401	< 0.001
Tpe/QTc ratio	+0.475	< 0.001	+0.393	< 0.001

Spearman correlation analysis.

Table 6. Correlation analysis of Tpe with clinical and laboratory parameters

Tpe	r	p
Age	-0.060	NS
Male gender	+0.291	0.004
Presence of amyloidosis	+0.463	< 0.001
Systolic BP	+0.040	NS
Diastolic BP	-0.072	NS
Proteinuria	+0.500	< 0.001
Albumin	-0.269	0.008
LAD	+0.283	0.005
LV mass	+0.301	0.003
LV mass index	+0.399	< 0.001
PWT	+0.305	0.002
IVST	+0.193	NS
LVESD	+0.340	0.001
LVEDD	+0.207	0.041
CRP	+0.151	NS
ESR	+0.143	NS
Fibrinogen	+0.131	NS
Urea	+0.052	NS
Creatinine	+0.165	NS
Na	-0.005	NS
K	+0.026	NS
Total cholesterol	-0.128	NS
TG	-0.049	NS
HDL	-0.005	NS
LDL	-0.135	NS

BP, blood pressure; LDL, low density cholesterol; HDL, high density cholesterol; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; EF, ejection fraction; LAD, left atrium diameter; LVESD, left ventricular end systolic diameter; LVEDD, left ventricular end diastolic diameter; IVST, interventricular septum thickness; PWT, posterior wall thickness.

amyloidosis, proteinuria, LV mass index, posterior wall thickness, and LVESD (Table 6 and Figure 2). There were no correlations between Tpe and age, inflammatory markers, blood pressure and the other laboratory parameters (Table 6).

Discussion

Several rheumatic disorders, such as rheumatoid arthritis and systemic lupus erythematosus, have been shown to be associated with cardiovascular morbidity and mortality, that cannot be attributed to traditional cardiovascular risk factors⁸. Major causes for these adverse cardiovascular effects are accelerated atherosclerosis, small vessel vasculitis within the heart, degeneration of the conduction system, and endocardium damage. Cardiac arrhythmias and conduction disturbances are part of the consequences of cardiac involvement in rheumatic diseases⁹. Likewise, secondary amyloidosis can produce cardiac arrhythmias and conduction disturbances as a result of deposition of amyloid fibrils within the myocardium and possibly autonomic nervous system dysfunctions¹⁰.

Nussinovitchetal published several studies regarding cardiac repolarization abnormalities in FMF patients. In their studies, FMF patients with and without amyloidosis had similar repolarization indices (QT interval, QTc interval and QT dispersion) to those of healthy controls^{5,11}. When colchicine resistant FMF patients were compared to healthy controls, they also revealed that cardiac repolarization indices were similar between the two groups¹². Another study from Turkey with a similar design also found that there were not differences in ventricular repolarization indices

between FMF patients and healthy controls¹³. Giese et al compared FMF patients without amyloidosis and Nussinovitch et al. compared FMF patients with amyloidosis to health controls to searched for supraventricular indices. Both of them found that P-wave duration and dispersions were comparable between FMF patients and healthy controls^{14,15}.

Young FMF patients with relatively short disease duration were included in this study to investigate cardiac arrhythmogenicity basis before and early after the development of overt amyloidosis. The sample size was relatively larger than previous studies and all patients were under colchicine treatment. QT interval and QTc values of both FMF patients and healthy controls were within the normal ranges and comparable, like findings in the aforementioned studies. However, in contrast to some of the previous studies, all indices that reflect ventricular repolarization abnormalities were significantly higher in FMF patients than in healthy controls. When we separated patients with and without amyloidosis, we found that QTd was higher in amyloidosis negative FMF patients than in healthy controls. This value was even higher in amyloidosis positive than in amyloidosis negative FMF patients. LV mass indices and the levels of proteinuria were highest in amyloidosis positive FMF patients and lowest in healthy controls. Proteinuria and amyloidosis were factors showing the best correlation with QTd. Markers of inflammation were comparable between healthy controls and FMF patients and they were not correlated with QTd.

In a cross-sectional study by Akcay et al., QTd was found to be higher in FMF patients similar to our results⁴. Arslan et al. looked for atrial arrhythmogenicity in pediatric FMF patients, and unlike other studies they found that P wave dispersion was higher in FMF patients than in healthy controls¹⁶.

Tpe interval is a relatively newer marker of ventricular arrhythmia and suggested to correspond to transmural dispersion of repolarization. Tpe/QT is constant at normal heart rates and has a mean value of 0.21 in healthy individuals¹⁷. Tpe and Tpe/QT were found to be associated with adverse outcomes in patients with myocardial infarction, Brugada syndrome, bradyarrhythmia, and hypertrophic cardiomyopathy^{7,18-20}. Tpe and Tpe/QT have not been studied previously to evaluate

ventricular repolarization in FMF patients. In our study, Tpe, Tpe/QT and Tpe/QTc were significantly higher in FMF patients as compared to healthy controls. These parameters were even more increased in patients who developed amyloidosis than in patients without amyloidosis. In correlation analysis, these parameters showed similar results to QTd correlations. Proteinuria, amyloidosis and LV mass index were factors showing the best correlation with Tpe, Tpe/QT and Tpe/QTc. These findings suggest that there may be subclinical amyloid deposition within the myocardium before the development of detectable cardiac amyloidosis, and the presence of renal amyloidosis (or proteinuria) may be a sign of more advanced disease.

Our study indicates that there may be subclinical arrhythmogenic potential in FMF patients, even before the development of overt amyloidosis. However, there is a lot of controversy in the literature regarding to whether there are repolarization abnormalities or tendency to arrhythmia in patients with FMF. The causes of this may include limitations of study designs, inter-observer and intra-observer variability in measuring intervals from ECG recordings, and using different ECG recorders. Another aspect of such studies is that they do not show whether the actual risk of ventricular arrhythmia is increased in FMF. In a prospective design, 24 to 72 hours of continuous ECG recordings in a large cohort of FMF patients and computer based measurements may provide with the actual prevalence of arrhythmia and its correlation to repolarization indices.

Conclusions

QTd, Tpe, Tpe/QT and Tpe/QTc were higher in FMF patients as compared to healthy controls, and these parameters were even more elevated in patients who developed amyloidosis. These parameters were moderately correlated with proteinuria, amyloidosis and LV mass index. Increased Tpe in FMF was shown in this study for the first time to our knowledge. The clinical significance of these findings has not been shown yet, but they suggest that arrhythmogenic potential may be increased in FMF patients. Data in the literature are not uniform and better study designs are needed to answer unresolved questions.

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