

Deteriorated Systolic Blood Pressure Recovery and Heart Rate Recovery After Graded Exercise in Children With Familial Mediterranean Fever

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ABSTRACT

Objectives: This study aims to investigate if cardiac involvement may occur in children with familial Mediterranean fever (FMF) without cardiovascular symptoms by using heart rate recovery (HRR) and systolic blood pressure recovery (SBPR) parameters.

Patients and methods: A total of 50 FMF patients (26 males, 24 females; mean age 151±33.4 month; range 60 to 216 month) and 30 healthy controls (18 males, 12 females; mean age 143±43.9 month; range 84 to 228 month) were included in the study. All patients were evaluated by echocardiography. All patients underwent a maximal graded exercise stress test. HRR and SBPR parameters were calculated.

Results: There was a significant decrease in HRR1 value in FMF group ($p=0.03$). SBPR1 and SBPR2 values were higher in FMF group compared to control group ($0.96±0.12$ vs $0.88±0.12$ and $0.95±0.09$ vs $0.91±0.11$, respectively); and the high SBPR1 value was statistically significant ($p=0.02$). FMF presence had a negative correlation with HRR1 ($r=-0.26$, $p=0.03$) and a positive correlation with SBPR1 ($r=0.29$, $p=0.02$). There was a negative correlation of M694V homozygous mutation with HRR1 and HRR2 values ($r=-0.43$, $p=0.004$, $r=-0.42$, $p=0.005$).

Conclusion: Cardiac involvement may occur in FMF patients without cardiovascular symptoms. Impaired SBPR and decreased HRR response may indicate increased cardiovascular risk in these patients despite normal exercise stress test results.

Keywords: Autonomic dysfunction; Familial Mediterranean fever; heart rate recovery; systolic blood pressure recovery.

Familial Mediterranean fever (FMF) is an autosomal recessive auto inflammatory disease characterized by recurrent fever attacks and inflammation of the serous membranes (peritonitis, pleuritis, pericarditis, arthritis, etc.).¹ Cardiovascular involvement is one of the major causes of mortality and morbidity in patients with FMF.²

The exercise stress test has been used to assess the cardiovascular performance of patients. Besides exercise capacity and chronotropic response, heart rate recovery (HRR) index and systolic blood pressure recovery (SBPR) rate can be calculated

by the exercise stress test.^{3,4} A normal HRR response occurs as a result of a balance between sympathetic and parasympathetic systems. The presence of abnormal HRR has been shown to be an independent marker of mortality. Increased sympathetic activity and delayed HRR response due to insufficient vagal reactivation have been shown as autonomic dysfunction findings in FMF patients.^{5,6} SBPR can be obtained by determining the ratio of the third-minute systolic blood pressure of the recovery period to peak exercise systolic blood pressure, or the first-minute systolic blood pressure. It represents the reduction in systolic blood pressure after exercise.^{7,8} A delay in the

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reduction of systolic blood pressure after exercise is an abnormal response and has been associated with increased cardiovascular risk.⁹ There have been studies in the literature demonstrating abnormal HRR findings in FMF patients. To the best of our knowledge, no study has been conducted on individuals with FMF using SBPR, which is known to be associated with increased cardiovascular risk. Therefore, in this study, we aimed to investigate if cardiac involvement may occur in children with FMF without cardiovascular symptoms by using HRR and SBPR parameters.

PATIENTS AND METHODS

This study was conducted by the Pamukkale University's Medical Faculty Pediatric Rheumatology Department and Cardiology Department between January 2015 and June 2015. A total of 50 patients (26 males, 24 females; mean age 151 ± 33.4 month; range 60 to 216 month) who were not in attack period and were being followed-up with a FMF diagnosis according to Tel Hashomer and a new set of criteria for children^{10,11} were included. In addition, 30 healthy controls (18 males, 12 females; mean age 143 ± 43.9 month; range 84 to 228 month) with no cardiologic or rheumatologic problems were included. Those with comorbid secondary chronic rheumatic problems to a FMF diagnosis were excluded. The onset age of disease, disease duration, clinical findings (fever, abdominal pain, chest pain, joint pain, and rash), dose and duration of medication, and Mediterranean fever mutation were recorded for each patient. All patients were evaluated by echocardiography before the study to eliminate congenital heart defects. The study protocol was approved by the Pamukkale University's Medical Faculty Ethics Committee. The study was conducted in accordance with the principles of the Declaration of Helsinki.

