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·Original Article·

QT wave dispersion in patients with panic disorder

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Abstract: Objective QT dispersion (QTd), defined as the maximal inter-lead difference in QT intervals on 12 leads of the surface electrocardiogram (ECG), reflects the regional heterogeneity of ventricular repolarization and has been suggested as an important marker for risk of arrhythmia in addition to the QT interval. Some investigators proposed that it might be a predisposing factor for arrhythmic events and sudden death. Thus, we aimed to investigate whether QTd differs in patients with panic disorder from that in healthy controls. **Methods** In 40 panic disorder patients and 40 healthy controls, Q_{max}, Q_{min}, and QTd values were measured. In addition, the Hamilton depression rating scale and the panic agoraphobia scale were scored for both patients and healthy volunteers. **Results** Q_{max} and Q_{min} values in the panic disorder patients were significantly higher than those in healthy controls. The mean corrected QTd was significantly greater in the patients than in the controls. One-way analysis of covariance (ANCOVA; using left atrial size, age and heart rate as covariates) also corrected the significant difference. In addition, ANCOVA revealed a significant main effect for the diagnosis, indicating a significantly higher QTd for patients compared with controls. **Conclusion** QTd might be associated with panic disorder. Future studies in larger samples evaluating the effects of treatment are required.

Keywords: QT dispersion; panic disorder

1 Introduction

Panic disorder, as defined by the *Diagnostic and Statistical Manual of Mental Disorders*, 4th ed. (DSM-IV), is a severe psychiatric disorder that causes significant impairment of life quality and social life functions. Both anxiety itself and panic states are suggested to be associated with coronary artery disease (CAD), because symptoms of panic-like anxiety and panic disorder are disproportionately prevalent among CAD patients, where panic disorder alone affects 10%–50% of patients with established CAD[1]. Moreover, there is evidence suggesting that panic disorder and panic-like anxiety are associated with poorer CAD prognosis, including increased risk for post-myocardial infarction in-hospital complications (e.g., acute ischemia, re-infarction, sustained ventricular tachycardia and ventricular fibrillation) and mortality[2].

In fear, anxiety and related clinical conditions such as panic states, the role of the hypothalamic–pituitary–adrenal axis (HPA) is well-established. Stressful events increase hypothalamic corticotropin-releasing hormone (CRH) production, stimulating the pituitary release of adrenocorticotropic hormone (ACTH). In association with this, cortisol production and secretion by the adrenal cortex rise. In all anxiety states including panic disorder, the symptoms of palpitations, chest pain and shortness of breath reveal the involvement of the autonomic nervous system (ANS)[3]. Recently, it has been emphasized that heart rate variability

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(HRV) is a tool to study the functioning of the ANS[4]. The ANS modulates both the duration of cardiac ventricular repolarization and the spatial heterogeneity of repolarization[5]. HRV is controlled by the continuous interplay of the sympathetic and parasympathetic divisions of the ANS[6]. Changes in HRV have been associated with an increased risk of sudden cardiac death, but the underlying mechanisms are obscure. Baumert *et al.*[7] assessed the relationship between the amount of norepinephrine released from cardiac sympathetic terminals and short-term HRV, and suggested that the predictive value of most HRV measures for sudden cardiac death might predominantly result from their capacity to capture vagally-mediated heart rate modulation. Using simple HRV indexes to assess the sympathetic outflow to the heart is of great interest. Power spectral analysis of HRV shows distinct low-frequency oscillations that may or may not be caused by sympathetic efferents, besides vagally-mediated high-frequency oscillations associated with respiration[8]. QT dispersion (QTd), defined as the maximal inter-lead difference in QT intervals on 12 leads of the surface electrocardiogram (ECG), reflects regional heterogeneity of ventricular repolarization and has been suggested as an important indicator of the risk of arrhythmia, in addition to the QT interval[9]. Normally, QTd is within 40–60 ms; when it exceeds 100 ms or rises by 100% from baseline, the condition is then considered to be pathologic[10]. Some investigators proposed that it may be a predisposing factor for arrhythmic events and sudden death[11]. Nakagawa *et al.*[12] used the head-up tilt test to investigate the influence of the ANS on HRV and QTd and found that QTd is positively correlated with HRV measures, accounting for increased sympathetic tone and/or decreased vagal tone. Piccirillo *et al.*[13] evaluated autonomic modulation in hypertensive subjects with anxiety, and reported that the QTd and the indexes of HRV were higher in the subjects with higher anxiety scores. In association with this notion, Nashoni *et al.*[14] compared the QTd in physically healthy patients with social phobia and normal controls and hypothesized that QTd would be higher in the patients because of the persistent anxiety and putative chronic autonomic imbalance associated with social phobia. Indeed, they found that QTd and rate-corrected QTd were significantly higher in the patients with social phobia than in the controls. Therefore, the present study aimed to investigate whether QTd differs in patients with panic disorder compared to that in healthy controls.

