EFFECTS OF NORTRIPTYLINE AND PAROXETINE ON QT VARIABILITY IN PATIENTS WITH PANIC DISORDER

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This study investigated beat-to-beat QT variability in patients with panic disorder before and after treatment with nortriptyline (n = 13) and paroxetine (n = 16), using an automated algorithm to compute QT intervals. An increase in QT variability appears to be associated with symptomatic patients with dilated cardiomyopathy and also with an increased risk for sudden cardiac death. QTvi (QT variability index: a log ratio of QT variance normalized for mean QT over heart rate variability normalized for mean heart rate) was significantly higher in supine posture in patients with panic disorder treated with nortriptyline (P = 0.006) but not paroxetine. Thus paroxetine may be a better drug of choice especially in patients with coexisting cardiac disease. These findings are important especially in view of the recent reports of increased risk for cardiovascular mortality and sudden death in patients with anxiety and depression. QTvi can be a valuable noninvasive measure of temporal repolarization lability, especially to study the side effects of medications which affect cardiac autonomic function. Depression and Anxiety 11:126–130, 2000.

Key words: *QT variability; heart rate variability; panic disorder; autonomic; cardiovascular mortality; sudden cardiac death*

INTRODUCTION

Antidepressants such as tricyclic antidepressants (TCAs) and serotonin reuptake inhibitors (SSRIs) are commonly used to treat depression as well as anxiety disorders. Cardiac side effects are frequently reported in patients treated with tricyclic antidepressants (TCAs). Recent literature suggests an association between anxiety and depression, and increased cardiovascular mortality and sudden death [Coryell et al., 1986; Weissmann et al., 1990; Kawachi et al., 1994a,b; Musselman et al., 1998]. Several reports in cardiac patients as well as apparently healthy subjects have shown an association between decreased heart rate (HR) or heart period (HP or RR interval) variability and increased cardiovascular mortality and sudden death [Bigger et al., 1992; Molgaard et al., 1991]. HR variability is influenced by several mechanisms including sympathetic and parasympathetic systems [Akselrod et al., 1981; Pomeranz et al., 1985; Malliani et al., 1991] and a decrease in heart rate (HR) variability is associated with significant cardiac mortality and sudden death. Our previous studies on HR variability and another study by Kawachi et al. also suggested decreased cardiac vagal function and/or a relative increase in cardiac sympathetic function in patients with panic disorder and anxiety [Yeragani et al., 1992, 1993, 1994a, 1995; Kawachi et al., 1995].

QT interval variability closely follows HR variability [Berger et al., 1997]. The QT interval on the surface electrocardiogram (ECG) reflects time for repolarization of the ventricular myocardium. Prolongation of QT interval is associated with ventricular arrhythmias [Jervell and Lange-Nelson, 1957; Schwartz and Wolf, 1978] and abnormal repolarization has been implicated in the genesis of life-threatening arrhythmias [Nguyen et al., 1986; Binah and Rosen, 1992; Tomaselli et al., 1994]. Berger and co-workers [1997] recently

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described an algorithm to calculate beat-to-beat fluctuations in QT interval automatically. They compared patients with dilated cardiomyopathy to normal controls and found that beat-to-beat QT variability is abnormally large in symptomatic patients with dilated cardiomyopathy. Atiga and coworkers [1998] measured the QT variability index (Qtvi) in 95 patients, presenting for electrophysiological studies, to test the ability of QTvi to identify patients with sudden cardiac death or sustained monomorphic ventricular tachycardia on presentation and a 2 year follow-up. Their results showed that QTvi was higher in patients with heart disease than in controls and higher in patients presenting with sudden cardiac death than in other patients with heart disease. In this study, QTvi was the only measure that predicted sudden cardiac death compared to the other measures such as spatial QT dispersion, signal averaged ECG, and heart rate variability. We have recently reported that a change from supine to standing posture and intravenous infusions of isoproterenol result in a significant increase in QTvi, which is a log ratio of QT variability normalized for mean QT over HR variability normalized for mean HR [Yeragani et al., 1999b,c]. Thus an increase in sympathetic activity may play a role in increasing QTvi. We have also found that patients with panic disorder and depression have significantly higher QTvi at baseline, compared to normal controls [Yeragani et al., 1999d].

