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Original Investigation

Heart rate variability in familial Mediterranean fever patients

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Abstract

Objective: Familial Mediterranean fever (FMF) is an autosomal recessive autoimmune disease, presenting with the attacks of fever and inflammation of serous membranes. One of the leading causes of death in autoimmune rheumatologic diseases is cardiovascular events. The purpose of this study is to evaluate the effects of FMF on the autonomic nerve and cardiovascular systems by measuring the indices of heart rate variability (HRV).

Material and Methods: Thirty FMF patients and the same number of healthy volunteers were enrolled to the study. Standard deviation of all R-R intervals (SDNN), the square root of the sum of the square of the differences between successive R-R intervals (RMSSD), standard deviation of 5-minute mean values of R-R interval (SDANN), low frequency (LF), and high frequency (HF) were measured.

Results: Time domain indices (SDNN, SDANN, and RMSSD) were: 124.67±40.79, 129.87±36.43 (p=0.605); 11.43±38.41, 11.23±38.98 (p=0.984); and 33.43±17.39, 38.17±12.8 (p=0.235) for FMF patients and controls, respectively, and similar in both groups. Frequency domain indices (HF, LF, and LF/HF) were: 290.41±290.25, 322.20±222.54 (p=0.639); 596.16±334.07, 805.80±471.00 (p=0.051); and 3.57±2.57, 3.05±1.40 (p=0.338) for FMF patients and controls, respectively, and similar in both groups.

Conclusion: The HRV parameters were similar in both groups. However, studies including larger populations and using different methods are required to clarify if autonomic dysfunction exists in patients with FMF.

Key words: Familial Mediterranean fever, autonomic nervous system, heart rate variability

Introduction

Familial Mediterranean fever (FMF) is an autosomal recessive autoimmune disease, presenting with attacks of fever and inflammation of serous membranes (1, 2). One of the leading causes of death in autoimmune rheumatologic diseases is cardiovascular events. There are several studies involving the cardiovascular and autonomic effects of rheumatologic disorders in the last decade (3-5). The clinical and subclinical cardiovascular effects of FMF were well defined by recent studies (6, 7). The major cause of sudden cardiac death is ventricular arrhythmia (8). There are 3 etiologic factors for ventricular arrhythmias: arrhythmogenic substrate, arrhythmogenic triggering, and autonomic tonus oscillations (9, 10). The heart rate variability (HRV) measurement is one of the best methods that evaluate the relationship between the autonomic nerve system (ANS) and cardiovascular system quantitatively (11, 12). In this study, the purpose is to determine the HRV in FMF patients by using 24-hour ambulatory ECG, evaluating the effects of disease on ANS and cardiac arrhythmia potential.

Material and Methods

Thirty patients (17 females/13 males, mean age 34.9±9.14) diagnosed as FMF according to Tel Hashomer criteria in a rheumatology outpatient clinic who were in an inactive period of disease and 30 healthy volunteers (19 females/11 males, mean age 33.27±8.6) were prospectively enrolled to the study. Exclusion criteria were as follows: diabetes mellitus, hypertension, valvular heart disease, coronary artery disease, cardiac arrhythmia, left ventricular ejection fraction <50%, chronic kidney disease, chronic liver disease, thyroid dysfunction, anemia, amyloidosis, acute or chronic infection, chronic lung disease, inflammatory disease except FMF, and pericarditis. A protocol consisted of a detailed history, physical examination, 12-lead ECG, transthoracic echocardiography, and 24-hour ambulatory ECG. All of the FMF patients were followed up in a rheumatology clinic with same-dose colchicine (1.5 mg/day), and there were no additional medications. Also, all of the healthy volunteers were free of any medications. All study subjects gave signed informed consent for participation in the study, and the study protocol was approved by the ethics committee of our institution.

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For the echocardiographic examination, Vivid 7 Dimension echocardiography (Vingmed Ultrasound, GE, Horten, Norway) was used. Left ventricular ejection fraction was calculated by modified Simpson method, and left ventricular mass index was calculated by Devereux formula (13).

