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## QT dispersion and P wave dispersion in schizophrenia

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### ABSTRACT

**BACKGROUND:** The difference between maximum QT (QTmax) and minimum (QTmin) on electrocardiography (ECG) is known as QT dispersion (QTd). An increase in QTd carries the risk of ventricular arrhythmia and subsequent death. P wave dispersion (Pd) shows the difference between maximum P (Pmax) and minimum P (Pmin). Prolonged P wave duration and an increase in Pd are a risk for irregular electrical transmission and atrial fibrillation.

**OBJECTIVES:** The aim of this study was to examine QTd and Pd values which indicate atrial fibrillation and ventricular arrhythmia in schizophrenia patients with whom cardiovascular diseases (CVD) are seen at a higher rate than the general population.

**METHOD:** The patient group consisted of 30 male patients diagnosed with schizophrenia according to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) and receiving treatment either as inpatients or outpatients in the Mental Health and Diseases Hospital. The patient group had no other psychiatric, neurological or physical disease. The control group comprised 30 age-matched healthy males with no history of neurological, psychiatric, or physical disease.

**RESULTS:** The cases in both groups were all males and there was no difference between the groups in respect of age. Corrected QTd was determined as  $25.55 \pm 13.18$  (ms) in the control group and  $54.26 \pm 8.46$  (ms) in the patient group ( $p < .001$ ). Pd was determined as  $36.22 \pm 10.08$  (ms) in the control group and  $46.32 \pm 5.87$  (ms) in the patient group ( $p < .001$ ). The differences in the values between the groups were statistically significant.

**DISCUSSIONS:** The QTd and Pd values which show increased CVD risk were found to be significantly greater in schizophrenia patients than in the healthy control group. However, there is a need for further studies to determine whether this is a result of the nature of schizophrenia or the effect of the treatment drugs used. Thus, future studies could be planned to compare the QTd and Pd values of treated and untreated schizophrenia patients.

### ARTICLE HISTORY

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Schizophrenia;  
electrocardiography; heart  
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## Introduction

The life expectancy of individuals with schizophrenia, bipolar affective disorder, and related spectrum disorders is 10–17.5 years shorter than that of the general population [1]. Although suicide has a role in the shorter life expectancy [2], a large proportion of the early deaths are the result of cardiovascular disease (CVD) [3]. In comparison with the general population, the deaths of more than two-thirds of schizophrenia patients are the result of CVD [4].

CVDs are seen at a rate 1.5–2-fold higher in schizophrenia patients than in the general population [5]. This is probably related to unhealthy lifestyle habits of schizophrenia patients such as high rates of smoking, alcohol and caffeine intake, lack of physical exercise, and a diet rich in fat and sugar and lacking in fruit and vegetables [6–9]. Central obesity, hypertension (HT), and the nuclear symptoms of metabolic syndrome (MS) such as hyperlipidaemia and dyslipidemia are known to be related to a high prevalence of CVD [10]. Previous studies have shown a worsening of the

lipid profile of schizophrenia patients in the acute period with a decrease in high-density lipoprotein (HDL) and an increase in low-density lipoprotein (LDL). This change is one of the risk factors with a role in the development of CVD [11].

The QT interval is a parameter representing ventricular repolarization and depolarization. The QT interval on ECG is the equivalent of the total duration of myocardial depolarization (QRS) and myocardial repolarization. An extension of one or both of these components causes the QT interval to be prolonged [12]. The difference between maximum QT (QTmax) and minimum (QTmin) on electrocardiography (ECG) is known as QT dispersion (QTd). QTd is an indicator of ventricular repolarization homogeneity and cardiac electrical stability. The greater the QTd, the lower the homogeneity of the ventricular repolarization and, therefore, the electrical instability is greater. An increase in QTd carries the risk of ventricular arrhythmia and subsequent death. P wave dispersion (Pd) shows the difference between maximum P (Pmax)

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and minimum P (Pmin). Prolonged P wave duration and an increase in Pd are risks for irregular electrical transmission and atrial fibrillation [12, 13].

QT dispersion has been shown to be increased in patients with acute coronary ischaemia, acute myocardial infarction, heart failure, hypertrophic cardiomyopathy, and diabetes mellitus [14]. In healthy individuals, the duration of the P wave on ECG is related to the impulse transmission rate and the atrium size and a prolonged P wave indicates atrium growth, left atrium HT, and transmission anomalies.

