

# Normal Heart Rate Variability in Colchicine-Resistant Familial Mediterranean Fever Patients

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**ABSTRACT:** **Background:** The relationship between autonomic nervous system (ANS) dysfunction and familial Mediterranean fever (FMF) is controversial. We recently reported normal heart rate variability (HRV), suggestive of normal ANS, in patients with uncomplicated FMF.

**Objectives:** To evaluate ANS function in colchicine non-responders by using the HRV tool.

**Methods:** The study group comprised 24 FMF patients suffering from recurrent FMF attacks despite treatment with a maximal colchicine dose. Electrocardiogram was measured under strict conditions and HRV parameters were calculated. Results were compared with age- and gender-matched unaffected controls.

**Results:** No statistically significant difference was found between the groups in any of the HRV parameters: maximal RR, minimal RR and average RR intervals, standard deviation of RR interval, square root of the mean squared differences of successive RR intervals, HRV triangular index, NN50, pNN50, and power spectral analysis parameters.

**Conclusions:** Although a small difference in HRV parameters in the current study cannot be entirely excluded, FMF patients in whom colchicine did not provide adequate symptomatic relief and who did not develop amyloidosis appear to have normal HRV parameters suggestive of normal ANS function, compared with healthy adults.

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**KEY WORDS:** familial Mediterranean fever (FMF), heart rate variability (HRV), autonomic nervous system (ANS), inflammation

Familial Mediterranean fever (FMF) is a hereditary disease appearing predominantly in North African and Iraqi Jews, Turks, Arabs, and Armenians. FMF attacks are characterized by spontaneously terminated bouts of fever, serositis and occasionally erysipelas-like erythema. The clinical spectrum is wide: some patients experience mild symptoms while others may develop debilitating frequent attacks and major complications, the most ominous of which is systemic deposition of AA amyloid. Renal amyloidosis may lead to end-stage renal failure

requiring renal replacement therapies. Colchicine treatment has dramatically changed the natural history of most FMF patients by decreasing the frequency and length of the attacks and preventing amyloidosis [1,2].

Evaluation of cardiac involvement in FMF patients has generated conflicting results with regard to increased atherosclerosis [3,4] and ventricular and supra-ventricular arrhythmia markers [5-8]. Similarly, there is contrasting evidence regarding the function of the autonomic nervous system (ANS) in FMF. While some researchers [9,10] reported that occult dysautonomia is common in FMF, we found normal heart rate variability (HRV) parameters in uncomplicated FMF [2]. HRV is a simple and reliable tool commonly used for ANS evaluation.

It was reported that sympathovagal imbalance is correlated with systemic inflammation (manifested as increased pro-inflammatory markers) in relatives of diabetic patients [11] and in hypertensive patients [12]. Therefore, one may speculate that the discrepancy between different studies aiming to evaluate ANS function in FMF originates from cohorts differing in patient characteristics, particularly the degree of inflammation – a well-established risk factor of cardiovascular disease. In the context of FMF, the most appropriate patient population to validate this hypothesis is one that responds inadequately to colchicine therapy, manifesting as recurring attacks and chronic elevation of inflammatory markers. In the present study, we used various HRV parameters to evaluate ANS in a subset of FMF patients unresponsive to colchicine.

## PATIENTS AND METHODS

A comparative case-series design was used. The study was approved by the institutional review board and fulfilled the ethical guidelines of the most recent Helsinki Declaration (Edinburgh, 2000). All participants gave written informed consent.

The study cohort consisted of 24 patients with FMF recruited from the outpatient clinic of the National Center for FMF, Sheba Medical Center, Tel Hashomer, Israel. Diagnosis of FMF was based on our published criteria [1]. Colchicine non-

responsiveness was defined as experiencing an attack from any typical site (abdomen, chest, joint) once a month or more, despite colchicine treatment of at least 2 mg/day. In addition, we included patients unable to tolerate such a high dose which is required to control their repeated attacks. Urine analysis showing no proteinuria, excluding amyloidosis, was required for inclusion. During recruitment, seven FMF patients were excluded due to acute or chronic conditions (acute anemia, hyperparathyroidism, polycystic kidney disease, nephrotic syndrome) or use of chronotropic drugs. All FMF patients were attack-free for at least one week prior to the study. The controls comprised 24 age- and gender-matched healthy individuals. Mild dyslipidemia for which lifestyle modifications or low dose statin treatments were recommended was not considered an excluding criterion in either group.

All participants were asked not to smoke, drink caffeinated beverages or take other stimulants 3 hours before the HRV test, and to avoid strenuous exercise for 24 hours prior to the test. Medications other than colchicine were discontinued for at least 12 hours prior to the test. The test was conducted between 9:00 am and 14:00 pm to avoid the circadian influence on heart rate and ANS function. Body mass index (BMI) was calculated by dividing weight (kg) by height squared (m). Obesity was defined as a BMI higher than 30 kg/m<sup>2</sup>. Both electrocardiographic (ECG) measurement for 5 minutes in a supine position, and data interpretation were conducted according to accepted standards for HRV evaluation using a commercial computer software (Norav Medical Inc., Israel).

