P Wave and QT Dispersion in Patients with Generalized Anxiety Disorder

Yaygın Anksiyete Bozukluğu Olan Hastalarda P ve QT Dispersiyonu

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ABSTRACT

Introduction: *The aim of this study is to investigate P wave dispersion (Pd) and QT dispersion (QTd), non-invasive predictors of atrial fibrillation and ventricular arrhythmia or sudden cardiac death, respectively, in patients with generalized anxiety disorder (GAD).*

Patients and Methods: *A total of 40 outpatients diagnosed as GAD and 29 healthy control subjects were included in the study. Beck Anxiety Inventory (BAI) and Beck Depression Inventory (BDI) were administered and 12-lead ECG measurements were obtained. Pd and QTd measurements were performed by blinded cardiologists.*

Results: *BAI scores (26.6 ± 11.8 vs. 3.4 ± 3.3, p< 0.001) and BDI scores (12.6 ± 4 vs. 3.7 ± 4.5, p< 0.001) were significantly higher in the patient group compared to the controls. P wave dispersion (Pd) [50.0 ± 17.5 miliseconds (ms) vs. 23.4 ± 7.7 ms, p< 0.001] and mean QT dispersion (QTd) (50.5 ± 18.1 ms vs. 28.3 ± 11.4 ms, p< 0.001) significantly increased in the GAD patient group compared to the controls.*

Conclusion: *Increase in Pd may suggest that GAD patients have increased risk of atrial fibrillation. Similarly, increased QTd may show that these patients have a higher risk of ventricular arrhythmia.*

Key Words: *ECG, heart, anxiety disorders.*

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ÖZET

Giriş: *Çalışmamızın amacı; yaygın anksiyete bozukluğu (YAB) olan hastalarda, ventriküler aritmi ve ani kardiyak ölümün noninvaziv belirleyicisi olan QT dispersiyonu ile atriyal aritminin noninvaziv belirleyicisi olan P dispersiyonunu araştırmaktır.*

Hastalar ve Metod: *Ayaktan 40 YAB olan hasta ve 29 sağlıklı kontrol çalışmaya dahil edildi, Beck Anksiyete Envanteri (BAE) ve Beck Depresyon Envanteri (BDE) uygulandı ve 12 derivasyonlu EKG ölçümleri elde edildi. Pd ve QTd ölçümleri tek kör kardiyolog tarafından yapıldı.*

Bulgular: *BAE puanları (26.6 ± 11.8 vs. 3.4 ± 3.3, p< 0.001) ve BDE puanları (12.6 ± 4 vs 3.7 ± 4.5, p< 0.001) kontrol grubuna göre hasta grubunda anlamlı olarak daha yüksekti. P dispersiyonu (Pd) [50.0 ± 17.5 milisaniye (ms) vs. 23.4 ± 7.7 ms, p< 0.001] ve ortalama QT dispersiyonu (QTd) (50.5 ± 18.1 msn vs. 28.3 ± 11.4 msn, p< 0.001)'nda kontrol grubuna göre hasta grubunda anlamlı olarak daha yüksekti.*

Sonuç: *Pd ve QTd belirgin olarak YAB hastalarında artmıştır. Bu sonuçlar, YAB olan hastalarda artmış Pd'nin atriyal aritmi riskini artırabileceğini, artmış QTd'nin ise ventriküler aritminin artmış riskini düşündürmektedir.*

Anahtar Kelimeler: *EKG, kalp, anksiyete bozukluğu.*

INTRODUCTION

Generalized anxiety disorder (GAD) is one of the anxiety disorders characterized by excessive worrying, anxiety, tension associated with symptoms of hypervigilance, and other somatic symptoms of anxiety. It persists six months or more and also is a member of anxiety disorders[1]. The association between psychiatric disorders and cardiovascular diseases has long been suspected, although a clear-cut relationship is difficult to demonstrate[2]. The comorbidity between GAD and major depression in coronary heart diseases has been shown[3]. Anxiety is one of the most common psychiatric disorders with a lifetime prevalence of 28.8% according to the National Comorbidity Survey Replication conducted in the United States[4]. The prevalence of GAD in the general population is estimated to be 5.7% whereas lifetime prevalence is 26% in cardiac patients[5,6]. GAD, classified in Diagnostic and Statistical Manual of Mental Disorders (DSM), is a special form of anxiety disorders in which excessive and uncontrollable worry is present for a variety of life events along with symptoms of motor tension and vigilance[7]. Additionally, GAD was determined to be a predictor of major adverse cardiac events in a two-year follow-up of 804 stable coronary artery disease patients[8]. However, compelling evidence is emerging regarding the relationship between anxiety and cardiovascular diseases. The Normative Aging Study, a community based prospective study, has shown that patients with two or more symptoms of anxiety were associated with a higher risk of fatal coronary heart disease and sudden cardiac death in men[9]. P wave dispersion (Pd), non-invasive marker of inhomogeneous and discontinuous propagation of sinus impulses through the atrial wall, defined as the difference between the maximum and the minimum P wave duration, and maximum P wave duration is an electrocardiographic marker which have been used to evaluate the discontinuous propagation of sinus impulses and the prolongation of atrial conduction time[10-13]. Atrial fibrillation (AF) is responsible for considerable morbidity and mortality, conferring a 4-5 fold increase in the risk of embolic stroke[14]. QTd, defined as the interlead QT variation in 12-lead electrocardiography (ECG), is a non-invasive measure of ventricular arrhythmia[15]. Increased QTd was shown to be a predictor of sudden cardiac death[16]. Physciatric disorders such a social phobia was found to be related with QTd[17].

