ARAŞTIRMA MAKALESİ / *RESEARCH ARTICLE*

Evaluation of Ventricular Repolarization Markers and Fragmented QRS in Patients with Bipolar Disorder

Bipolar Bozukluk Tanılı Hastalarda Biyokimyasal Parametreler ile EKG'de Ventriküler Repolarizasyon Markırları ve Fragmente QRS

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ABSTRACT

Aim: *Bipolar disorder (BD) is one of the chronic psychiatric diseases. It has been reported that cardiovascular diseases are seen twice as often in patients with BD. Fragmented QRS (fQRS) has been found to be associated with myocardial scarring and is used as a marker of arrhythmia and mortality. Ventricular repolarization (VR) is often evaluated using QT interval and T wave measurement data. In our study, we aimed to evaluate fQRS, QTc interval, QT dispersion (QTd), Tp-e interval, Tp-e/QT ratio results and VR, together with blood biochemistry parameter results of cases with BD.*

Material and Method: *Our research was conducted with 51 people diagnosed with bipolar disorder and 52 healthy people as the control group. fQRS, QTc interval, QT dispersion (QTd), Tp-e interval, Tp-e/QT ratio were measured using 12-lead electrocardiography (ECG). The results of the data obtained from ECG and blood biochemistry parameter levels were used to compare the healthy and patient groups.*

Results: *Tp-e interval (p=0.018) and Tpe/QT ratio (p=0.036) were found to be statistically significantly higher and total cholesterol level (p=0.006) lower in patients with bipolar disorder compared to the control group.*

Conclusion: *An increased Tpe/QT ratio, along with a prolonged Tp-e interval, may be a useful marker of ventricular arrhythmia risk in individuals with fQRS BD.*

Key words: *bipolar disorder; ventricular repolarization; electrocardiography; fragmented QRS*

ÖZET

Amaç: *Bipolar bozukluk (BB) kronik psikiyatrik hastalıklardandır. Bipolar bozukluk tanılı hastalarda kardiyovasküler hastalıkların iki kat daha fazla görüldüğü bildirilmiştir. Fragmente QRS (fQRS) miyokardiyal skar ile ilişkili bulunmuş ayrıca aritmi ve mortalite belirteci olarak kullanılmaktadır. Ventriküler repolarizasyon (VR) sıklıkla QT aralığı ve T dalga ölçüm verileri kullanılarak değerlendirilir. Bipolar bozukluk tanısı olan olguların kan biyokimya parametre sonuçları ile birlikte fQRS, QTc aralığını, QT dispersiyonu (QTd), Tp-e aralığını, Tp-e/QT oranı sonuçları ile VR'u değerlendirmek çalışmamızda amaçlanmıştır.*

Materyal ve Metot: *Araştırmamız Bipolar bozukluk tanısı olan 51 kişi ve kontrol grubu olarak sağlıklı 52 kişi ile yapılmıştır. fQRS, QTc aralığı, QT dispersiyonu (QTd), Tp-e aralığı, Tp-e/QT oranı 12 derivasyonlu elektrokardiyografisi (EKG) kullanılarak ölçüldü. EKG'den elde edilen verilerin sonuçları ile kan biyokimya parametre düzeyleri sağlıklı ve hasta grubundaki olguları karşılaştırmak için kullanılmıştır.*

Bulgular: *Bipolar bozukluk tanısı olan olgularda Tp-e aralığı (p=0,018) ile Tpe/QT oranı (p=0,036) kontrol grubuna göre istatistiksel olarak anlamlı olarak daha yüksek, total kolesterol düzeyi (p=0,006) ise daha düşük bulunmuştur.*

Sonuç: *Artmış Tpe/QT oranı, uzamış Tp-e aralığı ile birlikte fQRS BB tanısı olan bireylerde ventriküler aritmi riskinin faydalı bir belirteci olabilir.*

Anahtar kelimeler: *bipolar bozukluk; ventriküler repolarizasyon; elektrokardiyografi; fragmente QRS*

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Introduction

The physical health of individuals with chronic psychiatric illness is worse than other people in the community[1]. It has been shown that the average life expectancy of these individuals compared to the general population is up to fifteen years shorter[2]. The main reason for this shortening in life expectancy is cardiovascular diseases. Adoption of a sedentary lifestyle, smoking, frequent consumption of alcohol, and caffeinated beverages, and consumption of high-calorie foods are among the reasons why heart diseases are more common in these individuals[3]. Furthermore, obesity, hypertension, diabetes, and hyperlipidemia are also important causes of cardiovascular mortality[4–6].

