Normal P Wave Dispersion in Colchicine-Resistant FMF Patients

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Abstract: *Background*: Cardiac involvement in familial Mediterranean fever (FMF) has been receiving increasing attention. P wave dispersion (Pd) is an electrocardiographic marker for supraventricular arrhythmias. It was recently reported that uncomplicated FMF is associated with normal Pd.

Aims: Our aim was to evaluate Pd and P wave duration in colchicine-resistant FMF patients, thus testing the effect of the continuously increased inflammatory burden on cardiac electrical stability of FMF patients.

Methods: Twenty two patients with colchicine-resistant FMF, and 22 age- and sex-matched control subjects were investigated. All participants underwent a 12-lead electrocardiography under strict standards. P wave length and P wave dispersion were computed from a randomly selected beat and an averaged beat constructed from 7-12 beats in a 10 second ECG.

Results: Minimal, maximal, and average P wave duration and P wave dispersion calculated from either a random beat or averaged beats, were similar in colchicine-resistant FMF patients and healthy individuals.

Conclusions: FMF patients, nonresponsive to colchicine treatment, but without amyloidosis, have normal atrial conduction parameters. Therefore, FMF, even in colchicine nonresponsive patients, does not seem to be associated with an increased risk for supraventricular arrhythmias.

Keywords: Familial Mediterranean fever (FMF), P wave dispersion, supraventricular arrhythmia, colchicine resistant FMF, chronic inflammation.

INTRODUCTION

Familial Mediterranean fever (FMF) is a recessive inherited disease. As its name implies, it prevails in the Mediterranean region and among families living elsewhere, but originating from this area. Clinical manifestations may range from mild disease to repeated debilitating attacks of fever and sterile serositis [1, 2]. The FMF associated MEditerranean FeVer (MEFV) gene, is located on the short arm of chromosome 16, and encodes for an anti-inflammatory protein known as pyrin [1].

Mutations in MEFV underlie FMF attacks and systemic inflammation, reflected by an overwhelming rise in acute phase proteins, thus leading to a deposition of AA amyloid on various organs in many untreated patients. Renal deposits of AA amyloid may lead to renal failure and end-stage renal disease. Following the introduction of colchicine as the basis of care for FMF patients [3], most patients enjoy a remission from attacks. A sizeable percentage of the FMF patient population, however, fails to respond to cholchicine and continue to experience attacks, thereby exposed to constant elevated inflammatory markers [4].

Clinically overt cardiac disease is less common in FMF than in the general population [5]. Cardiac disease due to AA amyloidosis is unusual even in the presence of full blown systemic amyloidosis [6]. However, there are currently unresolved controversies as to subclinical atherosclerotic cardiac involvement in FMF. Evaluation of the flow-mediated dilatation of the brachial artery and intima-media thickness of the carotid artery has yielded conflicting results [7, 8]. Similarly, QT dispersion, an electrocardiographic marker for ventricular arrhythmias was reported as increased [9] or normal [10].

Abnormally elevated P wave dispersion (Pd) is an electrocardiographic marker indicating an increased risk in developing supraventricular arrhythmias. Pd is calculated by subtracting the shortest from the longest P-wave durations, as recorded from multiple different surface ECG leads [11]. Recently, Acar *et al.* [12]

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reported high Pd in FMF patients. We, however, found normal Pd parameters in FMF patients who responded well to colchicine and had not developed amyloidosis [10]. These conflicting findings could have resulted from different degrees of inflammation. In light of these controversial studies, we chose to evaluate FMF patients who did not respond well to colchicine therapy and were affected by ongoing inflammation, and determine whether this population has an increased risk for supraventricular arrhythmias.

METHODS

Study Design and Patient Population

A comparative case-control design was used. The study received approval by the local ethics committee. All participants gave written informed consent. The study group consisted of 22 patients (13 females) diagnosed with FMF according to the Tel-Hashomer criteria [13]. Colchicine non-responsiveness was defined as attacks involving any typical site, >1 per month, despite colchicine treatment of 2mg/d [14]. Repeated urine analyses were normal, thus excluding overt amyloidosis. Five other screened FMF patients were excluded from the study due to chronic medical conditions or intake of drugs that might affect the ECG. Dyslipidemia was treated with Low dose statins in the two patients who had increased LDL. Hypertension in the FMF group (3/22 patients) was treated with low dose angiotensin-converting enzyme inhibitors or low dose calcium channel blockers.

Twenty-two volunteers, matched for sex and age served as controls. The control subjects had no chronic illnesses other than mild dyslipidemia in one patient treated with diet alone. None of the control subjects were taking medications or had been previously hospitalized. Those with asthma were included in the study if there was no need for preventive treatment or no asthma attacks for at least one week prior to the study.

The study was conducted during the spring and summer. Participants were asked to avoid smoking and caffeinated or alcoholic beverages 3 hours prior to the procedure and strenuous exercise 24 hours prior to the procedure. Body mass index (BMI) was calculated by dividing weight (kg) by squared height (meters). Obesity was defined as a BMI >30 kg/m^2 [15]. The test was conducted between 9:00 am and 2:00 pm to avoid circadian influences on the electrocardiographic parameters. Room temperature was maintained at 20-23ºC.

