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Original Research

Tp-E interval, Tp-E/QT ratio and fragmented QRS parameters in patients with panic disorder

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Abstract

Aim: In the presented research, we intended to appraise ventricular repolarization and factors of myocardial change in patients diagnosed with panic disorder (PD).

Material and Methods: Fifty patients with newly diagnosed panic disorder and 50 healthy individuals as a control group were included in the research. All participants were administered Sociodemographic Data Form, Panic Disorder Severity Scale (PDSS), followed by electrocardiography (ECG).

Results: Tp-e interval, Tp-e/QT ratio and Tp-e/QTc ratio were found to be remarkably higher in PD patients than in the control group (p<0,001). The incidence of fragmented QRS in PD patients (72%) was significantly higher than the rate of fragmented QRS in the control group (36%) (p<0,001). The median PDSS score of PD patients with fragmented QRS on their ECG was 16.0 (13.5-18.5), and the median PDSS score of those without fragmented QRS on their ECG was 13.0 (9.0-16.0), thus there was a statistically remarkable difference between them (p=0.0.05). In PD patients, a moderately positive relationship has been found between PDSS scale score and Tp-e interval, Tp-e/QT ratio and Tp-e/QTc ratio, respectively (p=0.000 r=0.496) (p=0.002 r=0.436) (p=0.008 r=0.369).

Discussion: The study suggests that untreated PD patients may be at high risk in terms of arrhythmic events due to abnormal ventricular conduction and myocardial damage. Tp-e interval, Tp-e/QT ratio and fragmented QRS factors may allow evaluation of subclinical heart disease before the clinical presentation becomes apparent in PD.

Keywords

Panic Disorder, Tp-e Interval, Tp-e/QT, Tp-e/QTc, Fragmented QRS

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Introduction

Panic disorder (PD) is a chronic psychiatric disorder with recurrent panic attacks during which a person presents symptoms associated with the autonomic nervous system such as palpitations, chest pain, shortness of breath, sweating, tremors. These physical symptoms accompanying the attacks indicate increased sympathetic activity and therefore abnormally functioning autonomic nervous system [1]. In addition to the limited information available on a causal relationship between panic disorder and cardiovascular disease (CVD) [2], PD is related with an increased risk of CVD and mortality [3]. In PD patients, PD was found to be associated with CVD, cardiomyopathies [4], arrhythmia and decreases in heart rate variability [2, 5]. Among the arrhythmia markers, Tp-e/QTc ratio, Tp-e/QT ratio and fQRS parameters attract attention as predictors of mortality and morbidity [6, 7].

Fragmented QRS (fQRS) is a finding for the ventricular depolarization disorder that can show damage associated with myocardial fibrosis and can be readily determined in electrocardiography (ECG). It shows a conduction delay caused by myocardial fibrotic tissue. Fibrotic tissue decelerates the electrical conduction rate, causing non-homogeneous ventricular activation. This condition is displayed in the form of a kerf in QRS complex on the ECG and is considered superior to the Q wave in the determination of myocardial scar, and was associated with a short survey after acute myocardial infarction [8, 9]. In a study conducted on patients diagnosed with depressive disorder, the presence of fQRS was associated with the disease period, and it was reported that it could be used to detect subclinical cardiac damage [10].

One way to indicate myocardial repolarization is to measure the T wave. Transmural dispersion (TDR) of Tp-e, the spacing among the top and end of the T wave, is known to be a predictor of ventricular repolarization. The presence of TDR shows us that ventricular repolarization does not take place synchronously throughout the overall ventricle [11]. An increased Tp-e spacing and a high Tp-e/QT ratio in electrocardiography are remarkable indicators for the development of ventricular arrhythmia in electrocardiography [12]. Tp-e interval, Tp-e/QT ratio were investigated in schizophrenia sufferers, and ventricular arrhythmia has been shown to be predetermined in this patient group [13].

Some clinical studies have shown an increased risk of demise from cardiovascular illnesses or cardiovascular causes in patients diagnosed with panic disorders [14]. Therefore, we intended to assist the early diagnosis of subclinical patients by evaluating ventricular activation factors such as Tp-e interval, Tp-e/QT ratio and fQRS in PD patients.

Material and Methods

This study was approved by Fırat University, Medical Faculty Ethics Committee. (Date: 04.02.2021, Number: 2021/02-01). Informed consent was obtained from the individuals who participated in this study.