It has been reported that cardiovascular diseases comorbidly occur twice as frequently in individuals with bipolar disorder compared to the healthy control[7]. It has been shown that cardiovascular diseases are 3.9 times more common in men and 3.5 times more common in women in manic-depressive individuals compared to the general population[8]. Therefore, individuals with a diagnosis of bipolar disorder are at higher risk for cardiovascular diseases.

In individuals with bipolar disorder, deaths from causes related to cardiovascular diseases are 6.4 times higher in women and 3.8 times higher in men than in healthy individuals[8]. Cardiovascular diseases are the cause of 1/3 of disease-related deaths in these individuals. More than half of cardiovascular diseases are caused by ischemic heart disease. Hypertension, left ventricular hypertrophy, age, glucose intolerance, high serum cholesterol level, intraventricular conduction block, decreased pulmonary vital capacity and increased heart rate are risk factors for sudden cardiac death in these individuals[9].

Antipsychotic and mood stabilizer drugs are frequently used in the treatment of the bipolar disorder. These drugs increase the risk of cardiovascular disease. Lithium and valproic acid are the most commonly used mood stabilizers. Lithium can impair glucose metabolism as a result of causing weight gain[10.11]. Valproic acid, on the other hand, can cause serious metabolic side effects as a result of both weight gain and insulin resistance[12.13]. Today, second-generation antipsychotic agents are the most commonly used in the treatment and cause an increased risk of weight gain, insulin resistance, hyperlipidemia, and diabetes mellitus[14–16].

Electrocardiography is used frequently in cardiology. T wave evaluated on ECG may indicate ventricular repolarization. In the absence of structural heart disease, ventricular repolarization abnormalities may cause arrhythmias. As a result of the studies, it was determined that ventricular repolarization markers such as QT dispersion (QTd), Tp-e/QT ratio, QT and QTc interval, and Tp-e interval could predict life-threatening cardiac arrhythmias[17]. Another important parameter associated with ventricular repolarization is QT dispersion, which is equal to the difference between the maximum QT interval and the minimum QT interval in the standard 12-lead ECG. It is an indicator of the homogeneity of ventricular repolarization and thus of cardiac electrical stability. The greater the QT dispersion, the less homogeneous the ventricular repolarization, and thus the greater the cardiac electrical instability. It is known that increased dispersion of ventricular repolarization is also a serious risk for ventricular arrhythmias[18–20]. The Tp-e value, which is the T wave peak-to-end interval on the ECG, indicates ventricular repolarization. Moreover, the Tp-e/QTc ratio is a parameter used to evaluate ventricular arrhythmogenesis[21]. It has been reported that there is a relationship between the Tp-e interval and the increased Tp-e/QT ratio and the risk of ventricular arrhythmia[22–23]. fQRS has been associated with arrhythmia and mortality in coronary artery patients[24].

Fragmented QRS (fQRS) is an electrocardiography (ECG) finding that has been used frequently in recent years. It is defined as notching of the QRS complex in 2 consecutive leads in the absence of bundle branch block[25]. In a healthy heart, the electrical impulse takes place homogeneously in the myocardium. As a result of myocardial fibrosis, homogeneity in electrical conduction is impaired, and inhomogeneous conduction appears as fQRS on ECG. fQRS is seen in cases of structural myocardial damage[26.27]. fQRS detected in ECGs of people diagnosed with or suspected coronary artery disease is associated with myocardial scarring. . In addition, fQRS is more sensitive than Q wave in showing scar tissue[25]. It has also been suggested that fQRS may be a marker for mortality and arrhythmia in coronary artery disease[24].