Roose et al [1998a,b, 1999] have reported that treatment with nortriptyline, a TCA, was associated with a significantly higher rate of cardiac events compared to paroxetine, an SSRI. We have also reported that nortriptyline and paroxetine decrease high frequency power modulated by vagal activity (HF:0.15–0.5 Hz) of HR, which is related to respiratory sinus arrhythmia [Yeragani et al., 1994b; 1999a]. Previous studies have shown that TCAs result in prolongation of QTc interval and that SSRIs appear to be safer compared to TCAs in patients with cardiac disease [Glassman et al., 1987; Roose et al., 1998a,b]. Thus the investigation of beat-to-beat QT variability may prove to be a valuable addition to investigate cardiac side effects of TCAs, SSRIs, and other medications. In this study, we investigated beat-to-beat QT variability in patients with panic disorder before and after nortriptyline and paroxetine treatments.

METHOD

SUBJECTS

The data on HR variability on those patients treated with nortriptyline and paroxetine were presented previously [Yeragani et al., 1994b, 1999a]. The present study includes mainly data on QT variability. Thirteen patients with panic disorder (5 females and 8 males; age: 30.1±4.7 years) (mean±SD) were included in nortriptyline study. We used means and standard deviations (SD) to present all the data in this report. Only supine data could be used for calculation of QT intervals in nortriptyline study, since the standing ECG data of many subjects had noise that precluded the accurate estimation of QT intervals. Sixteen patients with panic disorder (12 females and 4 males; age:37.3±7.7 years) were included in paroxetine study. These studies were approved by the Institutional Review Boards at the Wright State University School Of Medicine, Dayton, OH and Wayne State University School of Medicine, Detroit, MI, and conform to the code of ethics of the World Medical Association. A signed informed consent was obtained from participants. The subjects were physically healthy with no history of hypertension, and their routine blood chemistry and ECG were with in normal limits. These subjects were not taking any medication at least for 2 weeks prior to the studies except for occasional non-opioid analgesics. All patients were diagnosed according to DSM-III R criteria [Spitzer et al., 1987]. Patients were symptomatic at the time of recruitment. All subjects were rated on Spielberger's State Anxiety Inventory (SAI) [Spielberger et al., 1970] before and after treatment with either drug (Table 1). The dosage of nortriptyline was 82±21.6 mg per day for a duration of 11.1±4.7 weeks and of paroxetine, 19.7±4.7 mg per day, for a duration of 15±5.3 weeks.

DATA COLLECTION

Postural studies were conducted in the morning. The ECG was recorded in lead II for 10 min during spontaneous breathing in supine posture after the subjects rested for 5 min. From these records, 256 sec of artifact-free supine data were analyzed.

ANALYSIS OF THE DATA

The ECG was sampled at 500 Hz for the analyses. Thus the accuracy of RR and QT intervals in the present study is 2 msec. QT Variability algorithm has been recently described by Berger and co-workers in full detail [Berger et al., 1997]. This was performed on a PC by using Solaris Desk Top UNIX software (Sunsoft, Mountainview, CA). This program uses a graphical interface of digitized ECG. First, the time of "R" wave is obtained by using a peak detection algorithm, after which the operator provides the program with the beginning and the end of the QT wave template. This algorithm finds the QT interval for each beat by using the time-stretch model. If the operator chooses a longer QT template, all QT intervals will be biased accordingly, but the QT variability measures will be relatively unaffected as we correct the variability for the mean QT interval. Berger and co-workers clearly mention that this algorithm should be used to quantify the QT variability and not the mean QT interval. For further details of this algorithm the readers are referred to the article by Berger and co-workers [Berger et al., 1997]. We have used the same technique in our previous reports [Yeragani et al., 1999b,c].