The research was planned as case-control. Local ethics board approval has been obtained for the study. Fifty patients with newly diagnosed panic disorder according to the diagnostic criteria of the Diagnostic and Statistical Manual of Mental Disorders-5 (DSM-5) were included in the study, while 50 healthy individuals with socio-demographic characteristics similar to the patient group were recruited as control groups. After completing the diagnostic and treatment phases with regard to the patient's complaint, a face-to-face interview was conducted with the participants for about 15 minutes. After the participants were informed about the goal of the research prior to the survey, their written and verbal informed consent was obtained. A socio-demographic Data Form and the Panic Disorder Severity Scale were applied to all participants. After applying the scales, all participants underwent non-interventional electrocardiography (ECG).

Criteria for inclusion in the patient group

The containment conditions for the case group were as follows: diagnosis with panic disorder according to DSM-5 criteria for the first time, age range of the patients between 18-65 years, literacy requirement, signing an informed consent form, no another accompanying psychiatric disorder, no known drug treatment, no systemic and metabolic disease, no dementia, mental retardation, cognitive impairment or neurological disease history, not current psychiatric treatment and no use of alcohol and substance abuse in the last 6 months, no known cardiovascular disease (no history of cardiac failure, valvular heart disease, cardiomyopathy, myocardial infarction, and cardiovascular diseases such as bundle branch block and arrhythmia, no history of bypass surgery, stent implantation, pacemaker implantation and hypertension) and the nonexistence of pathology in ordinary blood and biochemical tests.

Criteria for inclusion in the control group

The containment conditions for the control group were as follows: age 18-65 years, no history of another psychiatric disorder, no history of medical treatment, no serious neurological diseases and systemic diseases, nonexistence of pathology in ordinary blood and biochemical tests, absence of any heart diseases.

Measurement of Tp-e/QT, Tp-e/QTc and fQRS on ECG

Regular 12-lead ECG monitoring was applied in outpatient ECG rooms for all patients and controls. The room was isolated from noise, so the ECG records were not influenced by the exterior determinants. Recordings were carried out when the participant achieved sufficient natural breathing (after a waiting time of 5-10 minutes), when the participant was in a supine situation and was not permitted to talk during the ECG recording. All participants were applied a regular 12-lead body surface ECG (Nihon Kohden, Tokyo, Japan) at a paper speed of 50 mm/s. The Tp-e interval, QT and QTc interval, Tp-e/QT and Tp-e/QTc ratio, and the presence of fragmented QRS were manually appraised by 2 cardiologists. Special ECG reading rulers were used to obtain a precise measurement. The QT interval was appraised in milliseconds from the first deviation of the QRS complex up to the T wave reached isoelectric line. The QTc interval was computed using the Bazett technique (QTc = QT/VRR). The Tp-e interval was calculated by measuring the time in milliseconds from the top of the T wave to the point where the deflection line intersects the isoelectric line. These assessments were made from precordial leads, which are most suitable for measurement. Cases with significant U-wave or negative or biphasic T wave in surface ECG were excluded from the study.

Detection of Fragmented QRS in ECG

Fragmented QRS was described as an extra R wave (R'), or notch in the R or S wave in at least 2 successive leads that do not display typical branch block characteristics and match a coronary blood supply area [15]. Cases showing a typical branch block pattern were excluded from the study.

Scales used in the study:

1) Sociodemographic Data Form: It is prepared by researchers for the purposes of the study. It is a form that includes demographic data such as age, marital status, educational status, place of residence, working status and economic situation, as well as clinical evaluation questions such as how many years has the patient suffered from psychiatric disorders, presence of psychosocial stress factor, history of inpatient treatment, and use of tobacco or alcohol.

2) Panic Disorder Severity Scale: The purpose of the panic disorder severity scale is to detect symptom severity in panic disorder with or without agoraphobia, the frequency of panic attacks, to measure limited symptom attacks, the severity of anticipatory anxiety, phobic avoidance, and functional impairment. The evaluation is made by taking the last month into account. It consists of seven items. The lowest score that can be obtained from the scale is 0 and the highest score is 28 [16].

Statistical analysis

The analysis is evaluated using the SPSS 22 package program (Statistical Package for Social Sciences; SPSS Inc., Chicago, IL). Descriptive data were shown with n, % values in categorical data and mean ±standard deviation, median, interquartile range values (25-75 percentile values) in continuous data. The Chi-square analysis (Pearson's Chi-square) was administered to compare categorical factors between groups. The suitability of continuous variables for normal distribution was assessed using the Kolmogorov-Smirnov test. The independent Samples t-test was used to compare factors that matched normal distribution between the two groups, and the Mann-Whitney U test was administered to compare variables that were not normally distributed between the two groups. Spearman's correlation test was used to investigate the link of continual factors. In the evaluation, the level of statistical importance was taken as p<0.05.