Although many cardiac parameters have been examined in patients with bipolar disorder, there is no study examining fQRS and our study is the first of its kind. The aim of this study is to evaluate some blood parameters and ECG measurements in patients with bipolar disorder by comparing them with the control group.

Material and Methods

The research is of the case-control type. Before the cases were included in the study, the Ethics Committee of Kafkas University was consulted and approval was obtained in the session number 04 dated 26.02.2020. Our research was carried out at Kars State Hospital between 01/03/2020-01/06/2021.

The patient group with bipolar disorder who applied to the Kars State Hospital psychiatry outpatient clinic and the control group with healthy individuals with similar socio-demographic characteristics were formed. After the subjects were told what they should do in this study and our aim, their consent was obtained from those who agreed to participate in the study.

Inclusion criteria of the research: for the case group, being diagnosed with bipolar disorder, being between the ages of 18–65, agree to participate in research. For the control group, it was determined as being between the ages of 18–65 and agree to participate in research. Exclusion criteria of the stud: refuse to participate in research for both the case and control groups, dementia, mental retardation, heart valve disease, rhythm and conduction disorder, pericardial or myocardial disease, congenital heart disease, antiarrhythmic drug, known to affect QT interval or sympathetic nervous system activity identified as drug use.

Triglyceride, whole blood, fasting blood sugar, cholesterol, low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol, high-sensitivity C-reactive protein (Hs-CRP) levels were measured in all subjects included in our study.

Electrocardiography of each case was taken. In these recordings, the filter was 100 Hz, the alternating current filter was 60 Hz, the paper flow rate was 25 mm/s, and the amplitude was 10 mm/mV. Tp-e/QT, QTc interval, Tp-e, and Tpe/QTc were calculated. QT and Tp-e duration measurements were made by the cardiologist using a magnifying glass. The ECGs were scanned into the Computer system and calculations were made. Two cardiologist performed separate, blinded measurements on a subset of ECGs. The heart rate at the time of recording was accepted as the resting heart rate. The interval from the beginning of the QRS complex to the end of the T wave was accepted as the QT duration. The longest QT duration measured from the 12 leads was defined as the maximum QT (QTmax) time, and the shortest QT duration was defined as the minimum QT (QTmin) time. QTd was calculated by subtracting the minimum QT duration from the maximum QT duration. Tp-e time was measured from lead V6. Measured values were corrected for heart rate using the Bazzett formula. Corrected QT time (cQT=QT/√(R–R interval) and corrected Tp-e time (cTp-e=Tp-e/√(R–R interval)) Tpe/QT ratio was calculated.

To calculate the dispersion values, the maximum and minimum values of each interval in the 12 leads were measured. The dispersion (d) values (QTd) of the relevant interval were calculated by subtracting the minimum value from the maximum value. According to the guidelines of the Society of Cardiology, we determined the cutoff value of 480 ms for Long QTC (LQTC) in our study[28].

Statistical Analysis

Statistical Analysis was performed in Statistical Package for Social Sciences (SPSS) program version 24.0 software (SPSS Inc., Chicago, IL). Kolmogorov-Smirnov test was used to evaluate the conformity of continuous variables to normal distribution. Normally distributed data were compared using the independent group t-test and non-normally distributed data using the Mann-Whitney U test. The Chi-square test was used to compare nominal variables. $P<0.05$ and $p<0.01$ values were considered statistically significant.

Results

Our research was conducted with 103 (54 men and 49 women) people. Fifty-one people (24 women and 27 men) were included in the patient group, and 52 people (25 women and 27 men) were included in the control group. Considering the mean age, it was 45.78±10.68 years in the patient group and 48.90±9.63 in the control group. There was no statistically significant difference between the two groups in terms of mean age and gender parameters (p=0.124 and p=0.918,

Table 1. *Comparison of the clinical and demographic data of the participants*

	Patient (n=51)	Control (n=52)	p
Age, Mean. ± Sd	45.78±10.68	48.90±9.63	0.124**
Male	27	27	0.918*
Female	24	25	
Smoker (%)	18 (35.3)	10 (19.2)	0.067*
Diagnosed with hypertension (%)	34(66.7)	35(67.3)	0.945*
Dignosed with diabetes (%)	4(8)	9(17.3)	0.159*
Diagnosed with hyperlipidemia (%)	17(34)	24(46.2)	0.211*
Family history of hypertension (%)	10(20)	11(21.2)	0.885*

Sd: Standart deviation; *: Chi-square test; **: Independent samples t test, Mann-Whitney U testi.

