

## Electrocardiographic Evaluation of the Ventricular Arrhythmia Risk in Patients Diagnosed With Schizophrenia

### ABSTRACT

**Objective:** The purpose of this study was to examine electrocardiographic ventricular arrhythmia predictors in patients with schizophrenia by comparing with healthy controls.

**Methods:** The study included 100 patients with schizophrenia and 100 healthy controls. Electrocardiography (ECG) was performed on all participants in resting position. T-wave peak to end (Tp-e), QT ranges, P-wave dispersion (Pd), and R-R range were measured. Then, the Schizophrenia Positive and Negative Syndrome Scale (PANSS) and the Calgary Depression Scale for Schizophrenia (CDSS) were applied to the schizophrenia group.

**Results:** The PANSS positive symptom subscale was calculated as 10.41 (SD = 2.27), the negative symptom subscale was calculated as 14.44 (SD = 5.42), and the overall functionality level was calculated as 27.04 (SD = 5.43). The mean CDSS score was determined to be 3.74 (SD = 2.15). No differences were detected in the heart rate measurements of the patient and control groups in ECG results ( $P = .427$ ). The minimum QT interval and minimum Tp-e wave times were found to be low in the patient group ( $P < .001$  for both intervals). Corrected QTc dispersion, Pd, Tp-e dispersion, and QT dispersion were found to be higher in the patient group than in healthy controls ( $P < .001$  for all intervals).

**Discussion:** Based on our results, it is possible to speculate that patients with schizophrenia are at a risk of developing cardiac arrhythmia and cardiac dysfunction if they do not receive treatment. For this reason, clinicians should pay attention to cardiac transmission problems when organizing the treatment of patients. Further studies should be conducted to determine cardiac problems in patients with schizophrenia.


**Keywords:** Schizophrenia, electrocardiography, QT-interval


### Introduction

Schizophrenia is a serious psychiatric disorder that has significant effects on both individuals and society owing to its early onset and its nature. Although the results of the disease are not as negative as widely believed, more than half of the individuals diagnosed with it have intermittent and long-term psychiatric problems, and the disease becomes chronic and disability occurs at a rate of approximately 20%.<sup>1</sup> Schizophrenia has been reported by the World Health Organization as the mental illness that causes loss of abilities at the highest rate.<sup>2</sup> With the nature and chronic status of the disease, problems of compliance occur in work and social life. The burden on the community is also quite high, with frequent hospitalization, social support, and treatment costs at an estimated 80% to 90% rate.<sup>3,4</sup> Compared with the general population, life expectancy has decreased by as much as 15 years now.<sup>5</sup> The main cause of this early average is shown to result from cardiovascular diseases.<sup>4,6</sup>

In patients with schizophrenia, cardiac diseases are diagnosed 1.5 to 2 times more often.<sup>7</sup> The way of life and habits of the patients are considered to be contributing factors for cardiac diseases, including smoking, alcohol, caffeinated drinks, not following physical exercise programs, and eating high-calorie and sugar-rich foods.<sup>7-9</sup> Compared with the general population, it is also report-

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ed that there is an increase in sudden cardiac death risk in patients with schizophrenia.<sup>10</sup> In this respect, electrocardiography (ECG) is a non-invasive and widely used cardiological evaluation tool.<sup>11</sup> It was reported in the ECG studies on mental diseases in the literature that there were variations in the QT range, QTc, QT, and P-wave dispersion (Pd) times. The mental health diseases on which these studies were conducted were obsessive-compulsive disorder, panic disorder, bipolar disorder, hypochondriasis, and schizophrenia.<sup>8,12-15</sup> In the light of all these data, the purpose of this study was to examine the risk predictors for electrocardiographic ventricular arrhythmia in patients with schizophrenia who did not have drug use by comparing with healthy controls.