The patients and control group underwent a maximal graded exercise stress test using a Quinton treadmill system with the modified Bruce technique developed for children.¹² The 12-lead electrocardiographic monitorization was performed continuously during the test. Blood pressure and heart rate were measured automatically using a Tango exercise blood

pressure-monitoring device before every stage and at the second minute in every stage of the exercise stress test. Maximal target heart rate during the exercise stress test was calculated as subtraction of age (year) from 220. The exercise stress test was continued until reaching 95% of the maximal heart rate. The HRR differences within the first five minutes after exercise (HRR1, HRR2, HRR3, HRR4, and HRR5) were calculated by subtracting the heart rate at each minute from the maximal heart rate. The ratio of the third-minute systolic blood pressure (SBP) of recovery period to peak SBP was considered to be SBPR1. Additionally, the ratio of the third-minute SBP of recovery period to the first-minute SBP was considered to be SBPR2.⁸ When the exercise capacity reached peak exercise, it was calculated as the total metabolic equivalent units.

Statistical analysis

All data were evaluated using the SPSS version 16.0 software (SPSS Inc., Chicago, IL, USA). Continuous variables were expressed as mean \pm standard deviation and categorical variables were expressed as percentages. The Chi-square test and unpaired t test were used for evaluating comparisons of categorical and continuous variables between the two groups. Correlations between HRR and SBPR parameters were calculated by the Pearson's correlation analysis. A *p* value of ≤ 0.05 was considered statistically significant.

RESULTS

All of the children's growth-development and physical examinations were normal. The mean age, height, and weight of FMF and control groups were similar (151 ± 33.4 month, 143 ± 43.9 month $p=0.46$), (151 ± 15.9 cm, 148 ± 17.5 cm $p=0.46$), and (44.5 ± 14.6 kg, 42.6 ± 15.2 kg $p=0.5$), respectively). The most common clinical symptoms observed in the FMF group were abdominal pain (86%) and fever (62%). The clinical findings of FMF are presented in Table 1. All patients underwent genetic analysis for the Mediterranean fever mutation. The M694V mutation was the most commonly obtained mutation (32%). Comparison of the exercise stress test parameters of FMF and control groups is summarized in Table 2. Although all HRR parameters obtained were lower in the FMF group compared to the control group, there

Table 1. Demographic and clinical features of patients with familial Mediterranean fever

	n	%	Mean±SD
Age (month)			151±33.4
Height (centimeter)			151.4±15.9
Weight (kg)			44.5±14.6
Age at diagnosis (month)			100±39
Disease duration (month)			49.9±26.8
Dose of colchicine (mg/day)			1.1±0.21
Clinical manifestation			
Fever	31	62	
Abdominal pain	43	86	
Chest pain	1	2	
Rash	1	2	
Arthritis/arthralgia	16	32	
Mutation			
Homozygous	20	40	
Heterozygous	11	22	
Compound heterozygous	17	34	
No mutation	2	4	

SD: Standard deviation.

was a significant decrease in the HRR1 value ($p=0.03$). In addition, the SBPR1 and SPBR2 values obtained were higher in the FMF group compared to the control group (0.96 ± 0.12 vs. 0.88 ± 0.12 and 0.95 ± 0.09 vs. 0.91 ± 0.11 , respectively); and the high SBPR1 value was statistically significant ($p=0.02$). Other exercise stress test parameters were similar between both groups.