TABLE 1. QT and HR variability measures (mean±SD) before and after nortriptyline (n=13) and paroxetine tratment in supine posture (n=15)*

	Nortriptyline		Paroxetine	
	Pre-	Post-	Pre-	Post-
SAI score	44.7 ± 3.0	37.3 ± 2.6	39.7 ± 11.9	27.4 ± 4.8
HRm (bpm)	75.2 ± 10.6	87.2 ± 6.2	69.8 ± 8.8	68.7 ± 6.8
HR HF Power (0.15–0.5 Hz)	0.99 ± 1.08	0.42 ± 0.93	0.91 ± 0.74	0.32 ± 0.87
QTm (msec)	410 ± 43.3	387 ± 15.7	426 ± 24	410 ± 43
QTvm (Ln)	–9.7 ± 1.1	–9.1 ± 0.64	–9.8 ± 0.90	–10.2 ± 0.66
QTvi	–1.53 ± 0.32	–1.08 ± 0.45	–1.72 ± 0.40	–1.64 ± 0.30
VLF Coherence (0–0.04 Hz)	0.49 ± 0.18	0.50 ± 0.24	0.56 ± 0.16	0.47 ± 0.18
LF Coherence (0.04–0.15 Hz)	0.45 ± 0.13	0.39 ± 0.23	0.51 ± 0.22	0.43 ± 0.20
HF Coherence (0.15–0.5 Hz)	0.31 ± 0.13	0.31 ± 0.14	0.36 ± 0.13	0.32 ± 0.11

**bpm; beats per minute; msec; milliseconds; SAI; State Anxiety Inventory. Units for HF power are in Ln of beats per minute squared.*

The RR interval and QT interval data were sampled at 4 Hz to obtain instantaneous HR and QT intervals [Berger et al., 1986]. These data were edited by using software, which eliminated any glitches due to premature ventricular beats using a linear spline approach. All data sets had more than 95% qualified beats. The data were then detrended using a linear detrending technique by using the best-fit line prior to the computation of spectral analyses.

The heart rate mean (HRm) and detrended variance (HRv), QT interval mean (QTm), detrended variance (QTv), and QT Variance corrected for mean QT interval, QTvm (Detrended QT variance/mean QT^2) were calculated from the instantaneous HR and QT time series sampled at 4 Hz.

A normalized QT variability index (QTvi) was calculated as described by Berger and co-workers [Berger et al., 1997]:

$$QTvi = Log_{10}\left[\frac{QT_v / QT_m^{\,2}}{HR_v / HR_m^{\,2}}\right]$$

This index represents the log-ratio between the QT interval and the HR variabilities, each normalized for the corresponding mean.

HR and QT interval time series were subjected to spectral analysis and the power-spectrum was computed from 256 sec (1,024 point) segments with the Blackman Tukey method [Berger et al., 1989]. We also obtained the coherence values between HR and QT for the VLF (0–0.04 Hz), LF (0.04–0.15Hz) and HF (0.15–0.5 Hz) range according to the method described by Berger and co-workers [Berger et al., 1997].

STATISTICAL ANALYSIS

We used BMDP statistical software (Berkeley, CA) to perform the analyses. Natural log-transformation (Ln) was used when the variables were not normally distributed. We used a two-way ANOVA by using paroxetine vs. nortriptyline as the grouping factor and pre- and post-treatment measures as the repeated measures factor to compare HR and QT measures for supine posture. When the ANOVA showed a significant group or interaction effect, post-hoc paired *t*-tests were used to compare pre-and post-supine HR and QT variability measures for each drug. We used a probability value of 0.05 as significant for the analyses.

RESULTS

There were significant drug, treatment and interaction effects for HRm and QTvi and significant drug and interaction effects for QTm and QTvm (Tables 1 and 2). Post-hoc tests showed a significant increase of HR and a significant increase in QTvi for nortriptyline condition only (P = 0.007 and 0.006, respectively). There was a significant treatment effect for HR HF power that showed a significant decrease of HF power during both the drug conditions.