## Methods

### Participants and Procedure

Patients between the ages of 18 and 55 years receiving treatment at Elazığ Mental Health and Diseases Hospital who were diagnosed with schizophrenia according to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition criteria, and who had quit their old recommended drugs at least one month ago were included in the study after it was determined that they volunteered, were literate, and could provide written consent. People with the low general condition, chronic liver disease, chronic renal failure, mental retardation, and alcohol-substance use disorders were excluded from the study. Those who had known coronary artery disease that might affect ECG results, heart failure, moderate or severe heart valve disease, cardiomyopathy, heart rhythm and transmission disorder, a permanent pacemaker, hyperlipidemia, hypercholesterolemia, obesity, and diabetes mellitus and people receiving anti-arrhythmic treatment were not included in this study. In addition, people who were receiving any psychiatric medications were also excluded from the study. People who matched the patient group in terms of demographic data but who did not already have any psychiatric illnesses and met the inclusion criteria were included in the study as the healthy control group. For the healthy control group, those who had known coronary artery disease that might affect ECG results, heart failure, moderate or severe heart valve disease, cardiomyopathy, heart rhythm and transmission disorder, a permanent pacemaker, and hyperlipidemia were not included in this study. The study was approved by Local Ethical Board of Gaziosmanpaşa University and was implemented in accordance with the Helsinki Declaration (Approval Date: June 18, 2020; Approval Number: 83116987-308; 20-KAEK-049).

All participants signed written informed consent forms. Thereafter, the Sociodemographic Data Form, the Schizophrenia Positive and Negative Syndrome Scale (PANSS), and Calgary Depression Scale for Schizophrenia (CDSS) were applied to the schizophrenia group.

### MAIN POINTS

- *P-wave maximum and P-wave dispersion rate were prolonged in schizophrenia patients*
- *QTc minimum, maximum and dispersion rate prolonged in patients with schizophrenia.*
- *Tp-e wave maximum rate and Tp-e dispersion were calculated as high in the schizophrenia patient group.*
- *It was found that the Tp-e/QTc ratio was extended in the schizophrenia group.*

## Measures

**Sociodemographic Data Form:** Prepared by the researchers, this form included questions on age, marital status, education level, and working and economic status and clinical evaluation questions such as duration of psychiatric disease, inpatient treatment history in the service, and alcohol or smoking status required treatment in the family.

**Positive and Negative Syndrome Scale:** PANSS is a 30-point and 7-score semistructured interview scale used for rating severity in patients with schizophrenia. Seven items of the scale are about the positive symptom subscale, 7 items are about negative symptom subscale, and 16 items are about the general psychopathology subscale. It was developed by Kay et al.<sup>16</sup> and was adapted into Turkish by Kostakoğlu et al.<sup>17</sup>

**Calgary Depression Scale for Schizophrenia:** CDSS is used to assess the level and severity of depressive symptoms in patients with schizophrenia. The total score consists of 9 items, ranging from 0 to 3, and the total score range is from 0 to 27. It was developed by Addington et al.<sup>18</sup> and was adapted into Turkish by Oksay et al.<sup>19</sup>

Laboratory data such as hemogram, glucose, sodium, potassium, magnesium, urea, creatinine, thyroid functions, total cholesterol, low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol, and triglyceride values of all participants were studied. Then, ECG was performed on all participants. ECG evaluation consisted of routine ECG monitoring in all participants included in the study with 12-derivation ECG with Nihon Kohden Cardiox ECG-9132. In these records, the filter was 100 Hz, the alternative current filter was 60 Hz, the paper flow rate was 25 mm/s, and the amplitude was 10 mm/mV. ECG records were evaluated by 2 different cardiologists who were unaware of the clinical data of the patients. The electrocardiograms were transferred into a computer by using the scanner and were viewed with x400% using the Adobe Photoshop CS2 Program (Adobe Systems Inc.; San Jose, California, USA).