Results

The research consisted of 100 people in total, 50 patients with panic disorders and 50 healthy individuals as a control group. The mean age of the case group was 35.9±9.4 (min=20-max=60) years and the mean age in the control group was 34.5±9.3 (min=18-max=60) years, and there was no statistically significant difference between the groups (p=0.469). It was observed that 56% of the participants in the case group were male, and 40% of the participants in the control group were male. There was no significant difference in gender between the groups (p=0.109). It was observed that the educational status of the patient group was notably higher than that of the control group (p=0.03). The probability of being a housewife in the control group (50%) was significantly higher than in the case group (20%) (p=0.007). There were no significant differences between the groups in terms of marital status (p=0.224), place of residence (p=0.061), economic status (p=0.811), family history of heart disease (p=0.817) and smoking (p=0.509) (Table 1).

The PDSS score of the patient group was significantly higher than that of the control group (p<0,001). The Tp-e interval, Tp-e/QT ratio and Tp-e/QTc ratio in the case group were significantly higher than in the control group (p<0,001). The incidence of fragmented QRS in the case group (72%) was significantly higher than the incidence of fragmented QRS (36%) in the control group (p<0,001) (Table 2) (Figures 1, 2).

In the case group, the median PDSS score of those who displayed fragmented QRS on the ECG was 16.0 (13.5-18.5), and the median PDSS score of those whose ECG did not present a fragmented QRS on the ECG was 13.0 (9.0-16.0), thus there was a statistically remarkable difference between them (p=0.0.015).

It was established that there was a moderate positive relationship between PDSS scale score and Tp-e interval, Tp-e/QT ratio and the Tp-e/QTc ratio in the case group (p=0.000 r=0.496), (p=0.002 r=0.436), (p=0.008 r=0.369) (Table 3) (Figure 3).

Table 1. Comparison of the sociodemographic data of the case and control groups

	Case		Control		p*
	n	%	n	%	
Age, Mean±SS	35,9±9,4		34,5±9,3		0,469**
Gender					
Male	28	56,0	20	40,0	0,109
Female	22	44,0	30	60,0	
Marital status					
Single	10	20,0	14	28,0	0,224
Married	40	80,0	34	68,0	
Education status					
Widower/divorced	0	,0	2	4,0	0,03
Illiterate	0	,0	1	2,0	
Literate	0	,0	3	6,0	
Primary school	9	18,0	17	34,0	
Secondary school	17	34,0	8	16,0	
High-school	15	30,0	9	18,0	
University	9	18,0	12	24,0	
Place of residence					
Village	2	4,0	8	16,0	0,061
Town	12	24,0	6	12,0	
City	36	72,0	36	72,0	
Economic situation					
Low	12	24,0	10	20,0	0,811
Middle	33	66,0	36	72,0	
High	5	10,0	4	8,0	
Profession					
Housewife	10	20,0	25	50,0	0,007
Working	25	50,0	15	30,0	
Unemployed	15	30,0	10	20,0	
Family history of heart disease					
Yes	12	24,0	13	26,0	0,817
No	38	76,0	37	74,0	
Smoking					
Yes	13	26,0	16	32,0	0,509
No	37	74,0	34	68,0	

* Chi-square analysis, ** Independent Samples t-test has been applied. SS: standard deviation

Table 2. Comparison of the scale score and ECG findings of the case and control group

	Case Median (IQR)	Control Median (IQR)	p
PDSS	16,0 (13,0-18,0)	2,0 (1,0-4,0)	<0,001*
Tp-e interval, Mean±SS	86,0±13,2	71,3± 12,4	<0,001**
Tp-e/QT rate	,236 (,214-,272)	,196 (,171 -,219)	<0,001*
Tp-e/QTc rate, Mean ±SS	0,218±0,032	0,173±0,026	<0,001**
Fragmented QRS			
Yes	36 72,0	18 36,0	<0,001***
No	14 28,0	32 64,0	

* Mann-Whitney U test, ** Independent Samples t-test,
*** Chi-square analysis has been applied.
PDSS: Panic disorder severity scale, SS: standard deviation

Table 3. Correlation of the scale score of the case group with ECG findings

	PDSS	
	r	p
Tp-e interval	,496	,000
Tp-e/QT rate	,436	,002
Tp-e/QTc rate	,369	,008

