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P wave and QT dispersion in familial mediterranean fever

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Abstract. – OBJECTIVE: Familial mediterranean fever (FMF) is the most common auto-inflammatory disease that is characterized by recurrent, self-limited attacks of fever and serous membrane inflammation. Patients with inflammatory rheumatic diseases are considered to have a raised cardiovascular diseases risk. The aim of this study was to investigate; by means of P wave dispersion (Pd) and QT dispersion (QTd) parameters detected by simple standard electrocardiogram (ECG), atrial and ventricular repolarization changes in pregnant women with and without FMF.

PATIENTS AND METHODS: In this case-control study including 37 pregnant women with FMF who already put on colchicine treatment and 40 healthy, uncomplicated pregnancy cases, were prospectively assessed using 12-lead ECG and echocardiography.

RESULTS: No differences in Pd and corrected QT values were found between the groups. Epicardial fat thickness values were significantly higher in the FMF group compared with the control group (p = 0.015). A positive correlation was found between FMF duration and epicardial fat thickness (r = 0.350, p = 0.042).

CONCLUSIONS: Pd, a non-invasive marker of potential atrial arrhythmia and QT-d, a non-invasive marker of potentially lethal ventricular tachyarrhythmia, constitute a recent contribution to the field of noninvasive electrocardiology. Pd and QT-d values were not altered in pregnant women with FMF who already put on colchicine treatment, with no increased risk of atrial or ventricular arrhythmias indicated. Colchicine may have a cardio-protective effect beyond the effect mediated through suppression of inflammation.

Key Words:
Arrhythmia, Heart, Inflammation, Pregnancy.

Introduction

Familial Mediterranean Fever (FMF) is the most common hereditary monogenic auto-inflammatory disease that is characterized by recurrent, self-limited episodes of fever and sterile inflammation of serous membranes. FMF is caused by mutations in Mediterranean fever gene that encodes pyrin, which is essentially responsible for the regulation of apoptosis, cytokines and inflammation[1]. The diagnosis, is still based on clinical criteria since there is no specific diagnostic test. Tel Hashomer criteria are widely used for diagnosis of FMF[2]. The treatment of patients with FMF is aimed at suppressing the inflammation. Colchicine, an anti-inflammatory drug that can be used safely in pregnancy is the standard treatment of choice to prevent both FMF attacks and its long-term complications such as amyloidosis[1,3,4].

One of the most important factors, which contribute to increased cardiovascular risk, appears to be systemic inflammation. Patients with inflammatory rheumatic diseases are considered to have an increased risk of cardiovascular diseases[5]. However, the exact nature of etiological association between FMF and cardiovascular risk is rather controversial[6].

Pregnancy itself bears metabolic and homeostatic risk factors along with high cardiac output, hypercoagulability, insulin resistance with dyslipidemia and increased inflammatory activity[7]. Pregnancy, therefore, acts as a challenge, even a medical stress test for the mother, particularly in women who conceive with one of the chronic medical disorders. The limited reserves of an impaired organ will be unmasked and the organ

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would fail to show the adaptation to the physiological changes of pregnancy[8,9].

Previous population-based[10-14] studies have shown that non-specific electrocardiographic (ECG) changes are important in evaluating cardiovascular disease morbidity and mortality. While P-wave dispersion (Pd), a simple ECG parameter reflects homogeneity of atrial conduction, QT interval dispersion (QTd), on the other hand, demonstrates ventricular electrical instability that can be used in predicting atrial and ventricular arrhythmias. However, the association between FMF and increased Pd and QTd is controversial[15,16].

Pd and QTd changes have never been investigated in pregnant women with FMF. In this study, for the first time to our knowledge, we aimed to evaluate whether any electrical conduction problem exists and, therefore, could be used as a cardiovascular marker in pregnant women with FMF.

Patients and Methods

This case-control study was conducted at Zekai Tahir Burak Women's Health Education and Research Hospital and Yuksek ihtisas Education and Research Hospital and Ankara, Turkey. Local Institutional Review Board approved the study and the universal principles of the Helsinki Declaration were applied. Informed consent was obtained from each participant.

Forty-five consecutive pregnant women with FMF and 50 healthy women with uncomplicated pregnancy (as the control group), all in the third trimester and matched for maternal and gestational ages, were recruited between January 2014 and July 2015. All of pregnant had Turkish ethnicity determined by country of origin. The diagnosis of FMF was made according to the Tel Hashomer criteria[1].