T-wave peak to end (Tp-e) and QT ranges were measured and calculated. Each measurement was repeated at least twice by 2 different researchers, and the mean values of the data were used. QT and R-R measurement ranges were obtained from V2 to V5 derivations. QT range was defined as the time from the onset of QRS to the point where the T-wave returned to the isoelectric line at the end of the T-wave. R-R range was measured as the average of 3 consecutive pulse complexes, and Bazette's Formula was used to calculate the heart rate and QTc range. Those who had U-wave in their ECG were excluded from the study. The range between the electrocardiographic T-wave peak corresponding to transmural dispersion of the repolarization and the range, in the end, was measured as Tp-e. Pd was calculated by subtracting minimum P-wave time from maximum P-time.

### Statistical Analysis

Statistical Package for Social Sciences for Windows 20 (IBM Corp.; Armonk, NY, USA) was used in the analyses. The qualitative variables of the study were whether there were relationships among demographic data. Cross-table and chi-square tests were used to evaluate whether there was a relationship between qualitative variables. Quantitative variables were the scores from the scales applied to the participants and ECG measurement results. To evaluate whether there was a relationship between quantitative variables, the impor-

tance test of the difference between 2 mean values was used. *P* values were considered to be statistically significant when  $< .05$ .

## Results

A total of 100 patients and 100 healthy control group individuals who met the criteria for inclusion and who had ECG measurements before starting treatment were included in our study. No statistically significant differences were detected between the gender, age, residence, and educational status of the participants ( $P > .05$ ). Participants' characteristics are presented in Table 1. The smoking participants in both groups smoked 1 packet/day. Although alcohol or substance use did not exist in the healthy control group, 9 participants (9%) in the patient group had alcohol intake once a week.

**Table 1. Demographical Characteristics of Participants**

	Control group (n = 100)	Schizophrenia group (n = 100)	<i>P</i>
Age, years, mean (SD)	41.08 (11.31)	40.92 (10.11)	.916
Gender (female/male)	19/81	14/86	.601
Marital status (married/single)	39/61	15/85	.041
Educational status			
Primary school graduate	60	50	.055
High school graduate	27	30	
University graduate	13	20	
Working status			
Full-time job	30	0	$< .001$
Part-time job	16	2	
Unemployed	52	85	
Retired because of disability	0	13	
Economic status			
Low/moderate/high	60/25/15	89/5/6	$< .001$
Disease year, mean (SD)	-	10.70 (9.45)	-
Chi-square test was used for calculations. Values in the table are given as %.			

**Table 2. Analysis of Quantitative Variables of Participants**

	Control group (n = 100), mean (SD)	Schizophrenia group (n = 100), mean (SD)	<i>P</i>
Heart rate	82.94 (11.6)	84.34 (13.23)	.427
QTmin	327.46 (13.45)	317.2 (10.29) <sup>a</sup>	$< .001$
QTmax	351.39 (13.04)	353.9 (11.98)	.157
QTd	24.05 (4.54)	35.44 (8.56) <sup>a</sup>	$< .001$
Pmin	73.7 (2.62)	73.66 (2.73)	.923
Pmax	91.37 (4.08)	100.29 (5.61) <sup>a</sup>	$< .001$
Pd	17.67 (3.64)	26.74 (5.84) <sup>a</sup>	$< .001$
Tp-e min	70.92 (3.53)	67.13 (4.72) <sup>a</sup>	$< .001$
Tp-e max	84.83 (5.35)	89.16 (8.49) <sup>a</sup>	$< .001$
Tp-e d	13.91 (3.32)	22.03 (5.66) <sup>a</sup>	$< .001$
QTc min	375.13 (7.37)	388.67 (7.47) <sup>a</sup>	$< .001$
QTc max	399.81	434.17 (10.31) <sup>a</sup>	$< .001$
QTc d	24.68 (4.46)	45.5 (6) <sup>a</sup>	$< .001$
Tp-e / QTc	0.21 (0.01)	0.20 (0.2) <sup>a</sup>	.002

Abbreviations: QT, electrocardiography QT interval; P, Electrocardiography P wave; Tp-e, Electrocardiography Tp-e wave; significance test for difference between two mean values was used.