The FMF clinical findings and correlation analysis results among the exercise stress test parameters are summarized in Table 3. The FMF presence had a negative correlation with HRR1 ($r=-0.26$, $p=0.03$), but a positive correlation with

SBPR1 ($r=0.29$, $p=0.02$). Moreover, there was a negative correlation of the M694V homozygous mutation with the HRR1 and the HRR2 values ($r=-0.43$, $p=0.004$; and $r=-0.42$, $p=0.005$). There was no correlation of the HRR and the SBPR values with age and daily dose of colchicine.

DISCUSSION

In this study, we detected deteriorated exercise stress test parameters in children with FMF.

Table 2. Comparison of exercise stress test characteristics between patient and control groups

	FMF patients		p
	Mean±SD	Controls Mean±SD	
Exercise capacity (METs)	11±1.5	11.1±1.3	0.745
Preexercise SBP (mmHg)	118±14.6	117±18	0.813
Preexercise DBP (mmHg)	75±13	73±13	0.711
Peak exercise HR, beats/min	172±17	173±17	0.804
Peak SBP (mmHg)	132±21	137±18	0.330
Peak DBP (mmHg)	74±14	68±16	0.213
Recovery SBP 1 st min (mmHg)	133±21	132±19	0.893
Recovery SBP 3 rd min (mmHg)	125±15	119±15	0.148
SBPR1	0.96±0.12	0.88±0.12	0.020
SBPR2	0.95±0.09	0.91±0.11	0.17
HRR 1 st min, beats/min	48±14	57±20	0.035
HRR 2 nd min, beats/min	63±13	71±20	0.077
HRR 3 rd min, beats/min	65±13	71±17	0.110
HRR 4 th min, beats/min	67±11	72±17	0.203
HRR 5 th min, beats/min	69±12	71±13	0.531

FMF: Familial Mediterranean fever; SD: Standard deviation; METs: Metabolic equivalent units; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; HR: Heart rate; SBPR: Systolic blood pressure recovery; HRR: Heart rate recovery.

Table 3. Correlation analysis between clinical characteristics of familial Mediterranean fever patients and exercise stress test characteristics

	Existence FMF		Age		Daily dose of colchicine		M694V homozygous	
	r	p	r	p	r	p	r	p
SBPR1	0.294	0.020	0.047	0.715	-0.144	0.416	0.248	0.090
SBPR2	0.176	0.172	0.105	0.417	0.147	0.405	0.116	0.428
HRR 1 st min, beats/min	-0.269	0.035	0.080	0.537	-0.074	0.677	-0.430	0.004
HRR 2 nd min, beats/min	-0.227	0.077	0.098	0.447	0.058	0.744	-0.421	0.005
HRR 3 rd min, beats/min	-0.205	0.110	0.163	0.206	0.101	0.572	-0.068	0.645
HRR 4 th min, beats/min	-0.164	0.203	0.145	0.262	0.064	0.720	-0.158	0.285
HRR 5 th min, beats/min	-0.081	0.531	0.134	0.299	0.131	0.462	-0.014	0.927

FMF: Familial Mediterranean fever; SBPR: Systolic blood pressure recovery; HRR: Heart rate recovery; Correlation coefficients: r value.

Firstly, the HRR1 value was decreased in children with FMF compared to the control group. Secondly, the SBPR1 value was significantly increased in children with FMF. Thirdly, a negative correlation was found between FMF presence and HRR1, but a positive correlation was found between SBPR1 and FMF presence. Lastly, the presence of an M694V homozygous mutation was negatively correlated between HRR1 and HRR2 values.