In the analysis, a standard ambulatory ECG recording system (Century 2000/3000 HRV Package System, version 1.32, Biomedical Systems, St. Louis, ABD) was used. All of the records were manually calculated for R-R intervals and analyzed by using this package system. In the analyses, only the cycles with normal morphologic characterized beats were used. The HRV was evaluated by two ways: time domain analysis and frequency domain analysis. Time domain analysis was evaluated by using the standard deviation of all R-R intervals (SDNN), the square root of the sum of the square of the differences between successive R-R intervals (RMSSD), and the standard deviation of the mean N-N intervals of 5-minutes segments (SDANN). Spectral measurements were calculated by Fast Fourier converting method. All of the records were obtained by taking the average of different 5-minute recordings in concordance with European Society of Cardiology and North American Society of Pacing and Electrophysiology rules. The power of the pulse spectrum between 0.003 MHz and 0.4 Hz is defined as total energy (ms^2). This power was divided into two components: low frequency (LF) (0.04-0.15 Hz) and high frequency (HF) (0.16-0.4 Hz). The HF is the indicator of parasympathetic activity, and the LF is the indicator of sympathetic activity. Additionally, the ratio of LF to HF was calculated, showing the sympathovagal balance (14). High values of this ratio show dominant sympathetic activity.

Statistical Analyses

All data were processed using the SPSS statistical package, version 12.0 (SPSS, Inc, Chicago, IL, USA), and a p value of less than 0.05 was considered to be significant. Mann-Whitney U- and student t-tests were used for statistical significance analysis of measurable values, and Q-square test was used for non-measurable values.

Results

The basic clinical and echocardiographic features of the study group are shown in Table 1. The HRV parameters of the study group are shown in Table 2. Time domain measurements SDNN, SDANN, and RMSSD were similar between groups (p values 0.605, 0.984, and 0.235, respectively). Frequency domain measurements total power (TP), HF, LF, and LF/HF were similar between groups (p values 0.073, 0.639, 0.051, and 0.338, respectively).

Table 1. The basic clinical and echocardiographic features of the study groups

	Patient group (n=30)	Control group (n=30)	p
Age, years	34.90±9.14	33.27±8.60	0.479
Sex (female/male)	17/13	19/11	0.920
BMI (kg/m^2)	25.67±4.12	22.82±5.82	0.033
BSA (m^2)	1.8±0.4	1.8±0.5	0.832
Pulse rate	77.87±11.17	77.67±9.85	0.942
SBP (mm Hg)	106.33±12.10	105.50±6.99	0.745
DBP (mm Hg)	70.43±6.65	70.83±5.09	0.795
LVEDD (mm)	46.87±4.30	45.57±3.89	0.225
LVESD (mm)	29.57±3.60	28.83±3.52	0.429
IVS (mm)	9.23±1.1	9.1±1.22	0.116
PW (mm)	8.50±1.25	8.27±0.785	0.116
LVmass index (g/m^2)	90.3±15.3	88.3±16.7	0.448
LVEF (%)	66.40±5.51	66.70±5.28	0.830
LAD (mm)	31.60±5.74	30.53±4.40	0.423
Disease period (months)	88.4±97.3		

BMI: body mass index; BSA: body surface area; DBP: diastolic blood pressure; IVS: interventricular septum thickness; LAD: left atrium diameter; LVEDD: left ventricular end-diastolic diameter; LVEF: left ventricular ejection fraction; LVESD: left ventricular end-systolic diameter; PW: left ventricular posterior wall thickness; SBP: systolic blood pressure

Table 2. The heart rate variability parameters of the study groups

	Patient group (n=30)	Control group (n=30)	p
SDNN (ms)	124.67±40.79	129.87±36.48	0.605
SDANN (ms)	11.43±38.41	11.23±38.98	0.984
TP (ms^2)	2898.31±1652.70	3738.01±1896.15	0.073
RMSDD (ms)	33.43±17.39	38.17±12.80	0.235
LF (ms^2)	596.16±334.07	805.80±471.00	0.051
HF (ms^2)	290.41±290.25	322.20±222.54	0.639
LF/HF (ms^2/ms^2)	3.57±2.57	3.05±1.40	0.338

HF: high frequency; LF: low frequency; RMSDD: the square root of the sum of the square of the differences between successive R-R intervals; SDANN: the standard deviation of the mean N-N intervals of 5-minute segments; SDNN: the standard deviation of all N-N intervals; TP: total power

Discussion

Familial Mediterranean fever is an autosomal recessive autoimmune disease coursing with relapsing fever and inflammation of serous membranes (1, 2). It is important to assess autonomic surge in FMF patients, because some of the studies proposed that autonomic fluctuation might predispose one to ventricular arrhythmias (10, 11).