<sup>a</sup> $P < 0.05$ .

The patients were admitted and received treatment at least 1 month ago because they had stopped their medication. No differences were detected in the heart rate measurements in the ECG results of the patient group and healthy control group ( $P = .427$ ). QT interval minimum and Tp-e wave minimum duration were found to be low in the patient group (both parameters  $P < .001$ ). The values of patients with schizophrenia were high in all other parameters compared with those of healthy control group ( $P < .001$  for all values) (Table 2). No statistically significant differences were detected in the routine examinations between total cholesterol, HDL cholesterol, LDL cholesterol, and triglyceride values of the participants (*P* values were .089, .150, .521, .106, and .729, respectively).

## Discussion

It was shown in our study that the risk of ventricular arrhythmia increased before treatment in patients with schizophrenia. In our results, QT interval, P wave, Tp-e time, and QTc interval dispersions were higher in patients than in healthy controls. QT interval and Tp-e duration minimum values were calculated to be lower in the patient group. The P-wave minimum value and maximum QT interval value was not different between the groups. All other ECG parameters were calculated to be extended in the patient group.

ECG is a non-invasive and widely used cardiological evaluation tool. Evaluation of T-wave with ECG is one of the most important components of ventricular repolarization. In the absence of structural heart disease, ventricular repolarization abnormalities are associated with cardiac arrhythmias. Studies showed ventricular repolarization markers such as QT and QTc range, QT dispersion (QTd), Tp-e range, and Tp-e/QT ratio can predict life-threatening cardiac arrhythmias.<sup>11</sup> The extension in QT interval and QTc periods, which can easily be detected with ECG, and torsades de pointes (ventricular polymorphic tachycardia, which can cause syncope and even sudden cardiac death) are some of the risk parameters that can be used. In fact, the extension of the QT interval was reported to be a risk factor for cardiac and coronary diseases and sudden cardiac death.<sup>20</sup> In the literature, a maximum QTc interval value being 450 ms in men over 470 ms in women is considered to be clinically important.<sup>21</sup> In our results, the maximum QT interval value was 353.9 (SD = 11.98) in the patient group. However, the corrected QTc interval value was found to be 434.17 (SD = 10.31), which was considered clinically important. Studies were conducted in the literature reporting gender diversity for the QTc interval. It was reported that men had shorter values than women.<sup>22,23</sup> In our results, in contrast, because most patients with schizophrenia were male, the control group was also selected in male gender, and no differences could be determined between genders. In a study that examined ECG results in patients with schizophrenia, the QTd value of patients was found to be approximately twice as high as healthy controls.

QT dispersion was calculated in this study; corrected QT values and QT maximum and QT minimum values were not given. In addition, ECG was carried out when the patients were under atypical antipsychotic treatment.<sup>8</sup> In our results, the corrected QTc dispersion value was similarly approximately twice as high as that for healthy controls. It was found to be 24.68 (SD = 4.46) in healthy controls and 45.5 (SD = 6) in the patient group. Our patient group terminated their medication at least 1 month ago, and the ECG was carried out before antipsychotic therapy began. Similar to a previous study, the maximum QT

value was found to be extended compared with healthy controls.<sup>24</sup> Although our results did not differ compared with healthy controls at maximum QT value, corrected QTc values (maximum-minimum) and both QT and QTc dispersion values were higher than healthy controls.