The autonomic nervous system plays a major role in the regulation of cardiovascular functions. Studies in the literature have investigated the relationship between autoinflammatory diseases and cardiac autonomic dysfunction.^{13,14} HRR is a frequently used technique for assessing cardiac autonomic dysfunction.¹⁵ Deterioration was found in the HRR indexes of adult patients with FMF compared to healthy individuals in recent studies that Ardic⁵ and Canpolat et al.⁶ conducted. Contrary to these studies, Sahin et al.¹⁶ found no difference between groups in terms of HRR parameters in their study conducted on children patients. In our study, deterioration was found in the HRR1 value for children with FMF compared to the healthy control group. These controversial results between Sahin et al.¹⁶ and our study may arise from the different clinical and genotypical characteristics of the patient populations. While M694V mutation prevalence was 17% in their study, it was 32% in our study group. Also, the mean age of our patients was higher than in Sahin's study group.

Cardiovascular complications contribute to the morbidity and mortality rates in rheumatologic and autoinflammatory diseases. An insufficient reduction in heart rate after exercise has been

shown to be a marker of autonomic dysfunction.¹⁷ In addition, it has been documented as an independent indicator of all mortalities caused by cardiovascular and other diseases.^{18,19} This autonomic dysfunction, characterized by insufficient vagal reactivation besides excessive sympathetic activation, has been associated with FMF.^{20,21} Moreover, deteriorated HRR at the first minute after exercise is a powerful marker of mortality, independent from the increased workload of the heart during exercise, and myocardial perfusion defects.²²

Changes in SBPR have been proposed to be associated with sympathetic and parasympathetic activity, systemic vascular resistance, and baroreflex sensitivity. A decreased SBP ratio after exercise has been considered to be a reflection of the physical activity and general health of an individual. A greater decrease in SBP in the recovery period after peak exercise reflects that the individual's physical activity and aerobic capacity are good. This response occurs as a result of a reduction in systemic vascular resistance because exercise improves vascular endothelial function and vasodilator capability.²³⁻²⁷

In several recent studies, markers indicating endothelial damage, such as thrombomodulin, adrenomedullin, and nitrite, have been found to be high in FMF patients in the non-attack period as well.^{28,29} This finding proposes that ongoing subclinical inflammation and endothelial dysfunction are present also in the non-attack period in patients, and this is associated with increased cardiovascular problems.³⁰ We think that endothelial and autonomic dysfunction, together with subclinical inflammation, are responsible

for a significantly higher SBPR1 value in FMF patients compared to the control group.

Although insufficient HRR and autonomic dysfunction are well known, there has been limited information demonstrating the relationship between SBPR and the autonomic nervous system.³¹ Therefore, the demonstration of an insufficient SBPR1 response for the first time in FMF patients might be significant for indicating autonomic and endothelial dysfunction, which has been shown to be associated with FMF pathophysiology.

Considering the correlation analysis of clinical findings and the exercise stress test parameters of FMF patients, the presence of disease had a negative correlation with HRR1, and a positive correlation with SBPR1 also supported this finding. In addition, the negative correlation between HRR1 and HRR2 values in M694V mutation-positive patients was considered to be responsible for disease coursing with severe clinical symptoms.^{32,33} This suggests that M694V homozygote patients have an increased cardiovascular risk.

The exercise capacities of the patient and control groups were good. No significant difference was found in terms of exercise capacity, initial heart rate, and peak heart rate. Therefore, we suggest that insufficiency in HRR and SBPR developed due to autonomic and endothelial dysfunction.

One of the limitations of this study was the limited number of patients. In addition, we do not know the exact effect of FMF SBPR. Therefore, further studies are necessary to identify SBPR correctly after exercise stress tests in patients with FMF.

In conclusion, to our knowledge, this is the first study indicating SBPR impairment and its relationship to the HRR of patients with FMF. Cardiac involvement may occur in FMF patients without cardiovascular symptoms. FMF is associated with insufficient SBPR and delayed HRR after exercise. In our opinion, insufficient SBPR and decreased HRR response may indicate increased cardiovascular risk in these patients despite normal exercise stress tests. Further studies are necessary to demonstrate the clinical findings of deteriorated autonomic and endothelial

dysfunction in FMF patients, and to explain the exact underlying pathophysiological mechanisms in autoinflammatory diseases.

Declaration of conflicting interests

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