Of the women with FMF, regardless whether she is pregnant or not, were already on colchicine or if not, have started taking colchicine in appropriate doses to prevent attacks (1-2 mg/day), once the disease was first diagnosed. All patients were attack free at least for 2 weeks prior to the recruitment. Proteinuria, suggestive of renal amyloidosis, was excluded on the basis of repetitive urine testing.

The presence of any known pre-gestational liver or heart disease; multiple gestation or trophoblastic disease; history of systemic, inflammatory, endocrine, gastrointestinal, psychiatric, immunologic, or oncologic disease; smoking; alcohol consumption; or active labor were among the exclusion criteria. Patients with pain, fever, and vaginal discharge, suggestive of infection or of acute attack and patient with signs and symptoms of acute pericarditis, were also excluded from the study.

All cases and controls underwent standard ECG and transthoracic echocardiography. Blood samples were also drawn on the same echocardiographic evaluations were performed by the same investigator. Epicardial fat thickness was measured on the right ventricular free wall in at least two locations, from both parasternal longitudinal and transverse parasternal views in systole[17]. Left atrial diameter was measured at the end systole in the parasternal long-axis view. None of the pregnant women had any symptom of arrhythmia including palpitation, chest pain, dizziness, or fainting and all were in sinus rhythm. Maternal serum electrolytes were checked to rule out any electrolyte imbalance. None of the patients were on medications such as anti-arrhythmic and antihypertensive drugs, which are known to affect the cardiovascular system. The patients in both groups were asked not to consume caffeinated beverages within three hours prior to the procedure.

The 12-lead ECG was obtained at a paper speed of 50 mm/s and 1-mV/cm standardization. The ECGs were recorded between 8:00 and 10:00 am, in a quiet room with the subjects in the resting position. Two experienced cardiologists without the knowledge of the clinical characteristics of the patients and control group analyzed all the ECGs.

The standardization and interpretation of the ECG, including the correction of QT intervals, were carried out according to the American Heart Association (AHA), The American College of Cardiology Foundation (ACCF), and The Heart Rhythm Society (HRS) recommendations[18]. P and QT wave durations were measured manually. To improve accuracy, the measurements were performed with calipers and a magnifying lens to define the ECG deflection. ECGs without clearly identifiable QT waves were excluded from the QT wave analysis. QT wave duration was evaluated in all 12 leads. Pregnant women with measurable QT waves in more than nine ECG leads were included in the study. QT interval was measured from the start of the Q wave to the end of the T wave. QT intervals were

corrected for the patients' heart rate using the Hodges formula (QTc = QT + 1.75 (heart rate – 60)[19]. When U-waves were present, the QT was measured to the lowest point of the curve between the T- and U-waves. Maximum (QT max) and minimum (QT min) QT-wave durations were defined as the longest and shortest measurable QT-wave durations, respectively, in any lead. Accordingly, corrected QT dispersion (QTc-d) was calculated as the difference between maximal and minimal QTc intervals. P-wave duration was calculated in all 12 leads. Onset of the P-wave was defined as the first atrial deflection from the isoelectric line, and offset was defined as the return of the atrial signal to baseline. Maximum (Pmax) and minimum (Pmin) P-wave durations were defined as the longest and shortest measurable P-wave durations, respectively, of at least three P-waves in each lead. P-wave dispersion (Pd) was calculated as the maximum minus minimum P-wave duration (Pd = Pmax – Pmin). If the onset and termination of the P-wave could not be identified with certainty in a particular lead because of very low P-wave amplitude, that lead was excluded from the analysis.

Blood samples were obtained from the antecubital vein early in the morning, following ten hours of fasting. Serum concentrations of hs-CRP were determined by a Tinaquant CRP (Latex) high-sensitive particle-enhanced immunoturbidimetric assay on a Roche Modular P analyzer (Roche kit, Roche Diagnostics, Mannheim, Germany) according to manufacturer instructions. Minimum detectable concentration was $1x10^{-5}$ mg/L for hs-CRP. All of the other blood analyses were carried out within two hours of blood sampling, using a hematology analyzer (GEN-S; Beckman-Coulter Inc., Brea, CA, USA) at the central laboratories of Zekai Tahir Burak Women's Hospital.