There are studies in literature showing cardiac transmission anomalies in psychiatric disorders such as common anxiety disorder, panic disorder, social phobia, somatoform disorders, hypochondriasis, and conversion disorder. In those with common anxiety disorder, panic disorder and social phobia, increased anxiety and increased activation of the sympathetic nerve system of autonomic innervation and prolonged QTd have been shown [15, 16]. Studies of eating disorders and conversion disorder have shown increased QTd in patients accompanied by high anxiety and depression scores [17, 18]. In a previous study by the current authors that has not yet been published, the Qmax, Qmin, QTd, Pmax, Pmin, and Pd values were compared in 10 patients with vaginismus and 10 healthy control subjects and the Pd and QTd values of the patients with vaginismus were found to be statistically significantly higher than those of the control group (Atmaca et al., unpublished study). These results indicate an increased susceptibility to cardiac diseases in psychiatric patients.

With the evaluation of QTd and Pd on ECG in psychiatric disorders such as anxiety disorders [19, 20], obsessive compulsive disorder [21], somatization disorder [17], and vaginismus (Atmaca et al., unpublished study), the relationship between atrial fibrillation and ventricular arrhythmia has been examined in literature. It has been determined that in the pathophysiology of these conditions, which are associated with anxiety at a high rate, there could be a negative effect of cortisol on cardiac functions as a result of hypothalamo–pituitary–adrenal axis activation. The aim of this study was to measure QTd and Pd, which are indirect markers of atrial fibrillation and ventricular arrhythmia, in schizophrenia patients who have a high potential incidence of CVD and to draw attention to this risk.

## Materials and methods

### Study population and protocol

The study was approved by the Local Ethics Committee, and informed consent was obtained from all study participants. The study was conducted between April 2016 and October 2016. Forty-two patients were invited to the study. Eight of them did not meet the

inclusion criteria having comorbid diseases. Four of the patients declared that they had wanted to retreat from the study. The patient group comprised 30 male patients diagnosed with schizophrenia in the Psychiatry Polyclinic of the Mental Health and Diseases Hospital who were being treated either as inpatients or outpatients and met the criteria stated below.

### Criteria for inclusion or exclusion of the patients in the study group

The age of the study group was between 18 and 65 years, diagnosed with schizophrenia according to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5). Any concomitant DSM-5 disorder was excluded. The group had neither neurological disease nor a history of neurological disease or treatment nor any physical disease or physical pathology which could affect the distribution of the psychiatric symptoms in the patient. The control group comprised 30 age-matched healthy males.

### Criteria for inclusion or exclusion of the patients in the control group

The age of the study group was between 18 and 65 years. The group had no DSM-5 disorder and had not experienced a stressful life event. Those with a history of psychiatric or neurological disease, head trauma, and any physical disease or physical pathology were excluded.

Excluding comorbid diagnosis was made according to the history of the patients, laboratory test findings, physical examination findings, ECG findings, and echocardiographic evaluation results evaluated by the cardiologist. Laboratory examination was made of full blood and blood biochemistry (fasting blood glucose, triglycerides, LDL, very low-density lipoprotein (VLDL), HDL, total cholesterol, blood urea nitrogen (BUN), creatinine, sodium, potassium, chloride, magnesium, calcium, aspartate aminotransferase (AST), alanine aminotransferase (ALT), lactate dehydrogenase (LDH)), and any subjects with pathological values were excluded. There were neither history nor findings of heart disease in any patient or control group subject according to the results of examination made by the cardiologist (full blood and blood biochemistry, ECG). Ventricular hypertrophy, valvular diseases, or other structural diseases were excluded by echocardiographic evaluation.

We excluded the patients having impaired fasting glucose (fasting glucose 110 mg/dl), HT (systolic arterial blood pressure >130 mm Hg and diastolic >85 mm Hg for at least three measurements), high plasma lipids (serum level of total cholesterol >220 mg/dl, HDL cholesterol <40 mg/dl, LDL >130 mg/dl, and serum level of triglycerides >150 mg/dl). BMI greater than 30 kg/m<sup>2</sup>, in order to exclude MS as a confounding factor.

### Electrocardiographic measurement

12-derivation ECG at 25 mm/s and 1.0 mV/cm standardization was applied to the patient and control groups. The results were evaluated by manual measurements made by a cardiology specialist (M.Y.) blinded to the groups. The measurements obtained from the ECG records accepted the starting point of the QT interval as the starting point of the Q wave at the end of the PR interval and the finishing point of the QT distance as the turning point of the isoelectric TP line of the T wave. These measurements were used in the calculation of QTd and if there was a U wave, then the lowest point of the combined section of the T wave and the U wave was accepted as the finishing point of the T wave.