There are several ways to assess autonomic functions, such as mental stress tests, serum tests of some hormonal mediators, and pharmacological tests. Nowadays, one of the best methods of evaluating the relationship between the ANS and cardiovascular system is HRV measurement (11, 12). HRV is defined as beat-to-beat variability in heart rate. The heart rate increases with inspiration and decreases with expiration (15). The variability of heart rate in healthy individuals with normal sinus rhythm is an expected condition. The leading cause of HRV is autonomic tonus alterations. While sympathetic tone increases heart rate, the parasympathetic tone decreases it. The parasympathetic system controls heart rate, especially at rest. HRV is calculated by time or frequency methods based on ECG monitoring. The simplest measurement is time domain analysis. From the time domain analysis, SDNN, SDANN, and RMSSN are suggested (16). Frequency domain analysis divides the heart rate signals according to their frequency and intensity. The measurements in terms of frequency by power spectral density analysis consist of 5 frequency bands between 0 and 0.5. The most popular frequency bands are LF, HF, and LF/HF. While an increase in HF represents parasympathetic activity, an increase in LF represents sympathetic activity. In healthy individuals, LF/HF shows the balance between sympathetic and vagal tonus. The time-based parameters and frequency-based parameters are strongly correlated (14-16).

In our study, with 24-hour ambulatory ECG analysis, we found that the time-based parameters and frequency-based parameters were similar between FMF patients and controls.

Cardiovascular diseases are the leading causes of morbidity and mortality among patients with autoimmune diseases (17). Several previous studies investigated the association between autoimmune diseases and several indices of cardiac autonomic dysfunction, including rheumatoid arthritis, systemic sclerosis, Behçet's disease, and systemic lupus erythematosus.

Evrengül et al. (18) investigated that LF increased, HF decreased, and LF/HF increased in rheumatoid arthritis patients. They proposed that those changes might result in ventricular tachyarrhythmia and sudden cardiac death. However, in a recent study, Saraswathi et al. (19) showed decreased HRV in female RA patients; Avsar et al. (20) examined unchanged turbulence in RA patients.

Laversuch et al. (21) showed that HRV negatively affected systemic lupus erythematosus patients by using spectral analyses. It has been shown that HRV is suppressed in Behcet's disease patients by Ozdemir et al. (22) and in psoriatic arthritis patients by Gaydukova et al. (23).

In a study by Rozenbaum et al. (24) involving FMF patients using tilt table test, the rate of autonomic dysfunction, including postural tachycardia syndrome and orthostatic hypotension, was 18.1%. In another study by Rozenbaum et al., the cardioreactivity scores were compatible with insignificant levels of autonomic dysfunction in FMF patients (25).

In our study, the time-based parameters were similar, but there was a statistically insignificant difference in frequency-based parameters. Therefore, these data should be clarified by large-scale studies. In another study, by using the tilt table test, it was demonstrated that the cardioactivity scores correlated with autonomic dysfunction in FMF patients. The authors proposed that those scores might be used in the diagnosis of suspected FMF cases (26).

Nussinovitch et al. (27) showed that time- and frequency-based parameters were similar between FMF patients and controls. But, that was a limited study because of the shortness of the parameter records. In contrast, it has been demonstrated that the reliability of the HRV parameters correlates directly with recording time (28).

In our study, we analyzed the HRV parameters by using 24-hour ambulatory ECG. Inconsistent with the study of Nussinovitch et al. (27), the HRV values were similar between FMF patients and controls. FMF patients have been using low-dose colchicine regularly in both our and Nussinovitch's study (27). In an in vitro study, colchicine has been shown to have cardiac chronotropic effects (29). But, there are limited data in the literature about cardiac involvement during colchicine use. We do not know the autonomic functional changes in patients with high-dose colchicine and without colchicine yet. In studies with rheumatoid arthritis, Sjogren's syndrome, and systemic lupus erythematosus, the existence of autonomic dysfunction has been shown (30); our study and the study from Nussinovitch et al. (27) could not find autonomic dysfunction in FMF patients. Rheumatoid arthritis and systemic lupus are the diseases coursing with chronic inflammation. Furthermore, the mean age was higher from our study than in the aforementioned studies (30). Recent data showed a relationship between advanced age and inflammation with cardiac autonomic dysfunction (31). In the light of this knowledge, the possible causes of our different results may be as follows: FMF is a relapsing inflammatory disease that is different from chronic inflammatory disease, our patient group was in the inactive period of FMF, and the mean age of our patient group was lower.

There are some limitations of this study. The most important limitation of this study is the low patient number. Other limitations are that we used only one method (24-hour ambulatory ECG) for analyses and we did not use tilt table test or heart rate recovery index and genetic tests.

In conclusion, in this study, the HRV parameters gained from 24-hour ambulatory ECG analysis were similar between FMF patients and controls. We need large-scale studies containing more patients, genetic data, and different analyzing methods.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Sütçü İmam University Faculty of Medicine.

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

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