Introduction

Fibromyalgia (FM) is a chronic disorder characterized by widespread body pain. Its prevalence in the general population ranges from 0.5% to 7.5% and it is seven times more frequent in women. Its prevalence is up to 20% in rheumatology clinics. In addition to widespread pain, it often leads to fatigue, sleep disturbance, cognitive, and somatic symptoms. Although the exact pathogenesis of the disease is not known, autonomic nervous system dysfunction and a decreased pain threshold are the main mechanisms implicated in the formation of symptoms (1-4).

The P wave of the electrocardiography (ECG) reflects the atrial depolarization, while the QT interval reflects the total time for depolarization and repolarization of the ventricles. P and QT dispersions are simple and inexpensive measurements reflecting the regional heterogeneity of atrial and ventricular repolarization, respectively. QT dispersion can cause serious ventricular arrhythmias, and hence sudden cardiac death, by way of non-homogenous conduction velocities in different regions of the ventricles or in the re-entry mechanism of repolarization. The P wave dispersion is an index that reflects the risk of atrial and/or ventricular arrhythmias. These indexes have been shown to be associated with the activity of the autonomic nervous system dysfunction and a decreased pain threshold are the main mechanisms implicated in the formation of symptoms (1-4).

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Studies in the literature evaluating P wave and QT dispersions in patients with FM are limited, whereas there are many studies showing autonomic dysfunction in patients with FM (13-15). In this study, it was aimed to evaluate P wave and QT dispersions in patients with FM.

Material and Methods

Participants

In total, 48 FM patients and 32 healthy controls (HC) were included in the study. All the participants were women. All the FM patients met the criteria applied for classification in routine practice (1). The protocol of this study was approved by the institutional Ethics Committee, and all the participants gave informed consent to participate in the study.

The study involved 48 FM patients who fulfilled the established criteria and 32 healthy controls (HC). A standard 12-lead electrocardiogram was performed on all participants. QT dispersion was defined as the difference between the longest and the shortest QT intervals. Similarly, the differences between the shortest and longest P waves were defined as P wave dispersion.

Results

The QT dispersion and corrected QT dispersion were shorter in the FM group compared with the HC group (p<0.001 for both). In terms of the P wave dispersion value, there was no significant difference between the FM and HC groups (p=0.088).

Conclusion

Longer QT and P wave dispersions are not problems in patients with FM. Therefore, it may be concluded that fibromyalgia does not include an increased risk of atrial and/or ventricular arrhythmias.

Keywords: Fibromyalgia syndrome, QT dispersion, P wave dispersion

Abstract

Objective: Fibromyalgia (FM) is a chronic disease characterized by widespread pain. Somatic complaints associated with the cardiovascular system, such as chest pain and palpitations, are frequently seen in FM patients. P and QT dispersions are simple and inexpensive measurements reflecting the regional heterogeneity of atrial and ventricular repolarization, respectively. QT dispersion can cause serious ventricular arrhythmias. The aim of the present study was to evaluate QT dispersion and P wave dispersion in patients with FM.

Material and Methods: The study involved 48 FM patients who fulfilled the established criteria and 32 healthy controls (HC). A standard 12-lead electrocardiogram was performed on all participants. QT dispersion was defined as the difference between the longest and the shortest QT intervals. Similarly, the differences between the shortest and longest P waves were defined as P wave dispersion.

Results: The QT dispersion and corrected QT dispersion were shorter in the FM group compared with the HC group (p<0.001 for both). In terms of the P wave dispersion value, there was no significant difference between the FM and HC groups (p=0.088).

Conclusion: Longer QT and P wave dispersions are not problems in patients with FM. Therefore, it may be concluded that fibromyalgia does not include an increased risk of atrial and/or ventricular arrhythmias.

Keywords: Fibromyalgia syndrome, QT dispersion, P wave dispersion
consent before enrolling in the study. Patients under 18 years old, older than 80 years, or who were pregnant were excluded. In addition, patients using drugs that have the potential to affect the QT interval and/or having atrial fibrillation, ischemic heart disease, congestive heart failure, bundle branch block, and electrolyte disorders were excluded. Informed consent forms were obtained from each participant. For all the participants in the study, physical examinations were performed and medical histories were obtained. All the patients were questioned about their treatments and complications related to the disease.

The Hospital Anxiety and Depression Scale (HADS) form to obtain the profile of mental disorders and the Rome III diagnostic criteria for the detection of irritable bowel syndrome were applied to the patient and HC groups (16, 17).

Laboratory analysis
Blood samples were taken at 8:00 in the morning after 8-12 hours of fasting. Routine laboratory tests (fasting blood glucose, cholesterol, whole blood count, creatinine, total creatine kinase) were studied with the standard method for all the participants on the same day. Erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) levels were assessed by the classic Westergren method and the immunoturbidimetric method, respectively.

