QT And P Wave Analysis in Egyptian Fibromyalgia Patients as A Surrogate for Arrhythmias

Original Article

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ABSTRACT

Background: Fibromyalgia (FM) and chronic fatigue syndrome (CFS) frequently overlap clinically and have been considered variants of one common disorder. It is characterized by diffuse musculoskeletal pain and discomfort. Many studies confirmed the increased risk of heart rate abnormalities in FM patients. So, the aim of this study was to assess p wave dispersion and QT interval changes in female Egyptians with fibromyalgia.

Results: The mean QT and QTc dispersions were significantly lower in FM group compared with the HC group ($p<0.001$ for both). The minimum QT interval was significantly higher in the FM group ($p<0.001$). Regarding mean P wave dispersion, it was lower in FM group compared with the HC group but the result was not statistically significant ($p=0.088$). Relation between patient's results and types of graft used showed no statistically significant differences between them.

Conclusion: FM patients had abnormal repolarization manifested as prolonged QTcd which makes them at higher risk for developing ventricular arrhythmias and sudden cardiac death.

Key Words: Arrhythmia, Fibromyalgia syndrome, P wave dispersion, QT dispersion.

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INTRODUCTION

Fibromyalgia syndrome (FMS) is an idiopathic, chronic syndrome of nonarticular-muscular origin and is characterized by widespread and well-localized anatomic points that are painful spontaneously especially during palpation [1].

In one study aimed at assessing the prevalence of fibromyalgia in Egyptian patients with other chronic illnesses, it was found that about 1.9% of chronic liver disease patients had fibromyalgia [2], and in another study, the frequency of fibromyalgia among university students with benign hyper mobility syndrome was 2.4% [3]. Approximately 2–10% of the US population is believed to meet the current diagnostic criteria for fibromyalgia [4]. Vital body functions as blood pressure, respiration and temperature are maintained by the autonomic nervous system [5].

Autonomic nervous system (ANS) dysfunction has been incriminated in the etiology of FMS. The degree of affection of the sympathetic and parasympathetic systems varies in FMS [6].

There are other associated features in FMS as Raynaud phenomenon, abnormal sleep patterns, anxiety disorders and irritable colon. Such disorders have been attributed to abnormal ANS dysfunction occurring with FMS [7].

The association between atrial fibrillation (AF) and parasympathetic nervous system (PNS) activation is well established. Also there is a link between sympathetic nervous system (SNS) dysfunction and AF in some patients [8].

In Surface electrocardiography (ECG), P wave represents atrial depolarization whereas QT interval is a reflection of the total time for both ventricular depolarization and repolarization. Abnormal P wave and QT dispersions reflects heterogeneity of atrial and ventricular repolarization which may be a substrate for atrial and ventricular arrhythmias and sudden cardiac death. The mechanism of such arrhythmias is usually re-entry mechanism of repolarization. The assessment of P wave and QT dispersions is easy and available with little cost [9].

In this study, our aim was to determine the risk of both atrial and ventricular arrhythmias in patients with fibromyalgia by evaluating certain surrogate endpoints of QT and P wave analysis.

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PATIENTS AND METHODS:

This study was a prospective, case-controlled study conducted upon female fibromyalgia patients aged 20-55 years who presented to the outpatient clinics of the rheumatology department. The diagnosis of FMS was based on 2010 FMS criteria [10]. The protocol of this study was approved by the institutional Ethics Committee and all the participants gave informed consent.

Patients were excluded from the study if they had known cardiac disorders (myocardial infarction, arrhythmia, left ventricular dysfunction or rheumatic valvular heart disease), electrolyte disorders, abnormal thyroid function, renal disorders or malignancies. Also patients on certain medications as beta blockers, calcium channel blockers or antiarrhythmic drug were excluded from the study. Patient with left bundle branch block and QRS duration more than 120 ms were also excluded as this makes measuring the QT dispersion inaccurate.

In total, the study included 51 female patients diagnosed with FM as they met the pre-specified criteria and 50 healthy controls (HC).

All patients had undergone clinical and laboratory assessment. The initial evaluation included demographic data, Symptom Severity Scale (SSS), Widespread Pain Index (WPI) scores and number of tender points. The laboratory evaluation included complete blood picture, renal functions, hepatic functions, acute phase reactants as erythrocyte sedimentation rate and C-reactive protein values as well as blood electrolyte and TSH.