Participants were instructed to lie motionless in a supine position for 10 minutes. Electrodes were placed in anatomical positions according to routine procedure. ECG strips were recorded with a standard device for 10 seconds. ECGs of inadequate quality were repeated. Onset of the P wave was defined as the point of first visible upward departure from baseline for positive waveforms or as the point of first downward departure from baseline for negative waveforms. Return to the baseline was considered the end of the P wave. P wave length was measured from all leads with computer software validated for accuracy and consistency. Maximal and minimal P wave lengths were identified. Pd was computed from one randomly selected beat in a steady state by subtracting the minimal from the maximal P wave length in 12 leads. In addition, 7-12 beats were averaged during 10 seconds of ECG measurements. Averaged P wave parameters were computed. Similar measurements were performed on each study patient and on each of the control subjects. The normal range of various P wave values were obtained from published studies [10, 16].

Data Analysis

Data were analyzed with Microsoft Excel version 2003 (Microsoft Corp., Seattle, WA) and JMP version 7.0 (SAS Institute, Cary, NC, USA). The results are presented as mean and standard deviations (age, BMI and P wave parameters) or as proportions (clinical characteristics). Abnormal results were defined as more than 2 standard deviations from the normal range. Findings were compared between the groups by the Mann-Whitney-Wilcoxon test (normal approximation for numerical data) and the Fisher's exact test (for categorical data). A p value < 0.05 was considered statistically significant.

RESULTS

Patient Demographics

Clinical and demographic characteristics of the study and control groups and P wave parameters are presented in Table **1**.

No significant differences in age, male to female ratio, BMI, smoking rate and obesity rate, were observed. None of the patients had a history of myocardial infarction or diabetes. In addition, there was no statistically significant difference in the rate of hypertension, dyslipidemia and asthma among the two groups.

Table 1: P Wave Length and P Wave Dispersion in Colchicine-Resistant FMF Patients Compared to Control Subjects[a]

Parameter		Colchicine-Resistant FMF Patients (N=22)	Controls (N=22)	P Value
Age (years)		38.0±11.1	32.2±13.3	NS
M / F		9 /13	9 /13	NS
BMI (kg/m^2)		24.0±5.6	22.0±2.2	NS
Obesity (%)		13.64%	0%	NS
Smokers (%)		13.64%	36.36%	NS
s/p myocardial infarction (%)		0%	0%	NS
Diabetes (%)		0%	0%	NS
Hypertension (%)		13.64%	0%	NS
Dyslipidemia (%)		9.09%	4.55%	NS
Asthma (%)		9.09%	0%	NS
Random beat	Maximal P (ms)	108.5±7.8	107.9±9.4	NS
	Minimal P (ms)	83.7±6.8	82.0±11.3	NS
	Average P (ms)	97.9±7.1	97.0±9.1	NS
	P dispersion (ms)	24.8±6.3	25.9±5.9	NS
Averaged beat	Maximal P (ms)	109.9±9.4	110.9±9.8	NS
	Minimal P (ms)	84.2±8.6	83.5±11.3	NS
	Average P (ms)	97.7±7.8	99.6±8.7	NS
	P dispersion (ms)	25.7±6.6	27.4±10.6	NS

[a]NS - nonsignificant (p>0.05).

Maximal P wave duration, minimal P wave duration, average P wave duration and Pd were similar in FMF patients and healthy individuals both for a randomly selected beat and for an averaged beat. P wave parameters of both groups were also within the reported normal range of P waves in healthy individuals.

DISCUSSION

Measurement of Pd is based on the assumption that surface ECG reflects regional changes in atrial activation time. Pd was used for assessing the risk of developing supraventricular arrhythmias such as atrial fibrillation, an association which was found to be highly specific and sensitive in previous trials [17-19]. In the current study, normal P wave parameters and Pd were determined in FMF patients despite resistance to colchicine, suggesting not increased susceptibility to supraventricular arrhythmias in this unique population.

Acar *et al*. [12] evaluated Pd and maximal P wave duration manually in 33 FMF patients and 33 controls and reported that FMF patients displayed significantly higher values of Pd. They suggested that structural and electrophysiological changes in the atrial myocardium and a state of chronic inflammation might be involved in the electrocardiographic abnormalities, and that FMF might contribute to the development or recurrence of atrial fibrillation [12].

Recently, we conducted a similar study using automated software in uncomplicated FMF patients, who responded to colchicine and did not develop amyloidosis. We reported that neither maximal, minimal nor average P wave durations were prolonged in FMF compared with healthy individuals. Moreover, Pd was similar in both groups [10].

The difference in study results might be attributed to variance in genetic backgrounds, methodological approaches and differences in disease activity, thus leading to a higher exposure to inflammatory mediators in the published Turkish FMF population.

In the current study, we aimed to test this assumption by further exploring Pd in colchicine nonresponsive FMF patients. This subgroup of FMF patients experienced recurrent attacks and were exposed to a chronic inflammatory state that might lead to accelerated atherosclerosis [4]. As indicated above,

no differences were found in Pd compared to healthy individuals. Our results are supported by the lack of a higher reported rate of supraventricular arrhythmias in FMF patients in the medical literature.

It is important to emphasis that Pd lacks standards of measurements and accepted normal reference values. Moreover, various methodologies limit the comparison of different studies.

FMF patients who do not respond well to colchicine and are therefore at increased exposure to inflammatory mediators, have normal Pd and normal P wave durations. Consequently, colchicine-resistant FMF patients do not seem to have an increased risk for developing supraventricular arrhythmias. Future studies should focus on evaluating P waves by using signal averaging ECG and longer follow-up to evaluate whether specific FMF patients have an increased risk for atrial fibrillation.

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