ANOVAs did not reveal any significant differences in coherence between HR and QT intervals in VLF, LF, and HF bands for the two drug conditions before and after treatment (Table 1).

DISCUSSION

Our previous reports on HR variability showed significant decreases of SAI scores after treatment with nortriptyline as well as paroxetine and also a significant decrease of HR HF power after treatment [Yeragani et al., 1994b, 1999a]. These results suggested that both treatments were associated with significant anticholinergic effects. The main finding of the present study is a significant increase in QTvi associated with the TCA, nortriptyline. Paroxetine did not result in any significant change in QTvi in spite of its anticho-

TABLE 2. Results of ANOVA comparing the two treatment conditions (df=1,27)*

	Drug[a]	Treatment	Interaction
HRm (bpm)	F=29.9; *P*=0.00001	F=6.4; *P*=0.02	F=9.3; *P*=0.0005
HR HF power (0.15–0.5 Hz)	F=0.08; NS	F=22.3; *P*=0.0001	F=0.02; NS
QTm (msec)	F=13.4; *P*=0.001	F=1.3; NS	F=5.9; *P*=0.02
QTvm (Ln)	F=4.3; *P*=0.05	F=0.4; NS	F=9.7; *P*=0.004
QTvi	F=11.0; *P*=0.003	F=14.8; *P*=0.0007	F=7.1; *P*=0.01

**Drug, Paroxetine vs. Nortriptyline; Treatment: Pre- vs. Post-treatment.*

linergic effect as evidenced by the significant decrease in the HR HF power. QTvi is a noninvasive measure of temporal repolarization lability and, to our knowledge, this is the first report on QTvi in patients with panic disorder before and after treatment with antidepressants. These findings are important in view of our recent findings of increased QTvi in patients with panic disorder compared to normal controls [Yeragani et al., 1999c]. This is especially important in view of the recent findings of Atiga and co-workers [1998]suggesting an association between sudden cardiac death and increased QTvi. Atiga and co-workers have also found that patients with hypertensive cardiomyopathy caused by beta-myosin heavy chain gene mutation exhibit labile repolarization quantified by QTvi and that QTvi may particularly be abnormal in these mutations associated with a poor prognosis [Atiga et al., 2000]. However, we did not find any significant decrease of coherence between HR and QT in VLF, LF or HF bands for either treatment condition.

Our recent report on the effects of postural challenge and infusions of isoproterenol has shown that enhanced sympathetic activity can result in a significant increase in QT variability [Yeragani et al., 1999b,c]. Thus the higher QTvi in patients with panic disorder may partly be due to increased cardiac sympathetic activity [Yeragani et al., 1999d]. Nortriptyline produced a significant increase in QTvi, while paroxetine did not result in such a change. Thus nortriptyline may not be as safe as paroxetine in treating patients with coexisting cardiac disease. In fact, Roose et al. [1998a,b, 1999] report that SSRIs are safer than nortriptyline in treating patients with coexisting cardiac disease. The findings of the present study are interesting because paroxetine did not result in a significant increase of QTvi in spite of its anticholinergic effects as shown by a significant decrease in HR HF power. This suggests that an anticholinergic effect may not have a substantial effect by itself on the values of QTvi.

CLINICAL IMPLICATIONS

The association of increased QT variability with an enhanced cardiac sympathetic activity may increase the chances of ventricular arrhythmias in susceptible patients. Patients with anxiety and depression appear to have increased QT variability and thus it becomes very important to treat these conditions with pharmacological agents, which do not increase QTvi. Also in patients with coexisting cardiac illness, SSRIs should be preferred as the first line of treatment.

STUDY LIMITATIONS

We have measured QT variability only in 256 second segments in the morning time and this may not adequately reflect the circadian changes. The methodology for identifying QT intervals is new [Berger et al., 1997] and further studies are needed to validate this technique. These treatment studies are open and thus the results should be considered preliminary.

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