PDSS: Panic disorder severity scale

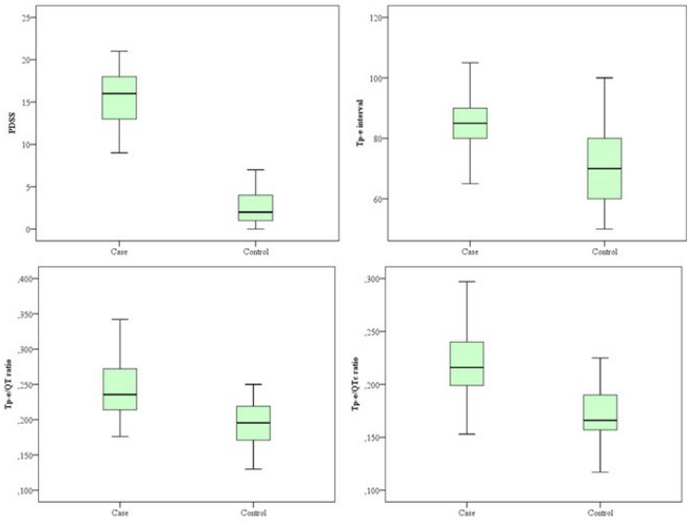

Figure 1. Comparison of the scale scores and ECG findings of the case and control groups.

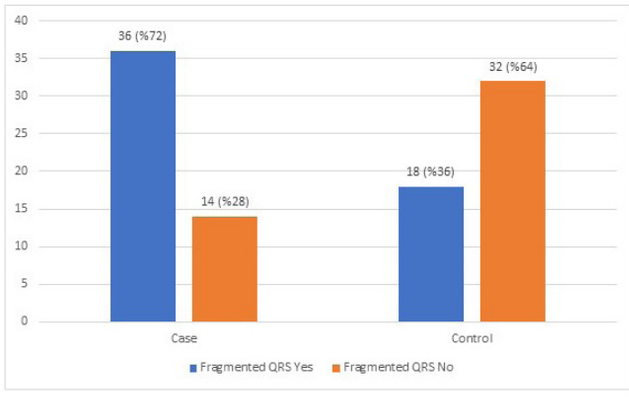

Figure 2. Comparison of the fragmented QRS incidence of the case and control groups.

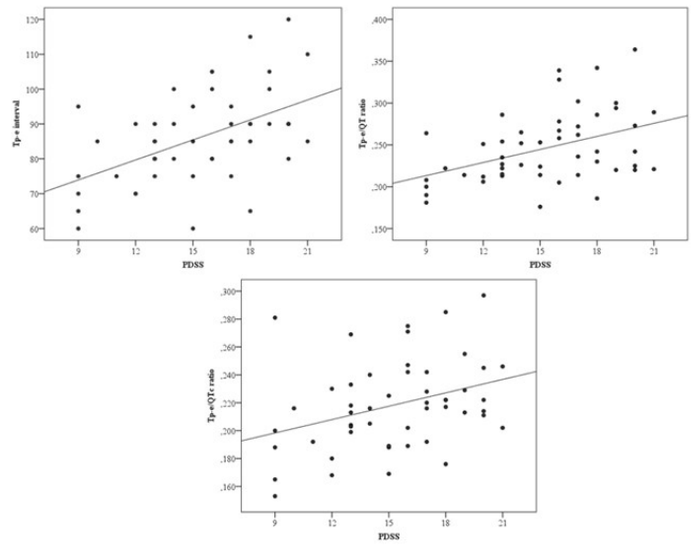

Figure 3. Correlation between the scale score of the case group and ECG findings.

Discussion

One of the most important findings of our research is that the Tp-e interval, Tp-e/QT ratio and Tp-e/QTc ratio, which are TDR markers in the PD patient group, are significantly higher and there is a moderate positive relationship between these parameters and symptom severity. Another finding is that the incidence of fQRS in PD patients was 72%, which is higher than in the control group, and the symptom severity in PD patients with fQRS was higher than in those without fQRS. As far as we know, our research is the first in this field to show the variability in fQRS among patients with PD. All these findings may demonstrate an increased risk of cardiac arrhythmia in PD patients. While a high risk of cardiovascular mortality was mentioned in anxiety disorders in general [17], PD was specifically related to an increased risk of CVD and mortality [3]. In a research involving 35 patients with panic disorders, higher rates of myocardial alterations were detected in patients, including left ventricular hypertrophy, and it was mentioned that care should be taken in terms of subclinical myocardial alterations in these patients [4]. In a prospective study conducted on 5,303 people in 2010, it was found that non-fatal CVD developed among patients with anxiety disorders, including PD, during 3 years of follow-up [18]. Fleet et al. [19] reported that panic attack can induce myocardial perfusion defects in patients with CVD and PD, despite the use of cardiac medication, by using the panic-inducing effect of carbon dioxide.