The age, body mass index (BMI), resting heart rate, blood pressure, and hs-CRP, fibrinogen, levels of each participant were recorded. The perinatal outcome parameters, including gestational age at delivery, preterm delivery, stillbirth, birth weight, 5-minute Apgar score, neonatal intensive care unit admission, and meconium-stained amniotic fluid, were also assessed.

Reproducibility

Twenty electrocardiograms were randomly selected for evaluation of the inter- and intra-observer variability of QT and P wave interval measurements by two independent observers. The same measurements were repeated twice, 2 days apart. The intra and inter observer correlations were 0.97 and 0.95, respectively ($p < 0.001$).

Statistical Analysis

Statistical analysis was performed using SPSS version 18 (Statistical Package for the Social Sciences, Chicago, IL, USA). The data were summarized as mean ± standard deviation and median (minimum-maximum). Comparisons of parametric variables between the groups with a normal distribution were made by one-way analysis of variance. The Kruskal-Wallis test was performed to compare continuous variables that did not have a normal distribution. A Chi-square test was performed for nominal or ordinal variables between groups, where appropriate. Correlations between epicardial fat, FMF duration and hs-CRP were assessed using Pearson partial correlations. Results were considered significant when the p value was < 0.05.

Results

Sixty-one pregnant diagnosed with FMF were followed throughout pregnancy during the study period. A total of 12 pregnant with FMF were excluded from the study due to the fact that 2 had concomitant connective tissue diseases, 3 had thyroid disorder, 2 developed preeclampsia, 2 were diagnosed to have gestational diabetes, 2 had multiple pregnancy and 1 had proteinuria associated with amyloidosis and was also a smoker.

Forty-nine patients with FMF who met the inclusion criteria were recruited as the study group and fifty consecutive healthy pregnant without any pregnancy complications were recruited as controls. Three pregnant in the FMF group and 2 pregnant in the control group were excluded since echocardiographic examination revealed mitral valvular prolapse in three and mild mitral valve regurgitation in two of them. Another one in the FMF group had to be discarded from the study due to right bundle branch block, detected on the ECG examination. Seven patients in the FMF group and 10 in the control group were further excluded due to missing clinical or laboratory files. In the end, the data of 37 pregnant with FMF and 40 healthy pregnant women were evaluated for the final analysis.

Table I. The comparison of patient characteristics in the pregnant women with and without FMF.

	FMF (n = 37)	Control (n = 40)	*p*-value
Maternal age, year ± SD	27.3 ± 5.1	28.9 ± 4.6	0.13
Parity (range)	0 (2)	1 (2)	0.18
Gestational week at assessment, week ± SD	35.6 ± 1.43	36.1 ± 1.47	0.67
BMI at assessment, kg/m^2 ± SD	25.5 ± 3.94	26.1 ± 3.26	0.49
Duration of disease, year ± SD	5.2 ± 2.4	–	–
Heart rate, bpm ± SD	75.3 ± 5.7	77.8 ± 6.2	0.98
Systolic BP, mmHg ± SD	123 ± 8.6	120 ± 8.5	0.91
Diastolic BP, mmHg ± SD	76 ± 6.8	78 ± 7.0	0.96
Hemoglobin (g/dL) ± SD	12.1 ± 0.6	11.9 ± 0.3	0.93
WBC (103/µl) ± SD	10.5 ± 2.26	9.8 ± 1.63	0.16
Fibrinogen, g/L ± SD	468 ± 93	438 ± 105	0.24
hs-CRP (mg/L) ± SD	12.1 ± 5.1	5.8 ± 2.7	< 0.01

Data expressed as mean ± SD, *The mean difference is significant at the 0.05 level. BMI, body mass index; bpm, beats per min; BP, Blood pressure; hs-CRP: high-sensitivity complement-reactive protein, WBC: white blood cell.

Age, parity, BMI, gestational week at assessment, maternal resting heart rate, and blood pressure were comparable between the two groups. The hs-CRP values were significantly higher in the FMF group compared with the control group (p = 0.01). The demographic and laboratory data of the FMF and control groups are shown in Table I.

There were no differences in Pmax, Pmin, Pd, mean QTc interval and QTc-d values between the groups. Electrocardiographic assessment results are presented in Table II.