To quantify the HRV time domain, the following variables were automatically calculated in patients lying in a supine position: standard deviation of RR intervals (SDNN) representing the cyclic variability of the heart rate during the recording period; RMSSD, the root mean square of successive differences of RR intervals; NN50, the number of intervals differing by more than 50 ms from the preceding interval; pNN50, calculated by dividing NN50 by the total number of RR intervals; and HRV triangular index measurement, the integral of the density distribution divided by the maximum of the density distribution. Power spectral analysis was conducted using the non-parametric fast Fourier transform. Integral calculations of the area beneath the power spectral density curve for frequency range were made in absolute values of power (ms<sup>2</sup>). The spectral components were divided into low and high frequency components (LF 0.04–0.15 Hz and HF 0.15–0.4 Hz, respectively).

RMSSD, NN50 and pNN50 are primarily affected by vagal influence during respiration; an increase in SDNN, NN50 and pNN50 reflects active ANS and good compliance of the heart to autonomic innervation. HF is also highly dependent on vagal activity, reflecting respiratory influence on sinus arrhythmia. LF is a more controversial parameter as it may reflect both sympathetic and parasympathetic balance and is believed to be influenced by the baroreceptors [2].

**STATISTICAL ANALYSIS**

Data were analyzed by Microsoft Excel version 2003 (Microsoft Corp., Seattle, WA, USA) and JMP version 7.0 (SAS Institute, Cary, NC). Results are presented as mean and standard deviations. Two or more standard deviations from the normal range were considered abnormal. Findings were compared between the groups by the Kruskal-Wallis one-way analysis test and Fisher’s exact test. A P value of less than 0.05 was considered statistically significant.

**RESULTS**

The clinical characteristics of the patient groups are outlined in Table 1. There was no statistically significant difference in age, sex ratio, BMI, obesity rate, habitual smoking rate, dyslipidemia treatment with statins, or presence of treated hypertension. None of the patients had diabetes mellitus or history of cardiac disease. Mean age of FMF onset was 4.7 ± 4.7 years. Mean colchicine dosage was 2.3 ± 0.5 mg/day. With regard to the genotype, 8 patients (33.3%) were homozygous to the M694V mutation, 4 (16.7%) were heterozygous to the V726A mutation, and the genetic background in 50% of the patients was unknown. The patients had on average 24.8 ± 44.4 attacks in the year prior to inclusion despite maximally tolerated colchicine therapy. Fourteen patients (58.3%) had chest attacks. C-reactive protein levels between attacks were available in 6 patients (19.4 ± 11.4 mg/L) and erythrocyte sedimentation rate was available in an additional 5 patients (36.6 ± 20.4 mm/h). The mean hemoglobin level was 11.51 ± 0.96 mg/dl (data available for 18/24 patients).

The HRV results are shown in Table 2. There were no statistically significant differences in the maximal RR, minimal RR and average RR intervals. Although the mean results of SDNN, RMSSD, HRV triangular index, NN50 and pNN50 appear somewhat lower in FMF patients compared with the

**Table 1.** Clinical characteristics of colchicine non-responding FMF patients compared to unaffected control subjects

	Colchicine non-responding FMF patients (N=24)	Control (N=24)	P value
Age (years)	36.4 ± 10.1	36.3 ± 11.8	NS
BMI (kg/m <sup>2</sup> )	23.0 ± 5.1	22.9 ± 2.7	NS
Gender: F/M	16/8	16/8	NS
Obesity (%)	8.3%	0%	NS
Smoking (%)	29.1%	37.5%	NS
Diabetes (%)	0%	0%	NS
Treated hypertension (%)	4.2%	0%	NS
Treated dyslipidemia (%)	4.2%	4.2%	NS
s/p myocardial infarction (%)	0%	0%	NS

NS = non-significant

**Table 2.** HRV parameters in colchicine non-responding FMF patients compared to unaffected control subjects

	Colchicine non-responding FMF patients (N=24)	Control (N=24)	P value
Maximal RR (ms)	996.3 ± 134.1	1038.6 ± 164.8	NS
Minimal RR (ms)	707.0 ± 69.2	705.2 ± 105.5	NS
Average RR (ms)	857.1 ± 86.7	877.3 ± 119.6	NS
SDNN (ms)	45.9 ± 20.1	48.4 ± 17.1	NS
RMSSD (ms)	35.1 ± 21.9	42.6 ± 23.6	NS
HRV triangular index	14.2 ± 5.5	14.5 ± 4.0	NS
NN50	19.8 ± 22.2	32.8 ± 31.3	NS
pNN50	6.1 ± 7.5	10.0 ± 10.2	NS
LF (ms <sup>2</sup> )	177.1 ± 64.0	159.3 ± 49.3	NS
HF (ms <sup>2</sup> )	128.8 ± 62.1	155.4 ± 89.4	NS