2 Subjects and methods

2.1 Subjects Forty subjects (24 female and 16 male, 31.17 ± 6.79 years) diagnosed with panic disorder according to DSM-IV were recruited. The diagnosis was based on the Structured Clinical Interview for DSM-IV Disorders–Patient Version[15,16]. The control group consisted of 40 healthy individuals (25 female and 15 male, 29.97 ± 4.89 years) matched by sex, age, and smoking status. A psychiatrist investigator evaluated the subjects with regard to diagnostic details. Some psychiatric comorbidities found: generalized anxiety disorder in three patients, obsessive compulsive disorder in two, and phobic disorder and major depressive disorder in one patient each. All subjects were normal on physical examination, 12-lead ECG, and routine blood tests. The inclusion criteria included not using either vasoactive or psychotropic agents (e.g., antipsychotics, anxiolytics) for at least two weeks. In addition, the patients should be either drug-naïve for at least two months or on a stable dose for at least one month. On the other hand, the exclusion criteria consisted of the following items[17]: current or previous evidence of congestive heart failure, resting blood pressure >180/120 mmHg, serious systemic illness (e.g. diabetes), and serious psychiatric or neurological states blocking the psychiatric interview such as mental retardation, any psychotic and mood disorder, dementia, delirium and amnestic disorders.

Under the standardized procedure, in order to reduce emotional distress or state anxiety during the electrocardiographic recording, all recordings were performed in the same quiet room during spontaneous breathing, after 10 min of adjustment in the supine position. Furthermore, to exclude the possible influence of diurnal variations, all the recordings were performed at 9:00 a.m. In addition, the Hamilton depression rating scale (HDRS) and the panic agoraphobia scale (PAS) were scored for both patients and

healthy volunteers[18,19]. Prior to examination, all subjects gave written informed consent to participate in the study.

2.2 Analysis of QTd A 12-lead surface ECG was performed in participants when they were breathing freely. During recording, they were asked not to speak. The ECGs were recorded at a paper speed of 50 mm/s. All derivations were completed for each subject, with ten heartbeats for each derivation. One investigator without any knowledge of participants' clinical status measured the QT wave durations. All QT interval measurements were performed manually with calipers. The QT interval was measured from the onset of the QRS complex to the end of the T wave, defined as the return to the T–P isoelectric line. QTd was defined as the maximal inter-lead difference in QT intervals. Echocardiography was performed using an ACUSON SEQUA 512 Machine with a 3-MHz transducer. M-Mode echocardiographic values for left atrial (LA) diameter and left ventricular ejection fraction (EF) were obtained on the basis of the standards of the American Society of Echocardiography[20].

2.3 Statistical analysis Data are presented as mean ± SD. Statistical analysis was performed using SPSS/PC version 13.0. Student's *t* test and Spearman's correlation were used. Furthermore, analysis of covariance (ANCOVA) was used, with LA size and heart rate as covariates. $P < 0.05$ was considered statistically significant for all these tests. In addition, power analysis was used to calculate the sample size of the study population with the following formula: $n = \sigma^2 \times (Z_\alpha + Z_\beta)^2 / d^2$. The first and second errors were taken as $\alpha = 0.05$ and $\beta = 0.10$ ($1-\beta = 0.9$, 90% power of a test). At the beginning of the study, ten patients served as a prior sample. Variance information from this sample was used to determine the sample size. Consequently, we decided to include 40 subjects in each group with the values of $\alpha = 0.05$ and $\beta = 0.10$, $1-\beta = 90\%$ power of study. On the other hand, the selection of Student's *t* test and Spearman's correlation was performed after analysis for Gaussian/non-Gaussian distribution of the analyzed data.