Table 2. *Comparison of the biochemical parameters of the participants*

	Patient (n=51) Mean ± Sd.	Control (n=52) Mean ± Sd.	p
Glucose	99.20±26.48	105.28±35.19	0.304***
LDL	100.87±35.86	114.42±36.75	0.066**
HDL	44.91±10.92	46.90±10.77	0.359**
Total Cholesterol	174.03±42.40	195.52±43.03	0.006***
Triglyceride	166.57±102.54	184.92±105.93	0.292***
Hs-CRP	5.98±13.62	2.91±1.88	0.989

LDL: low-density lipoprotein cholesterol; HDL: High-density lipoprotein cholesterol; Hs-CRP: High-sensitivity C-reactive protein; Sd: Standart deviation: *: Chi-square test; **: Independent samples t test; ***: Mann-Whitney U testi.

Table 3. *Comparison of the ECG findings of the participants*

	Patient (n=51) Mean ± Sd.	Control (n=52) Mean ± Sd.	P
Pulse	84.37±17.98	96.40±18.97	0.810***
Tpe	72.61±14.79	65.87±11.44	0.018***
Tpe/QT	0.19±0.36	0.17±0.34	0.036**
Tpe/QTc	0.17±0.03	0.17±0.12	0.06***
QTD	51.73±21.47	51.75±21.22	0.989*
	n (%)	n (%)	
fQRS	13(25.5)	6(11.5)	0.068*
Long QTC (>480 ms)	21(41)	24(46.2)	0.673*

Sd: Standart deviation; *: Chi-square test; **: Independent samples t test; ***: Mann-Whitney U testi.

respectively) (Table 1). In addition, no significant difference was found between the groups in terms of hypertension, hyperlipidemia and diabetes mellitus diagnoses (Table 1).

Except for 2 of the patients in the patient group, all of them were using 2nd generation antipsychotic drugs. Twenty-seven people were using sodium valproate, a mood stabilizer, and 18 people were using lithium. Six people were under treatment with only 2nd generation antipsychotic medication.

Considering the biochemistry parameters, no significant difference was found between the patient and control groups in terms of glucose, Hs-CRP, triglyceride, LDL, and HDL levels ($p>0.05$). A statistically significant difference was found between the groups in terms of total cholesterol values ($p<0.05$) (Table 2).

Considering the ECG parameters between the groups, there was no statistically significant difference between the two groups in terms of QTc interval ($p>0.05$), Tpe/QTc ($p>0.05$), QTd ($p>0.05$), fQRS ($p>0.05$), while Tp-Statistically significant difference was found between e/QT ($p<0.05$) and Tp-e ($p<0.05$) (Table 3).

Discussion

In this study, no statistically significant difference was found between the groups in terms of age and gender. There was no statistically significant difference between the groups in terms of medical conditions such as smoking, hypertension, hyperlipidemia, diabetes, family cardiac history. The fact that both groups have similar socio-demographic data is important in terms of giving accurate results in our study.

Hyperlipidemia is the primary risk factor for cardiovascular diseases. It is also known that hyperlipidemia is a risk factor for ischemic attack[29]. There is a relationship between total cholesterol level and deaths caused by coronary artery disease[30]. Total cholesterol level should be below 200 mg/dl, low molecular weight lipoprotein (LDL) cholesterol should be below 130 mg/dl, triglyceride value should be below 150 mg/dl, and HDL cholesterol should be 40–60 mg/dl[29]. Low HDL level is an important risk factor for cardiovascular diseases. It has been stated that a 1% decrease in HDL level increases the risk of heart disease by 2–3%. While low HDL levels are an important risk factor for CHD, high levels are considered a protective factor[29]. Considering the blood results, there was no statistically significant difference between glucose, LDL, triglyceride, and HDL levels between the two groups, but a significant difference was found between total cholesterol levels. Metabolic parameters, except for triglyceride values, were within normal limits in both groups.