The extension in P-wave time, which can be seen mostly in right atrial dilatation, is an ECG finding evaluating the inter- and intra-atrium times and the heterogeneous distribution of sinus impulses in atria that are prone to fibrillation.<sup>25</sup> Pd is calculated by measuring the distance between the longest and shortest P-value. It was reported that Pd extension is a sensitive and specific precursor for atrial fibrillation and can be used as an indicator for paroxysmal atrial fibrillation.<sup>26</sup> In a study reported in the literature, ECG measurements were evaluated in 30 patients with schizophrenia. As a result of the study, Pd was calculated as extended; and no data were reported on P-wave maximum and minimum values.<sup>8</sup> In our results, Pd was found to be extended similar to this study. In our results, although the P-wave minimum value was not different from that of healthy controls, the maximum value was extended.

In ECG, Tp-e value, which is the T-wave peak-end point interval, shows ventricular repolarization. In addition, the Tp-e/QTc ratio is a parameter used to evaluate ventricular arrhythmogenesis.<sup>27</sup> In some studies, a relationship was reported between Tp-e range and the increase in the Tp-e/QTc ratio and the risk of fatal ventricular arrhythmia.<sup>28,29</sup> QT and Pd were examined in studies conducted with ECG results in psychiatric patients. Tp-e interval and Tp-e/QTc ratio were dealt with in fewer studies. In these studies, the effectiveness of treatment in ECG measurements was evaluated.<sup>29-31</sup> In our results, it was determined that patients with schizophrenia who did not start medical treatments had minimum and maximum values and extended Tp-e dispersion. The Tp-e/QTc ratio is much more reliable than other parameters in showing the ventricular arrhythmia risk.<sup>32</sup> In our results, it was found that the Tp-e/QTc ratio was extended in the patient group.

Although the mechanism of schizophrenia cannot be fully explained, the risk for cardiological diseases has been reported to increase. It was determined that metabolic syndrome rates increased, and depending on this, the risk of cardiological disease also increased in patients undergoing antipsychotic treatment.<sup>33</sup> Similar to our results, it was found that Pd was extended, regardless of the antipsychotic treatment used in patients with schizophrenia.<sup>34</sup> In contrast, Pd was defined as an independent risk factor for atrial fibrillation, which is also a significant cause of morbidity and mortality.<sup>35</sup> Because of the nature of sudden cardiac death and schizophrenia disease, the data on drugs used in these are contradictory. General information is that typical antipsychotics increase drug-related arrhythmia.<sup>8</sup> In a wide series on atypical antipsychotics in drug-related arrhythmia, a fairly high probability was reported for sertindole although it was zero for olanzapine.<sup>36</sup> In one study, it was determined that QTd and T-wave abnormalities were related with mood regulators, not with antipsychotic treatment.<sup>37</sup> In our results, none of the patients had mood-regulating drug use. They had left their antipsychotic treatment at least 1 month ago, and the treatment that was used was atypical antipsychotic treatment.

The first of these limitations is the relatively inadequate number of samples. Other limitation was failure to determine the effects of previous antipsychotic treatment on ECG. Finally, the genders were not distributed in an equal range and the study had a cross-sectional na-

ture, which limits the generalization and interpretation of the results we obtained.

P wave, QTc and QTc dispersion, and Tp-e/QTc rate, which are important markers to predict ventricular arrhythmogenesis, ventricular fibrillation, and atrial fibrillation, were observed to be prolonged in patients with schizophrenia compared with healthy controls. On the basis of the results we obtained, it is possible to speculate that patients with schizophrenia are at a risk of developing cardiac arrhythmia and cardiac dysfunction risk. For this reason, it is recommended to physicians to be careful regarding cardiac conduction problems when organizing the treatment of patients.

**Ethics Committee Approval:** Ethics committee approval was received for this study from the Ethics Committee of Gaziosmanpaşa University (Date: June 18, 2020; Approval Number: 83116987-308; 20-KAEK-049).

**Informed Consent:** Informed consent was obtained from the patients who participated in this study.

**Peer-review:** Externally peer-reviewed.

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**Conflict of Interest:** The authors have no conflict of interest to declare.

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