3 Results

Panic disorder patients ($n = 40$) and the same number of healthy subjects did not differ with regard to age, female/male ratio, and smoking status (rate and duration). The mean duration of illness for the patient group was 4.90 ± 3.77 years (Table 1). Comorbid conditions were generalized anxiety disorder (3 patients), obsessive compulsive disorder (2), phobic disorder (1), and panic disorder (1).

The ECG data are presented in Table 1. With respect to the psychological testing, the mean PAS and HDRS scores of the patients were significantly higher than those

Table 1. Characteristics and cardiac parameters of patient and control groups

	Patients ($n = 40$)	Controls ($n = 40$)	*P* value	*t*
Age (years)	31.17 ± 6.79	29.97 ± 4.89	$P > 0.05$	1.22
Sex (F/M)	24/16	25/15	$P > 0.05$	
Duration of illness (years)	4.90 ± 3.77			
HDRS score	8.58 ± 4.29	5.80 ± 2.54	$P < 0.001$	3.52
PAS score	25.95 ± 5.68	6.33 ± 2.34	$P < 0.001$	20.19
QT_{max} (ms)	425.15 ± 31.71	349.03 ± 37.44	$P < 0.001$	9.81
QT_{min} (ms)	362.60 ± 29.12	314.65 ± 33.22	$P < 0.001$	6.87
QTd (ms)	62.15 ± 28.13	36.53 ± 13.69	$P < 0.0001$	5.18
LA size (mL)	32.96 ± 3.11	32.30 ± 2.78	$P > 0.05$	0.95
EF	61.45 ± 3.50	61.98 ± 4.10	$P > 0.05$	-0.62

EF, ejection fraction; F, female; HDRS, Hamilton depression rating scale; LA, left atrium; M, male; PAS, panic agoraphobia scale; QTd, QT wave dispersion; QT_{max}, maximum QT interval; QT_{min}, minimum QT interval.

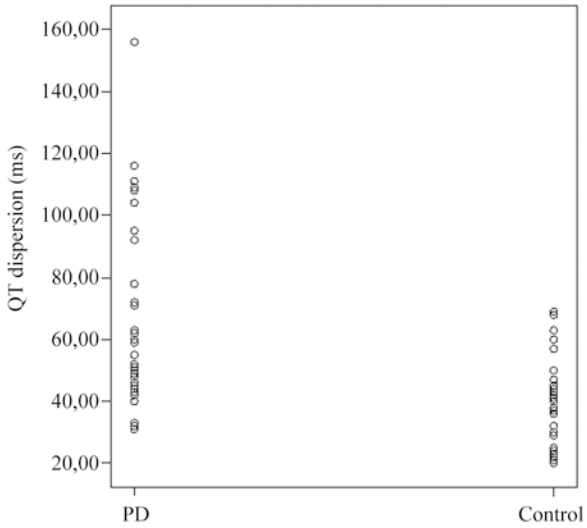

Fig. 1. Scatter graph of QT dispersion in panic disorder (PD) and control groups.

of the controls (25.95 ± 5.68 *vs* 6.33 ± 2.34, P <0.001 for PAS; 8.58 ± 4.29 *vs* 5.80 ± 2.54, P <0.001 for HDRS). The LA size (32.96 ± 3.11 for PAS *vs* 32.30 ± 2.78 mL for HDRS) and heart rate (78.63 ± 11.49 for PAS *vs* 77.75 ± 9.62 beats/min for HDRS) did not differ statistically between the groups. With respect to the ECG measurements, we found that the QT_{max} and QT_{min} values of the patients were higher than those of healthy controls (P <0.001 for both QT_{max} and QT_{min}). The mean corrected QTd, the main value measured, was markedly greater in the patient group than in the control group (P <0.001). One-way ANCOVA (using LA size, age and heart rate as covariates) also corrected the difference (P <0.001 for each of LA size, age, and heart rate). In addition, ANCOVA revealed a significant main effect for the diagnosis (F = 7.92, P <0.001) confirming a significantly higher QTd for patients compared with controls. No other main effects were found. Scatter graph of QTd by groups is presented in Fig. 1. Also, the PAS scores for the patient group were correlated with QTd values (r = 0.52, P <0.001). No other significant correlation was found among the other parameters.