The control group included age-matched healthy females who visited the outpatient rheumatology clinics with joint pain and did not fulfill the FMS criteria.

Clinical assessments

The pain severity in patients was assessed using Visual Pain Scale (VPS) in which pain was given a point from 0 to 10 and 0 meant no pain while 10 meant intolerable pain.

In the widespread pain index (WPI), a 0-19 count is given to the painful points reported by the patient. A 0-3 scale is then given by the patient according to the severity of the symptom, then these items were combined into a 0-12 Symptom Severity SSS. Tender points characteristic for FM are: Low cervical region, Second rib, Occiput, Trapezius muscle, Supraspinatus muscle, Lateral epicondyle, Gluteal region, Greater trochanter and Knee [10].

Fibromyalgia Impact Questionnaire (FIQ) was used to evaluate disease severity of FMS which evaluates 10 items as physical activity, feeling good, inability to go to work, number of work days missed, pain, morning tiredness, fatigue, stiffness, depression and anxiety. When the score is low, this means that the disease is mild while higher scores mean severe affection. The top of each item of evaluation does not exceed 10 points making the total score 100 points. The average score in FMS is 50 points but when the score is 70 points or more, this means severe affection.

Evaluation of risk of arrhythmia

Twelve-lead ECG was done to all study population using Schiller-U2 ECG machine (Schiller lnc., Baar, Switzerland). All ECGs were evaluated by the same cardiologist who was blinded of the study population. The ECG was done according to the standard parameters with a recording velocity of 25 mm/sec while the scale was scale of 1 mV/cm using. The ECG study parameters were calculated including P waves and QT analysis with an average obtained from three ECG cycles.

The beginning of the P wave was calculated from the onset of the wave from the isoelectric line whereas the end point was considered as the start of the next isolectric line. P dispersion (Pd) was calculated as the difference between maximum and minimum P wave intervals in milliseconds. Pd = Pmax - Pmin. The average duration of at least 3 P waves was used to calculate Pd.

QT Interval was considered from the beginning of the QRS wave to point of intersection of the T wave tangent with the baseline. In cases when there is no clear endpoint of the T wave, the point of intersection between the line from the descending limb of the T wave and isoelectric line was considered the termination point of the T wave. The difference between the longest, and the shortest QT intervals was called QT dispersion (QTd). QTmax, and QTmin are the shortest QT intervals respectively. Corrected QT (QTcd) intervals were estimated using Bazett formula to correct for heart rate variations. This conventional correction procedure aims to eliminate dependence of QT on heart rate. QTd = QTmax-QTmin. .Bazett formula: $QTdd = Qtd/\sqrt{(RR)}$.

STATISTICAL ANALYSIS:

Collected data were analyzed using Statistical Package for the Social Sciences (SPSS) version 25.0 (IBM Corporation, Armonk, NY, USA) and GraphPad software version 8 (San Diego, California, USA). Categorical variables were presented as frequencies and percentages (%). Quantitative variables were tested for normality with the Shapiro–Wilk and was presented as mean ± SD for normally distributed variables and as median (IQR) for non-normally distributed variables. IL-36α expression levels of the two groups were tested by Kruskal-Wallis test. The tests were two-tailed and the result was considered significant if $P < 0.05$.

RESULTS:

The study included 51 female patients and 50 control subjects. No significant difference was found between the patients and controls regarding the age. It was found that the educational level of the control group was relatively higher than patients. The mean disease duration was 0.37±0.1-2. The socio demographic data summarized.

It was found that 49% of FM patients had sleep disturbance while irritable bowel syndrome (IBS) was found in 48% of patients. Headache was also found in 45%, anxiety disorders in 54.9%, and depression in 78.4%. All the pervious features were significantly higher in patients than the controls subjects.

The mean of tender point count (TPC), which indicates disease activity was 15.3±2.4. The average FIQ scale was 56.2± 11.7 as evident in (Table 1).