In this study, we aimed to determine Pd and QTd in patients with GAD as a possible way of identifying patients at increased risk of atrial fibrillation and ventricular arrhythmia.

PATIENTS and METHODS

Forty (32 women, 8 men) outpatients with GAD aged between 20 and 45 participated in the study. They had been consecutively admitted to the Haydarpasa Numune Training and Research Hospital, Department of Psychiatry. All had already met Diagnostic and Statistical Manual of Mental Disorders Fourth Version (DSM-IV) DSM-IV criteria for GAD by using Turkish version of Structured Clinical Interview for DSM-IV (SCID)[7,18]. The control group consisted of 29 (23 women, 6 men) physically and mentally healthy volunteers among the hospital staff and the medical and nursing school students. Beck anxiety inventory (BAI) is a self-report inventory measuring the frequency of physiological and other symptoms of anxiety experienced during the previous week, which was adapted for use in Turkey by Ulusoy et al.[19,20]. Similarly, Beck depression inventory (BDI) is a self-report inventory which measures

the severity of the somatic, emotional, cognitive, and motivational symptoms in depression and was adapted for use in Turkey by Hisli[21,22]. Exclusion criteria for both patients and controls were the presence of a mental retardation, comorbid psychiatric disorder, other psychotic or mood disorders, dementia, delirium or other amnestic disorders, psychotic disorders secondary to general medical condition, chronic diseases that may impair general condition or cardiac functioning (thyroid diseases, hypertension, heart valve disorders, myocardial infarct, atherosclerotic heart disease, congestive heart failure, or other cardiomyopathies, diabetes etc.), and a psychotic disorder due to alcohol or psychoactive substance intoxication or withdrawal. All participants were no smokers, free of all medications at least in the previous one month, or chronic drug users. The study was conducted after approval by the Haydarpasa Numune Training and Research Hospital Ethics Committee, in accordance with the Helsinki Declaration. Written informed consent was obtained from all participants in this study, after comprehensive explanation of the entire procedure. All patients were underwent physical examination, routine biochemical evaluation, electrocardiogram recordings and venous blood samples were obtained between 9 a.m. and 11 a.m. to prevent diurnal variations. Comprehensive blood tests were performed to exclude any physiological abnormalities or underlying conditions that may influence the ECG test results. Blood tests included serum electrolyte levels, serum lipids, thyroid hormones, liver function tests, and whole blood count. A 12-lead surface ECG (Petas Kardiopet) was obtained from all subjects in the supine position. All patients were breathing freely but were not allowed to speak during the ECG recordings. The ECGs were recorded at a paper speed of 25 mm/s (20 ms= 0.5 mm at a paper speed of 25 mm/s) and standardized at a scale of 1 mV/cm. Blood samples were withdrawn on the following day of the ECG test and routine blood tests were conducted for differential diagnosis of any diseases that might lead to impaired cardiac functioning or anxiety disorder secondary to general medical condition. Cardiologist was blinded to the clinical findings of patients. Pd was calculated using average values of at least three P waves for each lead. The onset of P wave was defined as the first elevation or depression from the isoelectric line on positive and negative waves, respectively. The point of return to the isoelectric line was defined as the end of P wave. Pd defined as the difference between P_{max} is the longest conduction and P_{min} is the shortest conduction time obtained from all of the 12 derivations, was calculated. QT interval

was measured as described by Nahshoni et al. with the exception of rate correction[17]. Basically, QT interval was measured for all 12 leads from the onset of QRS complex to the end of T wave, defined as the return to the T-P isoelectric line or to the lowest point between T and U waves, if a U wave was present. Leads with unclear T waves were excluded. Recordings with more than eight clearly defined leads were included in the analysis. QTd was defined as the difference between the longest and shortest QT intervals among the 12 leads of an ECG trace.