4 Discussion

The present study was the first examination of QTd in patients with panic disorder. The major finding was that the QT_{max}, QT_{min}, and QTd values of the patients were significantly higher than those of healthy controls. Moreover, PAS scores in the patient group were correlated with the QTd values. QTd was first introduced in the expectation that it reflects spatial differences in ventricular repolarization (dispersion of repolarization), which is a firmly established and mechanistically confirmed risk factor for ventricular arrhythmia.

However, the association between the QTd and the true dispersion of repolarization was later disputed. The main controversy about the meaning of QTd came from Malik[8] who concluded that, despite the difficulties with the concept and despite the fact that a clear publication bias exists towards positive findings, the huge number of studies showing some meaningful results with QTd measurements cannot be dismissed lightly. The main argument presented against the concept is that morphologic T waveform variations associated with dipolar components of repolarization can produce large variations in the QTd[21]. While the arguments against the validity of QTd have considerably weakened its practical utility, that the concept is invalid has not been proven.

The effect of anxiety on cardiac functions in healthy persons has been discussed over the past two decades[22,23]. However, only in limited investigations of anxiety disorders have cardiac functions been investigated. Meanwhile, it is well-established that excessive anxiety itself affects cardiac autonomic balance in physically healthy subjects and increases the risk of coronary heart disease[14]. Probably the most striking example of this is from the study by Morris *et al*.[24] with a large sample in a prospective design, in which the risk of sudden cardiac death of men was significantly associated with anxiety at a multivariate odds ratio of 2.96. Because panic disorder is probably most associated with autonomic imbalance, the investigations of cardiac functions have been performed more in this disorder than in other anxiety-related states. In these studies, panic disorder has also been found to be associated with cardiovascular diseases. Among these, one examined the comorbidity of panic disorder with heart

disease and the prevalence of panic disorder in 128 outpatients presenting to cardiologists, and found that 16 patients (12%) met the criteria of panic disorder, and 73 (57%) had actual cardiac illness; of these, 10 (14%) had panic disorder[24]. Having previously shown that P wave dispersion in patients with panic disorder is significantly higher than in healthy controls, and correlates with PAS score[25], in the present study we aimed to evaluate another parameter, QTd. It has been shown that QTd and rate-corrected QTd are significantly higher in patients with social phobia than in healthy controls, and are highly correlated with the two Liebowitz social anxiety scale subscores, suggesting that prolonged social phobia is associated with an increase in QTd[14]. Likewise, here we found that QT_{max}, QT_{min}, and QTd in the patients were significantly higher than those of healthy controls, and the PAS scores in the patient group were correlated with QTd values.

However, some limitations need to be mentioned here. First, the results were limited by the small sample size, making this study preliminary. Further confirmation from larger studies with a longer follow-up is needed. Second, the lack of further biological assessments, including from the genetic point of view in first-order relatives, examination of markers of sympathetic activity, the HPA axis and long-term ECG and RR evaluations (heart rate variability, nocturnal depression of blood pressure), is also a limitation. Third, this study did not use a scale that evaluates general anxiety such as the Hamilton anxiety rating scale since here we specifically tested panic anxiety using the PAS scale. Fourth, variants such as weight and body mass index (BMI) that might influence the ECG were not included in the analysis. Finally, we measured QTd but normalized the measure of QT to RR variability (QTvi) or QT variability to the mean QT duration (QTvm). QTvi contains a heart rate-dependent component while QTvm just associates QT variability with the mean QT duration, having a complex relationship with the heart rate at different rates. In addition, these are affected by standing posture or tilting procedures[26].

In conclusion, this study showed that QTd might be associated with panic disorder. Future studies with a larger sample size and evaluation of the effects of treatment are required.

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