Table 1: Socio- Demographic characteristics and clinical features of the studied and control group

Character	FM(n=51)	HC(50)	*P*
Age(years)			
Mean ± SD	34.2 ± 9.9	40±15.32	0.22
Education n(%)			
Read and write	8(15.7%)	10(20%)	0.70
Moderately educated	11(21.6%)	4(8%)	0.61
More than moderately educated	18(35.3%)	13(26%)	0.30
Highly educated	12(23.5%)	20(40%)	0.52
Postgraduate	2(3.9%)	3(6%)	0.60
Occupation n (%)			
Work	44 (86.3%)	10 (20%)	0.12
Not work	7 (13.7%)	39 (78%)	0.15
Retired	0	1(2%)	0.23
Marital Status n (%)			
Single	21 (41.2%)	3(6%)	0.50
Married	28 (54.9%)	45(90%)	0.60
Divorced	2(3.9%)	2(4%)	0.42
Smoking (n %)			
Smoker	0 (0%)	0(0%)	
Non Smoker	51 (100%)	50(100%)	0.30
Disease duration (Years) Mean ± SD	0.37±0.1		0.61
TPC	15.3±2.4		
IBS n (%)	23(45%)	6(12%)	*<0.001**
Headache n (%)	40(78.4%)	10(20%)	*<0.001**
Depression n (%)	37(72.5%)	10(20%)	*<0.001**
Anxiety disorders, n (%)	28 (54.9%)	8(16%)	*<0.001**
Sleep disturbance n (%)	25(49%)	10(20%)	*<0.001**
FIQ Mean ± SD	56.2± 11.7		
BAS Mean ± SD	24.10±9.50	12±8.67	*<0.001**
BDS Mean ± SD	29.12±7.68	14.56±7.6	*<0.001**

TPC=Tender point count, SD=Standard Deviation, n=number

The maximum P wave duration was significantly higher in the HC group than the FM patients (*p=0.001*, Table 2) but regarding the minimum P wave duration there was no significant difference (*p=0.123*).

Mean P wave dispersion was lower in the FM patients group compared to the control group however, this result was not statistically significant. However, after adjustment for age and BMI, the P wave dispersion was similar in the study groups (ANCOVA, *p=0.391*).

The minimum QT interval was significantly higher in FM patients than control subjects. (*p<0.001*) while there was no significant difference between the two groups regarding the maximum QT interval as *p value* was 0.160. (Table 2).

Regarding minimum QTc interval, it was significantly higher in the FM patients but there was no significant difference between the two groups in terms if the maximum QTc interval as *P values* were 0.001 and 0.719, respectively. When it comes to the mean QT and QTc dispersions, both were significantly lower in the FM group compared with the control group even after adjustment for age and BMI as the *P value* was *<0.001* for both.

Table 2: P wave and QT analysis in both groups

	FM (n=51)	HC (n=50)	*P*
P wave dispersion, msec	36.5±11.7	41.5±12.9	0.088
Maximum P wave, msec	77.2±6.8	88.7±14.5	0.001
Minimum P wave, msec	41.6±7.8	47.9±12.9	0.122
QT dispersion, msec	37.56±5.075592	23.078431±5.14	*<0.001*
QT, msec	390.4±16.7	372.15±12	*<0.001*
QTc dispersion, msec	39.3±5.28	24.78±5.434	*<0.001*
QTc, msec	450±13.9	423.921569±20.6	*<0.001*

DISCUSSION

The etiology of FM is not fully explained, but neuro-hormonal and autonomic abnormalities are implicated in the very low threshold to painful stimuli causing the chronic pain inn FM patients [1].

The heart is a richly innervated organ with a large number of different receptors, thus it can be easily affected by any minor change either in the autonomic or the hormonal status.

Fibromyalgia and cardiovascular disease risk:

Many studies confirmed the increased risk of cardiac disorders in FM patients. Dogru *et al* found an increased mortality in 50 patients with FM and also the increased risk of developing supraventricular tachycardia in patients compared to controls [11].

In another study, Akkaya *et al* reported that the risk of developing AF is increased in patients with FM [12] while Pei-Shan *et al*., reported that the incidence of coronary artery disease (CAD) was higher in patients with FM [13].

Anthea *et al*., found out a significant number of chronic heart failure had FM and this association could be a good opportunity for improving outcome in patients with heart failure [14].