For the calculation of the dispersion values, after measurement of the maximum and minimum values within the 12 derivations of each interval, the dispersion values ( $d$ ) (QTd) of the relevant interval were calculated by subtracting the minimum value from the maximum value. Using the Bazett formula (corrected QT (cQT) =  $QT/\sqrt{(R-R)}$  interval), the corrected QT durations were found and the corrected QT dispersion (cQTd) values were calculated from those values [22]. The duration of the P wave was measured by accepting the starting point of the P wave as the point at which the P wave cut the isoelectric line and the finishing point as the intersection of the end point of the P wave and the isoelectric line. P dispersion (Pd) was calculated as the difference between the maximum P wave duration and the minimum P wave duration [23].

### Statistical analysis

Statistical analysis was performed using the SPSS version 22.0 for Windows software package (SPSS Inc., Chicago, IL, U.S.A.). The demographic and clinical characteristics of the patients were expressed as mean  $\pm$  standard deviation. Comparisons of continuous variables between two groups were performed using the Paired Samples  $t$  test. For all tests, a value of  $p < .05$  was considered statistically significant.

### Results

The mean age was determined as  $35.30 \pm 5.24$  years in the study group and  $34.66 \pm 5.87$  years in the control group.

Average duration of illness was  $10.69 \pm 7.32$  years.

Average BMI of the patients was  $26.39 \pm 3.93$  kg.

All patients were maintained on atypical antipsychotic medications as follows:

Olanzapin (10–30 mg/day,  $n = 9$ ), ketiapin (600–900 mg/day,  $n = 9$ ), klozapin (100–300 mg/day,  $n = 5$ ), aripiprazole (15–30 mg/day,  $n = 4$ ), risperidone (6–9 mg/day,  $n = 3$ ).

Over the course of the study the drug regimen was not changed. The study population was neither on vasoactive nor anxiolytic agents, except those mentioned above.

No statistically significant difference was determined between the groups in respect of mean age ( $t = 0.46$ ,  $df = 49$ ,  $p = .657$ ) and BMI ( $t = -0.11$ ,  $df = 49$ ,  $p = .915$ ). There was no statistically significant difference between the groups in terms of sociodemographic characteristics such as educational level, or marital and occupational status as shown in Table 1.

QTd was determined as  $25.55 \pm 13.18$  (ms) in the control group and  $54.26 \pm 8.46$  (ms) in the patient group ( $p < .001$ ) (Figure 1). Pd was determined as  $36.22 \pm 10.08$  (ms) in the control group and  $46.32 \pm 5.87$  (ms) in the patient group ( $p < .001$ ) (Figure 2). The differences in the values between the groups were statistically significant. The mean systolic arterial blood pressure in the patient group ( $113.10 \pm 15.38$  mm Hg) was determined to be lower than that of the control group ( $124.35 \pm 15.11$  mm Hg) ( $p = .011$ ).

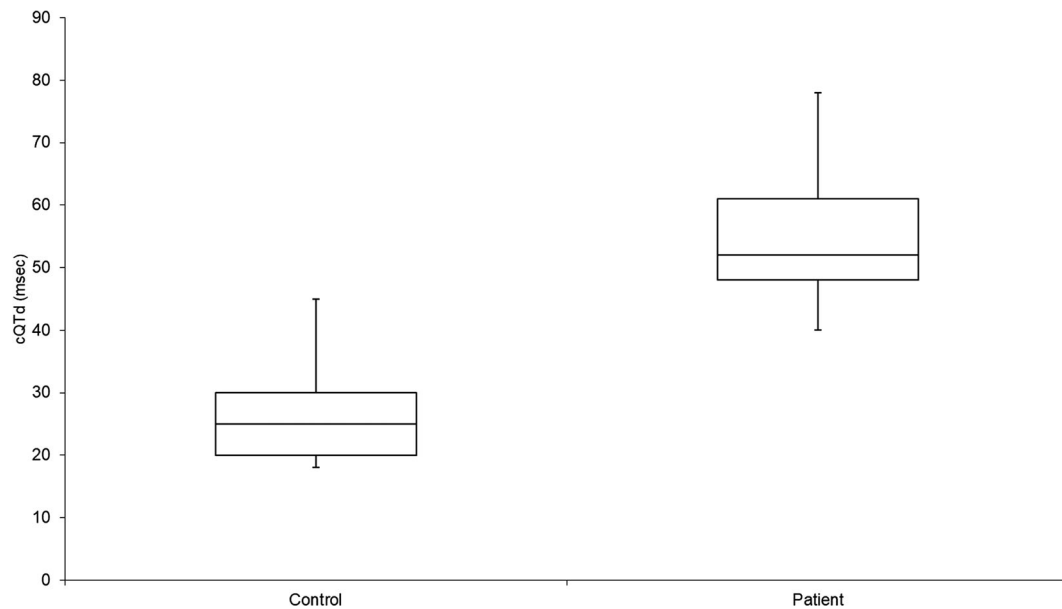
Post Hoc power analysis was applied using PASS 2008 software (Power Analysis and Sample Size, Number Crunching Statistical Software, Kaysville, U.S.A.). Group sample sizes were determined as 30 and 30 achieve 100% power to detect a difference of  $-28.7$  between the null hypothesis that both group means are 25.6 and the alternative hypothesis that the mean of group 2 is 54.3 with estimated group standard deviations of 13.2 and 8.5 and with a significance level (alpha) of 0.050 using a two-sided two-sample  $t$  test.