Tp-e interval and high Tp-e/QT ratio are cited as crucial factors in electrocardiography to forecast the development of ventricular arrhythmia in clinical trials, and their increased values have been related with cardiovascular mortality [12]. The same parameters were studied in schizophrenia patients, and it was demonstrated that Tp-e interval, Tp-e/QT could predetermine ventricular arrhythmia in this patient group [13]. In a recent study conducted on 40 PD patients, it was found that Tp-e interval, Tp-e/QT and Tp-e/QTc rates increased significantly compared to the control group, but fQRS was

not evaluated in this patient group [20]. In our study, these parameters with ventricular arrhythmia markers in patients with PD were found to be significantly higher than in a healthy individual in the control group, which is consistent with previous findings. In light of these findings, it may be necessary to refer to the heart rate connection between panic disorder and the autonomic nervous system. Increased sympathetic activity and decreased vagal tonus changes may explain our findings in PD patients.

QTc and Tp-e interval is directly related to heart rate. Evidence for a strong association between PD and cardiomyopathies, arrhythmia and reduced heart rate variability (HRV) has been presented in previous studies [2, 4-5]. Ventricular repolarization, which plays a considerable role in the occurring of ventricular arrhythmia, is controlled by the autonomic nervous system. It has been shown that patients with PD have a higher rate of autonomic nervous system disorders such as decreased vagal tonus and increased sympathetic system activation [1]. Heart rate variability is a vagal tonus marker and an indicator of autonomic nervous system activity. The reduction in HRV is a predictor of cardiac events. In the study conducted by Hovland et al., decreased heart rate changeability has been found in patients with PD, and they also reported that this was related with symptom intensity of panic disorder [21]. In our study, a moderately positive relationship was found between symptom severity of PD patients and the Tp-e interval, the Tp-e/QT ratio, and the Tp-e/QTc ratio. Although the Tp-e interval and QT are affected by heart rate, the Tp-e/QT ratio and the Tp-e/QTc ratio are not affected. This suggests that PD patients may be at increased risk of ventricular arrhythmia in proportion to the severity of the disorder.

Another arrhythmia predictor, fQRS, represents myocardial ischemic areas [6]. In a study devoted to depressive disorder, the presence of fQRS was associated with the disease, and fQRS was thought to be a useful tool for detecting subclinical cardiac damage in these patients [10]. In our study, patients with fQRS in PD patients had a higher symptom load. In their research, Esler et al. identified various cardiac arrhythmia, including atrial fibrillation, in emergency room admissions in PD patients, and reported that patients with severe chest pain were at cardiac risk.

During a panic attack, an intense sympathetic discharge occurs, as well as strong bodily sensations such as anxiety, shortness of breath, palpitations and chest pain. Thus, it is seen that panic attack causes real ischemia, which may be associated with adrenaline-mediated coronary vasospasm in CVD patients. Due to increased ventricular contractions, the increase in the need for myocardial O2 can lead to a possible myocardial ischemia. It was also determined that there was a 7-fold increase in serotonin cycle in patients when there were no panic attacks during rest [22]. These findings are likely related to the neurochemical infrastructure of the relationship between FQRS and PD.

The strength of our study is that the sampling consists of patients who had been diagnosed with PD for the first time and who did not have additional drug use. Antipsychotics cause anticholinergic effects with some substances that induce myocardial fibrosis and cause prolongation of QTc [23]. According to the TILDA study, one of the largest studies ever on antidepressants, autonomic imbalance antidepressants were found to be more associated with antidepressant medications [24]. In this research, the fact that the incidence of fQRS in PD patients who were treated with drugs was as high as 72%, and other ventricular arrhythmia parameters were significantly higher, suggests that these patients may be at risk of ventricular arrhythmia regardless of medication factor.

The main limitations of our study are the low number of cases, which is cross-sectional, and the inability to quantify myocardial fibrosis.

Conclusion

The findings of our study suggest that untreated PD patients may be at high risk for arrhythmic events due to abnormal ventricular conduction and myocardial damage. The Tp-e interval, Tp-e/QT ratio, and fragmented QRS parameters pose significant potential for noninvasive easy measurements that can evaluate subclinical heart disease without clinical clarification in PD.

Scientific Responsibility Statement

The authors declare that they are responsible for the article's scientific content including study design, data collection, analysis and interpretation, writing, some of the main line, or all of the preparation and scientific review of the contents and approval of the final version of the article.

Animal and human rights statement

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. No animal or human studies were carried out by the authors for this article.

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Conflict of interest

None of the authors received any type of financial support that could be considered potential conflict of interest regarding the manuscript or its submission.

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