Epicardial fat thickness values were significantly higher in the FMF group compared with the control group (p = 0.015). Echocardiographic assessment results are presented in Table III.

There were no cases of fetal chromosomal anomaly in neither of the groups. The duration of pregnancy was significantly shorter in the FMF group compared to the healthy pregnant women (p = 0.05). The perinatal outcomes of the pregnant women with FMF and the control cases are shown in Table IV.

In correlation analysis there was a positive correlation between FMF duration and epicardial fat thickness (r = 0.350, p = 0.042). There was no significant correlation between hs-CRP levels either with FMF duration (r = –0.061 p = 0.732) or epicardial fat thickness (r = 0.103, p = 0.42).

Discussion

In this study, for the first time in the literature, we demonstrated that while P-d and QTc-d values were not altered, epicardial fat thickness was significantly increased in pregnant women with FMF compared with the healthy ones. Furthermore, epicardial fat thickness was positively correlated with the duration of the disease in pregnant women with FMF.

It has been previously shown that attack-free intervals of the FMF are characterized by subclinical inflammation with overproduction of hs-CRP and the other acute-phase reactants. This

Table II. The electrocardiographic findings of the pregnant women with and without FMF (mean ± SD).

	FMF group (n = 37)	Control group (n = 40)	*p*-value
P_{max} (ms)	89.2 ± 10.6	87.3 ± 0.83	0.44
P_{min} (ms)	39.8 ± 13	38.8 ± 10	0.75
Pd (ms)	47.2 ± 8.5	44.3 ± 6.9	0.31
Maximum QTc interval (ms)	421 ± 31	411 ± 27	0.18
Minimum QTc interval (ms)	376 ± 30	379 ± 28	0.98
Mean QTc interval (ms)	398 ± 30	393 ± 26	0.50
QTc-d (ms)	45.6 ± 11.1	44.1 ± 11.1	0.59

The mean difference is significant at the 0.05 level. P_{max}: Maximum *p*-wave duration, P_{min}: Minimum *p*-wave duration; Pd; *p* Wave Dispersion; QTc; corrected QT; QTc-d, corrected QT dispersion. ms: millisecond.

Table III. The echocardiographic findings of the women with and without FMF.

	FMF (n = 37)	Control (n = 40)	*p*-value
LVEDD (mm)	46.1 ± 3.5	45.7 ± 1.1	0.82
LVESD (mm)	28.7 ± 4.8	28.9 ± 3.6	0.29
IVS Thickness (mm)	0.83 ± 0.85	0.82 ± 0.82	0.94
LAD (mm)	33.1 ± 3.5	34.6 ± 3.3	0.09
AAD, systole (mm)	25.3 ± 2.5	26.5 ± 2.6	0.08
EF (%)	67.3 ± 0.6	67.1 ± 0.6	0.16
Epicardial Fat Thickness (mm)	5.3 ± 1.2	4.5 ± 1.0	0.015*

The mean difference is significant at the 0.05 level. AAD, Ascending aorta diameter; EF, ejection fraction; IVS, interventricular septum; LAD, Left atrial diameter; LVEDD, left ventricular end diastolic diameter; LVESD, left ventricular end systolic diameter.

subclinical inflammation puts patients at risk of developing serious complications such as anemia, decreased bone mineral density, amyloidosis and heart disease[20,21]. Although clinically overt cardiac disease is uncommon in patients with FMF, the impact of inflammation on the cardiovascular system has not been adequately explored yet[22,23].

The data regarding the association between FMF and increased values of P-d and QT-d measurements have been conflicting. Acar et al[15] demonstrated that atrial electromechanical delay and Pd measurements were prolonged in FMF patients. They further claimed that the atrial electromechanical delay was closely associated with Pd and plasma CRP levels. The inflammatory state of FMF has been speculated to lead to the abnormal atrial conduction, thereby contributing to the seemingly increased risk of atrial arrhythmias. Contrarily, Nussinovitch et al[16] reported that FMF patients who were on colchicine treatment and free of amyloidosis had comparable Pd values as healthy controls. Likewise, the data regarding the FMF and QTd relationship[24-26] have also been conflicting.