### Discussion

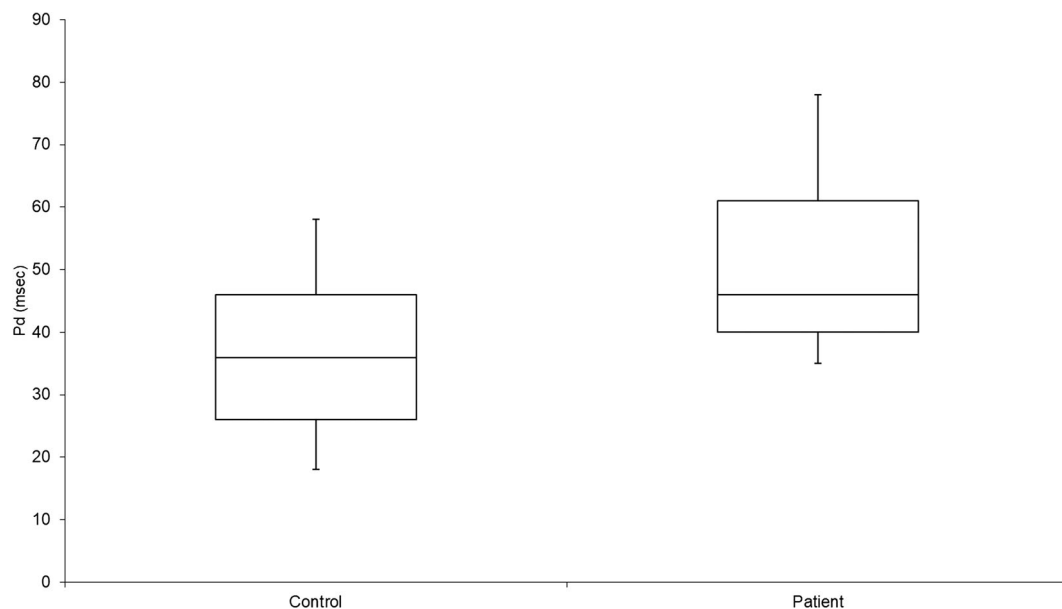
In the current study, statistically significant differences were determined between the groups in respect of the QTd and Pd values. The pathophysiological mechanism of the increased risk of CVD seen in schizophrenia is not fully known. The available evidence explains the common pathophysiological properties of severe mental diseases and CVD, such as hypothalamic–pituitary–adrenal axis dysfunction, mitochondrial dysfunction, peripheral immune activation, neuroinflammation, oxidative stress, and genetic connections [24].

**Table 1.** Sociodemographic characteristics of groups.

	Patient	Control	$p$
Age (mean $\pm$ S.D.)	$35.30 \pm 5.24$	$34.66 \pm 5.87$	0.657
Marital status			1.000
Married	5	5	
Single	25	25	
Employment status			1.000
Not working	30	30	
Working	–	–	
Education			1.000
Elementary	10	9	
High school	19	19	
University	1	2	



**Figure 1.** Distribution of QTd values.



**Figure 2.** Distribution of Pd values.

It is not clear whether the high prevalence of CVD in schizophrenia originates from poor living conditions, antipsychotic treatment or from the schizophrenia itself. MS which has a role in the aetiology of CVD has been reported at rates of 32–68% in patients who have received antipsychotic treatment and at 3.3–26% in those who have not received any antipsychotic treatment [25]. In treated patients, when the risk of MS is seen to be very high, and in patients who have undergone a first attack of schizophrenia and have not received treatment, there has also been shown to be lower levels of glucose tolerance and higher blood glucose levels compared with healthy control subjects [26]. This shows that schizophrenia, independent of treatment or disease progression, could be related to MS

and thereby, CVD [27]. In the study conducted by Emul et al. [28], the authors found that the initial P-wave dispersion was significantly longer in drug-free schizophrenia patients than in healthy controls and intramuscular ziprasidone administration does not seem to influence atrial and ventricular electrical conduction in drug-free inpatients with schizophrenia. However, schizophrenia might cause atrial fibrillation, which may be a result of some complications in inpatients with this schizophrenia.