Scarce data is found about the association between FM with its hormonal and autonomic dysfunction and the risk of arrhythmias. This study aimed at evaluating the risk of AF and ventricular arrhythmias through assessing P wave and QT parameters as surrogate end points respectively.

P wave analysis:

Pd has been found in several studied to be a surrogate for AF as in the study of Dilaveris *et al*. who found out that Pd in paroxysmal AF (PAF) patients was significantly higher when compared with the healthy group. They determined a Pd cutoff value of 40 msec is both (83%) sensitive and (85%) specific in determining the risk of developing AF risk while the positive predictive value was 89% [15].

Aytemir *et al*., in their effort to determine the correlation between P wave dispersion and AF, they reported a higher Pmax, and Pd values in patients with PAF in comparison to the control subjects [16]. In this study, it was found that the maximum P wave duration was significantly higher in the control group while no significant difference was detected between FM and control subjects regarding P wave dispersion and minimum P wave duration values. This means that FM infers no risk of developing AF over the control group.

In contrary to the result of our study, Sarifakioglu *et al*., studied 59 FM patients and 20 controls and they found out that FM patients had significantly higher P max and Pd. *P values* were 0.15 and .034 respectively. They concluded that FM patients had higher risk of AF [17].

In another study by Akkaya *et al*., which included a total of 140 female patients (70 FMS group, 70 healthy control group), Pd was significantly greater in the FMS group compared with the control group 46 (29–62) ms vs. 32 (25–37) ms, ($p < 0.001$). In the FMS group the P max was prolonged compared to the control group, but there was no significant change in the P min value. They concluded that FM patients are at high risk of developing AF which is also contrary to the results of our study [12].

Okin *et al*., studied the P wave parameters in FM patients and they reported that the mean P wave dispersion was lower in FM patients than control group but such result was statistically not significant as the *P value* was 0.088). After adjustment for other variables such as age and BMI, the P wave dispersion was similar in the two groups (ANCOVA, $p=0.391$). Such results are similar to the results of our study [18].

QT analysis:

QTd has been studied for a long time and increased QTd has been correlated with higher cardiovascular mortality due to abnormal repolarization and the liability to develop ventricular arrhythmias [19]. In this study, there was a significantly higher QTd in the FM group in comparison to the control group.

Sarifakioglu *et al*., in their study reported no significant difference in QT parameters between FM patients and matching controls as QTcd in (msec) was 43 (30-58) in FM patients and 43 (30-55) in controls with *P value* of 0.593 [17].

Yolbas *et al*. found out that the minimum QT interval was higher in the FM group ($p<0.001$) but no significant difference between the groups regarding the maximum QT interval ($p=0.160$). However, the mean QT and QTc dispersions were decreased in the FM group compared with the HC group, 50.5±16.5 and 71.9±17.6 respectively ($p<0.001$) [19].

Our data apparently contradicts two previous two studies as in one; there was no significant correlation between parameters obtained from ECG and arrhythmias while in the other the QTcd values were even decreased in FM patients indicating that FM patients are less prone to develop arrhythmias.

CONCLUSION

- This study showed that FM patients had abnormal repolarization manifested by prolonged QTcd which may render them at higher risk for developing ventricular arrhythmias and sudden cardiac death but further follow up is needed to prove this.

- Studies in the link between FM and abnormal electric cardiac properties are scarce and not consistent and sometimes conflicting.

STUDY LIMITATIONS

- Small number of study population.

- Holter monitoring should have been used to actually detect AF or ventricular arrhythmias which would have given accurate assessment of the magnitude of the problem.

LIST OF ABBREVIATIONS

ANS: Autonomic Nervous system.

AF: Atrial Fibrillation.

CAD: Coronary artery disease.

FIQ: Fibromyalgia impact Questionnaire.

HC: Healthy Controls.

PAF: Paroxysmal Atrial Fibrillation.

QTcd: Corrected QT dispersion.

QTd: QT dispersion

SSS: Symptom Severity Scale.

TPC: Tender Point Count.

TSH: Thyroid Stimulating Hormone.

VPI: Visual Pain Scale.

WPI: Widespread Pain Index.

CONFLICT OF INTEREST

There are no conflicts of interest.

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