Colchicine is one of the oldest known drugs used for prophylaxis of FMF attacks, and prevention of the development of amyloidosis[1,2]. Its anti-inflammatory mechanism differs from the other anti-inflammatory agents like non-steroidal anti-inflammatory drugs and glucocorticoids. Instead of being involved in the arachidonic acid pathway, colchicine promotes microtubule depolymerization leading to cytoskeletal changes through cell mitosis, exocytosis, and neutrophil motility. Colchicine not only inhibits neutrophil chemotaxis and the production of interleukin-1, but also down regulates the tumor necrosis factor alpha-receptors[27]. In addition, growing data suggests that in FMF, colchicine decreases the levels of subclinical inflammation markers. Although the effects of colchicine on cardiovascular morbidity and mortality have not been studied prospectively, accumulated data indicates additional benefit in a variety of cardiovascular disorders, including pericarditis, arrhythmias, cardiac hypertrophy and possibly heart failure[28,29].

In this study, in relation to the Pd and QTd measurements, we failed to demonstrate any difference between pregnant women with and with-

Table IV. The comparison of the perinatal outcomes of pregnant with and without FMF.

	FMF (n = 37)	Control (n = 40)	*p*-value
Gestational week at delivery ± SD	38.1 ± 1.8	39.6 ± 2.5	0.005*
Birth weight (grams) ± SD	3041 ± 515	3325 ± 363	0.11
Delivery < 37 weeks (n, %)	4 (11.4 %)	3 (7.8 %)	0.09
Fetal chromosomal anomaly	0	0	–
5 minute Apgar < 7 (n, %)	1 (2.8 %)	1 (2.6 %)	1.0
NICU admission (n, %)	1 (2.8 %)	0	1.0
Perinatal mortality (n, %)	0	0	–

Data expressed as number (%), mean ± SD; *The mean difference is significant at the 0.05 level; NICU, Neonatal intensive care unit.

out FMF. Also no correlation was found between Pd and QTd with any of the biochemical markers of inflammation we studied. Since all of our patients had already been on regular colchicine therapy on admission, we admit, at least theoretically that the anti-inflammatory and potential cardioprotective effects of colchicine could have altered our results.

Although there is a link between systemic inflammatory biomarkers, such as CRP and the cardiovascular risk, the cause and effect relationship is unclear. While the systemic inflammatory biomarkers may have a causal role in the atherogenesis, yet they may also be released secondary to cardiovascular risk factors[5].

Epicardial fat is the visceral fat deposit of the heart which is considered to be abnormal if exceeds 5 mm in thickness. Having the same embryological origin with omental and mesenteric adipose tissues, epicardial fat is considered as a metabolically active organ and being the source of vasoactive factors, growth factors and pro-inflammatory cytokines, it can potentially influence the myocardium and the coronary arteries adversely[17,30]. Measurement of the epicardial fat has been proposed as a marker of cardiovascular risk that seems to change with age, BMI, gender and ethnicity and excess epicardial adipose tissue has been shown to be associated with prevalence and severity of atrial fibrillation[17].

In the present study, since the BMI, the maternal age and the ethnicity were comparable between the groups, the possible confounding effects were eliminated. We demonstrated significantly increased epicardial fat thickness in pregnant with FMF compared to the healthy subjects (5.3 ± 1.2 mm and 4.5 ± 1.0 mm, respectively). Also, significantly higher serum hs-CRP levels were detected, even during the asymptomatic period in FMF pregnant women when compared to the controls. As also reported by the previous studies, both increased epicardial fat and hs-CRP measurements might suggest an increased risk of cardiovascular diseases in FMF patient.

Conclusions

We demonstrated that Pd, a non-invasive marker of potential atrial arrhythmia, and QTc-d, a non-invasive marker of potentially lethal ventricular tachyarrhythmia, were not altered in pregnant women with FMF who already put on colchicine treatment. We also showed that increased levels of epicardial fat thickness values in the same group. Therefore it could be speculate colchicine may have a cardio-protective effect beyond the effect mediated through suppression of inflammation.

Some limitations of the present study are the relatively small population size, the short-term follow-up, the absence of data related to Holter monitoring and strain rate parameters, as well as the lack of electrophysiological evaluation. Nevertheless, our study is the first of its kind to investigate the relationship between cardiovascular disease risk by measuring Pd and QTc-d characteristics and FMF in a pregnant population.

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Conflict of Interest

The Authors declare that there are no conflicts of interest.

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