Although the physiological role of Hs-CRP has not been fully demonstrated, it has been reported to be a marker of cardiovascular risk[30]. Abnormalities in Hs-CRP levels alone have been shown to be valuable in predicting mortality from myocardial infarction or heart disease, congestive heart failure, stroke, atrial fibrillation, peripheral vascular disease and sudden cardiac death. Hs-CRP value less than 1.0 mg/L is considered low risk[31]. Values between 1.0–3.0 mg/L are considered medium risk, and values higher than 3.0 mg/L are considered high risk[32]. According to the results of our study, there was no statistically significant difference between the patient and control groups in terms of Hs-CRP levels, while it was high risk in the patient group compared to the Hs-CRP value, but medium risk in the control group. In the light of the literature information we have given, it can be said that these people are at risk for cardiovascular diseases due to the high levels of triglycerides and Hs-CRP in the patients in the patient group.

When the ECG data were evaluated, there was a statistically significant difference between the two groups in terms of Tpe and Tpe/QT values, but no significant difference was found in terms of QTc, Tpe/QTc, QTd, or fQRS. Since there was a significant difference in Tpe and Tpe/QT between the two groups and the durations were longer in the patient group, we can say that people with a diagnosis of bipolar disorder are at higher risk in terms of cardiac arrhythmia.

In this study, LQTc was seen in 21 (41%) in the patient group and 24 (46.2%) individuals in the control group. But there was no statistically significant difference between the two groups. A systematic review found that antipsychotics (thioridazine, ziprasidone), second-generation antipsychotics (SGAs), (amisulpride and quetiapine) tri– and tetracyclic antidepressants, and some antidepressants (citalopram, fluoxetine, and paroxetine, venlafaxine) are associated with the highest risk for long QTc interval (LQTc)[33]. In our study, our patients were mostly using mood stabilizers and second generation antipsychotics. Medications are only one of several possible risk factors for QTc interval prolongation. There are also well-established non-drug risk factors based on the literature. Non-modifiable risk factors include female sex, advanced age, and metabolizer status[33]. In our study, there was no significant difference between the two groups, except for total cholesterol. Total cholesterol was significantly higher in the control group.

Our study has some limitations. Firstly, the sample group included individuals from only one center. Secondly, disease duration was not evaluated. Another limitation is the low number of cases in the case and control groups. However, this limitation may not be very significant because, in our a priori power analysis, it was sufficient to detect an effect of α=0.05, β=0.80, large (d=0.8), while it was sufficient for the case and control groups to consist of 26 individuals, whereas, in our study, 51 people are in the case group and 52 people are in the control group. It is thought that more precise data can be obtained by further studies with larger sample groups. The fact that structured psychiatric interviews were not conducted on the cases included in the study is another shortcoming of our study.

We analyzed the ECG results in order to determine the biochemical parameters that might be cardiac risk factors and cardiac pathologies in people who were under treatment for bipolar disorder. Considering the blood results, there was no statistically significant difference between glucose, LDL, triglyceride, and HDL levels between the two groups, but a significant difference was found between total cholesterol levels. When the ECG data were evaluated, there was a statistically significant difference between the two groups in terms of Tpe and Tpe/QT values, but no significant difference was found in terms of Qtc, Tpe/QTc, QTd, or fQRS. From the socio-demographic data, it was found that there was no significant difference between the two groups in terms of age and gender. We think that our study may be important because it is the first study to investigate fQRS in patients with bipolar disorder. Despite lack of statistical significance, number of fQRS seems greater in BD group which might propose an increased risk of ventricular arrhythmias if supposed by further larger-scale studies. Our study may guide multicenter studies with large participants to show that fQRS can be a biomarker that can be used to predict cardiac risk in patients with bipolar disorder.

Statement of Ethics

Our institutional human research ethics committee approved this prospective study (Approval no: 26.06.2020-06).

Conflict of Interest Statement

All the authors declare no conflict of interest.

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