In the current study, no statistically significant difference was determined between the groups in respect of age and BMI, and the mean systolic arterial blood pressure in the patient group was determined to be lower than that of the control group which might



help to exclude some of confounding variables such as further age, BMI related with MS and HT. It is showed with the meta-analysis studies that there is no association between gender and P-wave parameters and no significant association between Pmax and Pmin, and BMI; and no correlation, by any regression analysis, is found between age and Pd, Pmax, and Pmin values [15].

Although it is studied if there is a relationship between high incidence of unexplained sudden death and drug-induced arrhythmias in psychiatric patients, the results are contradictory. Phenothiazines (e.g. thioridazine and chlorpromazine), and butyrophenones (droperidol and haloperidol) have been linked to proarrhythmic events. QTc prolongation was found with the patients on typical antipsychotic treatment. The risk was higher with thioridazine and droperidol compared to other neuroleptics [29, 30]. Pimozide is a diphenylpiperidine neuroleptic drug that also may prolong the QT interval [31]. There seem to be clear differences in the propensity for different atypical antipsychotics to prolong the QT interval, with effects ranging from zero (e.g. olanzapine) to approximately (sertindole) but not strongly [32]. In a study which evaluated QTc-interval abnormalities of 495 psychiatric patients revealed that antipsychotic drugs caused QTc lengthening in a dose-related manner and risks were substantially higher for thioridazine and droperidol which might have an increased risk of drug-induced arrhythmia [33]. The study showed that abnormal QT dispersion or T wave abnormalities were not significantly associated with antipsychotic treatment, but were associated with lithium therapy [33]. In another study conducted by Nahshoni et al. [34], QT interval, QTd, and rate-corrected values were calculated before initiation of antipsychotic treatment and during the maintenance period of 12 children while 3 of them were concomitantly maintained on methylphenidate therapy. They found that QT interval, QTd, and their rate-corrected values were all within normal values both before and after successful drug treatment. In our study, none of the patients in the study group were taking typical antipsychotic treatment and mood stabilizer or antidepressant treatment which may strongly affect the QTd and Pd values. They were on single atypical antipsychotic drug treatment which is safer than typical antipsychotics by the meaning of cardiac effects. Nahshoni et al. [35] reported in another study that in psychotic schizophrenia inpatients maintained on antipsychotics and undergoing electroconvulsive therapy, QTd and the rate-corrected QTd showed a significant decrease after electroconvulsive therapy, concomitant with improvement in psychosis. In our study because the neurological and physical diseases were excluded in the study group, the patients were only on psychiatric treatment rather than any other pharmacological drugs.

From the starting point that CVD is seen 1.5–2-fold more often in schizophrenics than in the normal population, the results of this study which compared a schizophrenia patient group with a healthy control group in respect of QTd, which is a risk factor for ventricular arrhythmia and Pd, which is a risk factor for atrial fibrillation, showed that these values were greater in the patient group.

There were some limitations to this study. Although the QTd and Pd values were found to be significantly greater in the patients with schizophrenia compared to the control group, there is a need for further studies to determine whether this was the result of the effect of the drugs used in treatment, the poor living conditions brought about by the disease or the nature of schizophrenia itself. A further study can be made with the patients without medications although it is difficult to find patients free from medication in chronic psychosis like schizophrenia. As the study was conducted on male patients only, the results cannot be generalized for both genders. Therefore, studies could be conducted to compare the QTd and Pd values with a more extensive sample, including both genders and treated and untreated patients.

The high rates of CVD seen in schizophrenia patients may be due to poor living conditions, the side-effects of medication used or because of the nature of the disease itself. With follow-up of Pd and QTd values which are indicators of atrial fibrillation and ventricular arrhythmia, these patients can be helped with early diagnosis and intervention for CVD which results in death.

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## Disclosure statement

No potential conflict of interest was reported by the authors.

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