Data were analyzed using the Statistical Package for the Social Sciences, PC version 13.0 (SPSS/PC, 1998). A confidence interval (CI) of 95% and a 2-tailed p value of less than 0.05 were considered to be statistically significant for all analyses. Variables were tested for homogeneity of variance using the Levene test and for normality of distribution by utilizing the Kolmogorov-Smirnov test. Continues variables (age, body mass index, sodium, potassium, chloride, calcium, phosphorus, magnesium) which are distrubuted normally and homogenus as were analyzed by Student's t-test while non-parametric continues variables (BAI, BDI, Pd, QTd) were analyzed by Mann-Whitney U test. categorical variables, was used. Differences in sex ratio were assessed by a chi-square test.

RESULTS

No difference in terms of gender, age or body mass index variables was found between groups (Table 1). Biochemical data was within normal ranges and no clinically and statistically significant differences were observed between the groups. The mean values for serum electrolytes are shown in Table 1. BAI (26.6 ± 11.8 vs. 3.4 ± 3.3, p< 0.001) and BDI (12.6 ± 4 vs. 3.7 ± 4.5, p< 0.001) scores were significantly higher in the patient group compared to the healthy controls (Table 1).

Table 2 shows the summarized analysis of ECG data. Pd was significantly greater in GAD patients compared to healthy controls (50.0 ± 17.5 milisecond (ms), 23.4 ± 7.7 ms, p< 0.001). Similarly, mean QTd was significantly greater in the GAD group than the controls (50.5 ± 18.1 ms, 28.3 ± 11.4 p< 0.001).

DISCUSSION

Anxiety is a common comorbid condition in patients with cardiovascular disease[23,24]. Accumulating data, has showed that anxiety may play a critical role as a predictor of cardiovascular diseases[25]. Growing number of evidence indicates anxiety as a incentive trigger for fatal coronary heart disease and other major cardiac events. In

Table 1. Demographical profile, serum electrolyte levels, BAI and BDI scores of study subjects			
	GAD patients (n= 40)	Controls (n= 29)	p
Sex ratio, n (F/M)	32/8	23/6	0.944*
Age (years)	33.7 ± 7.5	31.1 ± 7.1	0.150**
BMI, kg/m^2	25.6 ± 4.7	23.4 ± 4.2	0.079**
Sodium (mmol/L)	139.8 ± 1.7	138.8 ± 2.5	0.074**
Potassium (mmol/L)	4.2 ± 0.3	4.2 ± 0.3	0.880**
Chloride (mmol/L)	104.5 ± 2.8	103.8 ± 3.1	0.289**
Calcium (mmol/L)	9.6 ± 0.4	9.4 ± 0.5	0.068**
Phosphorus (mmol/L)	3.4 ± 0.5	3.6 ± 0.5	0.202**
Magnesium (mmol/L)	2.3 ± 0.2	2.3 ± 0.2	0.847**
BAI, mean ± SD (median)	26.6 ± 11.8 (30.5)	3.4 ± 3.3 (2)	< 0.001***
BDI, mean ± SD (median)	12.6 ± 4 (10)	3.7 ± 4.5 (2)	< 0.001***

  * Chi-square test.
 ** Student t-test.
*** Mann Whitney U test.
GAD: Generalized Anxiety Disorder, BMI: Body mass index, BAI: Beck Anxiety Inventory, BDI: Beck Depression Inventory, SD: Standard deviation.

Table 2. P wave dispersion (ms) and QT dispersion in GAD patients and healthy controls [Data are given as mean ± SD (median)]			
	GAD patients (n= 40) mean ± SD (median)	Controls (n= 29) mean ± SD (median)	p
P wave dispersion	50.0 ± 17.5* (60)	23.4 ± 7.7* (20)	p< 0.001**
QT dispersion	50.5 ± 18.1* (40)	28.3 ± 11.4* (20)	p< 0.001**

 * Miliseconds (ms).
** Mann Whitney U test.
GAD: Generalized Anxiety Disorder, SD: Standard deviation.

addition, it was determined to be a significant predictor of AF after coronary artery bypass grafting[26,27]. Many studies investigated the relation of physciatric disorders with Pd and QTd which are predictors of increased risk of atrial and ventricular arrhythmia, respectively. However, there is no data regarding Pd and QTd in patients with GAD[11,17].