P and QT dispersion measurement
For all subjects, a 12-lead ECG at a 25 mm/sec speed and 1 mV amplitude was applied by using a commercially available electrocardiography machine (Nihon Kohden; Tokyo, Japan). The P wave onset and end points were considered as the intersection of the P wave by the isoelectric line and the intersection of the end point of the P wave with the isoelectric line, respectively. The maximum P wave duration was considered as the longest P wave and the longest atrial conduction time, and the difference between the longest and the shortest P waves was considered as the P wave dispersion. The interval between the points of the isoelectric TP segment intersected by the onset of the QRS complex and the descending branch of the T wave (T-wave end) was considered as the QT interval and was separately calculated for each derivation. The QT dispersion was determined as the difference between the longest and shortest QT intervals in any derivation in the standard 12-lead ECG. The corrected QT (QTc) was calculated using the Bazett’s formula (QTc=QT/√R). QTc dispersion was likewise taken as the difference between the longest and shortest QTc.

Statistical analysis
IBM Statistical Package for the Social Sciences (Version 21.0 IBM Corp.; Armonk, NY, USA) program was used in the statistical analysis. The continuous data was expressed as the mean±standard deviation. The normality of distribution for the parametric data was assessed by the Kolmogorov Smirnov test, while the Student’s t test was used for the parametric data and the Mann-Whitney U test for the non-parametric data. Categorical data were analyzed by the chi-square test. Pearson correlation analysis was used to determine the relationship between the data. Analysis of covariance (ANCOVA) was also used to adjust variables for age and body mass index (BMI), since there were significant differences between the groups in terms of age and BMI. A p value <0.05 was considered as significant.

Results
The demographic, clinical, and laboratory data of the study group are summarized in Table 1. The mean age and BMI were significantly higher in the FM group compared with the control group (p=0.047 and p=0.006, respectively). However, there was no significant difference between the groups with respect to triglycerides, low-density lipoprotein cholesterol (LDL), cholesterol, ESR, CRP, leukocyte, and hemoglobin. Total symptom index was 9.39±3.08, the fatigue score was 2.66±0.51, the score for waking not feeling refreshed was 2.45±0.74, the cognitive symptom score was 2.31±0.92, and the somatic symptom score was 2.41±0.76. In addition, for the FM patients, 27% smoked, while irritable bowel syndrome (IBS) was present in 48%, headache in 85%, anxiety disorders in 54%, and depression in 71%, and these values were significantly higher than in the control group (Table 1).

The maximum P wave duration was higher in the HC group than in the FM group (p=0.001, Table 2), while there was no significant difference in terms of the minimum P wave duration (p=0.123). However, the mean P wave dispersion was relatively decreased in the FM group compared with the HC group (p=0.088). However, after adjustment for age and BMI, the P wave dispersion was similar in the study groups (ANCOVA, p=0.391).

While the minimum QT interval was higher in the FM group (p<0.001), there was no significant difference between the groups in terms of the maximum QT interval (p=0.160, Table 2). Similarly, in the FM group, the minimum QTc interval was higher, but the maximum QTc interval was not altered (p=0.001 and p=0.719, respectively). However, the mean QT and QTc dispersions were decreased in the FM group compared with the HC group (p<0.001 for both). Even after adjustment for age and BMI,
they were shorter in the former group (ANCOVA, p<0.001 for both).

In the control group, QT dispersion was positively correlated with the LDL cholesterol (r=0.781, p=0.008) and hemoglobin (r=0.456, p=0.033) levels. In the FM group, it was negatively correlated with CRP (r=−0.301, p=0.042) and the widespread pain index score (r=−0.315, p=0.029). Nevertheless, the P wave dispersion was not significantly correlated with any clinical or laboratory data (p>0.05 for all).

### Discussion

The present study documents the P wave and QT dispersions in patients with FM. There was no significant difference between FM patients and healthy subjects in terms of the mean P wave dispersion length. However, the mean lengths of the QT and QTC dispersions were shorter in the FM patients than in the healthy subjects.

Fibromyalgia is a chronic, non-inflammatory locomotor system disease characterized by the presence of widespread pain and sensitive points in the body (18). Although the exact etiology is unknown, it is suggested that central mechanisms play a central role in the pathophysiology of FM. In FM patients, serotonin, noradrenaline, dopamine, and enkephalin levels are low in the brain and the substance P level is high in the cerebrospinal fluid. In addition, the response of the thyroid stimulating hormone to the thyroid releasing hormone is defective and the insulin-like growth factor-I level is decreased. A distortion in the non-rapid eye movement (REM) period of sleep and a reduction of regional cerebral blood flow in single photon computed tomography are also shown in FM (3, 4, 19). The central nervous system has a role in the modulation of the pain, and in FM pain can be perceived incorrectly or as abnormally painful stimuli and an exaggerated response to stimuli can occur via decreasing the pain threshold. Alloodynia or hyperalgesia occurs as a result of these events, in FM (20).

There is an endogenous modulation system between the hypothalamus, midbrain, and medulla conducting external stimuli like pain. The response to this stimulus varies depending on the intensity, duration, and repetitive features of the stimulus. The balance system between mediators, like substance P, bradykinin, prostaglandins, and leukotrienes, is deteriorated in FM. As a result of this, the stimulation threshold of nociceptors decreases and they become sensitive to even mild stimuli (21).