SDNN = standard deviation of RR intervals, RMSSD = the root mean square of successive differences of RR intervals, HRV = heart rate variability, NN50 = the number of intervals differing by more than 50 ms from the preceding interval, pNN50 = NN50 divided by the total number of RR intervals, LF = low frequency, HF = high frequency, NS = non-significant

controls, no statistically significant difference was noted. Power spectral analysis parameters were also similar in both groups. In addition, the HRV results in both groups were similar to those previously reported for healthy individuals of the same age [13-17]. Given these results, this study has a power of 77.9% at a significance level of 0.05 to detect a difference of at least 15 ms between the study groups (calculated for SDNN).

## DISCUSSION

In the present study we found statistically similar HRV parameters in 24 FMF patients resistant to colchicine prophylaxis (defined by one or more FMF attacks per month) compared with controls. These findings suggest normal ANS function in this FMF phenotype.

Clinically evident dysautonomia is extremely rare in patients with FMF, even in the presence of amyloidosis [18]. Nevertheless, FMF patients were reported to display an abnormal cardiovascular response to the heads-up tilt test, manifesting as postural tachycardia and orthostatic hypotension [9,10], and mild occult dysautonomia, manifesting as a high cardiovascular reactivity score [10]. Cardiovascular reactivity score is a mathematical index whose computation is based on blood pressure and heart rate changes during the head-up tilt test. Naschitz et al. [19] reported that none of 50 FMF patients in their study developed orthostatic symptoms following the head-up tilt test. Moreover, in our previous publication [2], consistent with clinically overt normal ANS function, normal HRV was found in uncomplicated FMF compared with healthy individuals. The present HRV results in normal individuals and in colchicine non-responding FMF patients are similar to the values found

in uncomplicated FMF patients [2,20]. The negative results in the current study are also supported by the results of Şahin and co-authors [21] showing that SDNN, SDNNi, RMSSD and HRV triangular index values in children and adolescents with FMF were similar to those of healthy controls, in 24 hour recordings.

The present study expands on our earlier findings of normal HRV parameters in uncomplicated FMF patients and thus includes a subgroup of FMF patients resistant to colchicine treatment. These patients are characterized as being subjected to a highly increased inflammatory burden. It should be noted that the different techniques for evaluating ANS are considered complementary and, therefore, further study of the ANS function in FMF is required. Besides HRV and physiological responses to the tilt-test, the ANS study in FMF might include evaluation of heart rate response to deep breathing, calculation of the Valsalva ratio, heart rate response to standing and squatting, quantitative sudomotor axon reflex test, thermoregulatory sweat test, evaluation of pupillometry, gastric scintigraphy, evaluation of colonic transit with radiopaque markers, and other tests [22]. Interestingly, a statistically non-significant trend towards lower HRV parameters was observed in the colchicine non-responders group in the current study. This finding, although lacking statistical significance, may suggest that dysautonomia in colchicine-resistant FMF patients is extremely subtle (and clinically insignificant). Therefore, any further autonomic investigation of FMF patients will require a battery of autonomic tests (thereby increasing the overall sensitivity) and inclusion of very large study groups before significance can be reached at all.

Inflammation is an established risk factor for ischemic cardiovascular disease [23] which, together with other risk factors for ischemic heart disease, has been associated with HRV parameters characterizing ANS dysfunction [24]. Moreover, it was reported that systemic autoimmune and inflammatory diseases such as systemic lupus erythematosus and rheumatoid arthritis have abnormal autonomic function, manifest as abnormal HRV parameters [25]. It remains unknown why the ANS seems to be spared (or affected in a non-significant manner) in active FMF. We speculate that colchicine may have a direct ANS protective effect beyond the effect mediated through suppression of inflammation.

## STUDY LIMITATIONS

Short-term HRV measurements are limited by the lack of normal reference values and a strict definition of abnormality. Interpretation of the current results is limited by the study's relatively small size (48 patients) which cannot entirely exclude small differences in ANS function. Also, we evaluated only HRV in the study group. While HRV is considered clinically useful and closely associated with other ANS dysfunction markers, as noted above, a full evaluation of ANS function requires a battery of tests. Therefore, other tools in addition

to cardiovascular reactivity score and HRV should be further evaluated in different subgroups of FMF patients.

## CONCLUSIONS

Some FMF patients do not respond well to colchicine and continue to experience FMF attacks. Nevertheless, even under such circumstances where inflammation is not suppressed, these patients have statistically similar HRV parameters compared with healthy individuals, suggestive of ANS function that is comparable to that in healthy adults. Further research is required to examine the association between this FMF phenotype and protective factors such as patient's genotype and colchicine use. Also needed are large cohorts and additional parameters for ANS evaluation in order to exclude any small differences between colchicine-resistant FMF patients and healthy individuals.

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