In this study we sought to determine the relationship of GAD with Pd and QTd. BAI was used to measure the anxiety. Pd and QTd were analyzed in 12-lead ECG of GAD patients and healthy controls for a possible way to determine the patients that are at high risk of atrial and ventricular arrhythmia. Recently two studies have implicated a relationship between anxiety and Pd. A study conducted on 726 healthy young male subjects indicated that the level of anxiety, measured by the Speilberger State and Trait Anxiety Inventory administered concomitantly with the ECG, is positively correlated with Pd and P_{max}[28]. In a case control study, conducted on patients with panic disorder and age-gender matched healthy subjects, Pd, P_{max} and P_{min} were determined to be significantly higher in patients with panic disorder. In addition, panic agoraphobia scale scores were found to be significantly correlated with Pd[11]. In the present study, patient group has higher BAI scores compared to that of the control group. In accordance with the literature GAD patients were showed to have significantly higher Pd and QTd than controls.

Pd indicates irregular propagation of sinus impulses across the 12-lead ECG. Recently, Pd was showed to be increased in various diseases such as hypertropic cardiomyopathy, rheumatoid arthritis, obstructive sleep apnea, and obesity, as well as during migraine attacks, and as a result of sleep deprivation[29,30]. It has been shown to be a useful non-invasive marker of AF in patients with paroxysmal AF[12,13]. The exact mechanism of anxiety induced atrial arrhythmia is not well recognised. It has been showed that P-wave durations were influenced by the autonomic

tone[31]. Increased autonomic tone may be responsible for tendency to atrial arrhythmia in patients with GAD. Similar to our findings, Hansson et al. demonstrated that psychic stress was the commonest triggering factor in hospitalized patients with paroxysmal atrial fibrillation[32]. The direct effect of anxiety on atrial fibrillation was best assessed in the Framingham Offspring study, conducted by Eaker et al.[33].

QTd is a known predictor of ventricular arrhythmia and sudden death[16]. Piccirillo et al. have shown that an anxiety score of two or more on Kawachi scale was correlated with increased QTd in apparently healthy individuals with a family history of cardiac disease[34]. In another study conducted on 726 physically and mentally healthy young men, anxiety, as measured by Speilberger State-Trait Anxiety Inventory, was found to be correlated with QTd[35]. Even in patients with preexisting conditions such as hypertension or eating disorder which may influence cardiac function, anxiety was correlated with higher QTd[36,37]. There is only one other study investigating QTd as a marker of anxiety induced cardiac dysregulation in symptomatic anxiety patients. Nahshoni et al. compared 16 patients diagnosed with social phobia according to SCID-P and 15 healthy controls in terms of QT interval variation and determined that QTd was significantly greater in patients with social phobia[17]. The levels of QTd reported in their study was 70 ± 21 ms for patients and 46 ± 10 ms for controls. The levels were considerably lower in our study (50.5 ± 18.1 ms vs. 28.3 ± 11.4 ms) even though a similar methodology was used in QT interval measurements. This could be due to user variation, differences in instruments or conditions in which ECG measurements were performed. However, such variability may pose a problem in trying to determine a cut-off level to be used as an indicator of increased risk of arrhythmia. QTd levels of 60-80 ms are considered to be present in patients with cardiac disease[16,17]. In consistence with the literature, the present study showed that GAD patients had significantly increased QTd when compared to that of control group. A relationship between depression and elevated QTd was previously shown in elderly patients with major depressive disorder[38]. Even though our primary goal in this study was to determine the relationship between anxiety and cardiac imbalance, a mild depression might have also contributed to the levels of QTd observed in GAD patients, as the mean BDI score was 13 ± 7 (median= 10). However, patient group did not meet DSM-IV diagnostic criteria for depression. This result may show that Pd and QTd were not related with depression in patients with GAD.

As a conclusion, GAD and the level of anxiety appear to be associated with an increase in Pd and QTd suggesting that GAD patients may be at an increased risk of atrial fibrillation, ventricular arrhythmia and sudden cardiac death. Since our patient group was at a relatively young age for showing any signs of AF and patients were not followed up in our study, a long term follow up of patients with anxiety or examination of an elderly patient population may help to determine whether AF is causally related to anxiety also QTd would be interesting to see if treatment for anxiety and life style improvements would similarly reduce QTd levels in patients with GAD.

The most important limitation of our study is small sample size. Additionally, manual calculations of P wave and QTd measurements by magnifying lens rather than computer programming contributed to limitations.

As a result, our findings suggest that GAD may be associated with Pd and QTd. Further studies with larger study groups and performing measurements with computer programming are needed.

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CONFLICT of INTEREST

None declared.

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