Three main symptoms that can be considered as a triad for FM are: widespread body pain, fatigue, and sleep disturbances (like waking up already fatigued). These three symptoms are present in the majority of FM patients (22). In addition, FM patients can show a wide variety of clinical signs related with psychological problems, neurological system, and many other systems. Therefore, the treatment of FM can be difficult and requires patience as it shares the differential diagnosis of many other diseases. Although it has non-inflammatory and benign character, it impairs daily life and the quality of life of the patient significantly (18). Any pathological finding, except the presence of characteristic sensitive points in the muscle and in the muscle-tendon junctions, is not usually detected. Laboratory tests, electromyography, and muscle biopsy are usually normal in primary FM patients. However, these processes can also be performed to exclude other diseases (18).

Somatic complaints associated with the cardiovascular system, such as chest pain and palpitations, can be frequently seen in FM patients. Patients can experience psychological trauma due to this complaint and this leads to extreme tests up to invasive procedures, such as coronary angiography, being applied.

Previous studies have shown that QT dispersion is an indicator for arrhythmia and CVD mortality (5-8). In addition, the QT dispersion length is longer in many rheumatic diseases, such as rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), juvenile idiopathic arthritis, systemic sclerosis, and Behçet’s disease, and those patients also have an increased risk of CVD (9-12). Yavuz et al. (11) found that the QT dispersion value was significantly higher in SLE patients than in the control subjects in their study. Moreover, QT dispersion was significantly increased in the SLE patients without overt cardiac involvement. These results suggest that prolonged QT dispersion could be a useful noninvasive and simple method for the early detection of silent cardiac involvement in SLE patients (11). Moreover, it was also shown that the QT dispersion length is longer in patients with RA than in controls (9, 23). RA patients with Sjogren’s syndrome (SjS) had more prolonged QT dispersion than in RA patients without SjS, and RA patients with a disease duration of over 5 years also had a more prolonged QT dispersion than those with new onset RA. This increased QT dispersion was shown as an important predictor of subclinical vascular disease in RA patients (23). Patients with higher QT dispersion also have a higher risk of cardiac death and total mortality (9, 23, 24).

However, no significant difference was detected between FM and control groups with respect to QT dispersion and conventional echocardiographic parameters in the study performed by Yazıcı et al. (25). We found no increase in P and QT dispersions consistent with their study; on the contrary, QT and QTC dispersions were detected to be lower in the FM group. Although risk factors such as age, BMI, and smoking were higher in FM patients, the lower P and QT dispersion supported the conclusion that there was no increase in the risk of arrhythmias and CVD in this non-inflammatory disease.

It has been documented that magnesium (Mg) applications decrease QT dispersion (26). Although patients with FM had lower serum Mg levels, hair Mg levels were higher than those in healthy subjects (27, 28). One cause of the decreased QT and QTC dispersions may be the

### Table 2. Demographic, clinical, and laboratory features of the study groups

|                     | FM (n=48) | HC (n=32) | p   |
|---------------------|-----------|-----------|-----|
| P wave dispersion, msec | 35.8±10.8 | 40.6±13.8 | 0.088 |
| Maximum P wave, msec  | 78.3±6.9  | 87.5±13.1 | 0.001 |
| Minimum P wave, msec  | 42.5±8.8  | 46.8±14.1 | 0.123 |
| QT dispersion, msec   | 42.1±15.6 | 61.9±13.6 | <0.001 |
| Maximum QT interval, msec | 378.6±35.2 | 367.3±33.4 | 0.160 |
| Minimum QT interval, msec | 336.6±35.5 | 305.4±31.9 | 0.001 |
| QTc dispersion, msec  | 50.5±16.5 | 71.9±17.6 | <0.001 |
| Maximum QTc interval, msec | 408.8±29  | 406.1±33.8 | 0.719 |
| Minimum QTc interval, msec | 358.2±30.8 | 334.2±29.4 | 0.001 |

Data are expressed as the mean±SD.

FM: fibromyalgia; HC: healthy controls; QTc: corrected QT
accumulated Mg in the tissues in FM patients. Another cause of the decreased QT and QTc dispersions may be reduced catecholamine levels in FM patients. Riva et al. (29) reported that serum noradrenaline, adrenaline, and dopamine levels were lower in FM. It has also been shown that beta-blockers decrease the QT and QTc dispersions (30, 31).

In conclusion, there is no increase in P and QT dispersions in FM patients. These results may support the conclusion that there is no increase in the risk of arrhythmias and CVD of the patients with FM.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Firat University School of Medicine.

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

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - S.Y., A.Y.; Design - S.Y., A.Y.; Supervision - S.S.K., M.N.D.; Resources - S.Y.; Materials - D.D., B.K.; Data Collection and/or Processing - D.D., B.K.; Analysis and/or Interpretation - S.Y., S.S.K.; Literature Search - S.Y., A.Y.; Writing Manuscript - S.T., D.D., B.K.; Analysis and/or Interpretation - S.Y., S.S.K.; Data Collection and/or Processing - A.Y.; Supervision - S.S.K., M.N.D.; Resources - S.Y.; Materials - D.D., B.K.; Critical Review - S.S.K., M.N.D.; Other - A.Y.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study has received no financial support.

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