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Twenty-Four-Hour QT Interval Variability: Increased QT Variability during Sleep in Patients with Panic Disorder

Vikram Kumar Yeragani[a] Robert Pohl[a] Richard Balon[a] V.C. Jampala[b] Anusha Jayaraman[c]

[a]Department of Psychiatry, Wayne State University School of Medicine, Detroit, Mich., and [b]Veterans Administration Hospital, Dayton, Ohio, USA; [c]Bangalore University, Bangalore, India

Key Words
QT variability · Heart rate variability · Cardiac mortality · Autonomic · Panic disorder · Diurnal changes

Abstract
Recent studies on beat-to-beat QT interval variability (QTV) have shown that it can be used as a noninvasive measure of cardiac repolarization lability. It is also a predictor of sudden cardiac death and is higher in patients with anxiety and depression. This study examined the diurnal measures in QTV in 32 normal adults and 22 patients using 24-hour electrocardiogram records. We obtained 8 5-min segments of ECG sampled at 1,000 Hz from the 24-hour records. Our results show that QTV measures at nighttime are significantly higher in patients with panic disorder compared with controls. These findings demonstrate blunted diurnal changes in ventricular repolarization lability in patients resulting in a higher QT variability index during sleep. We speculate that these effects may relate to a relative increase in cardiac sympathetic activity in patients with panic disorder, and may contribute to the increased risk for cardiac mortality in patients with anxiety.

Introduction

Spectral analysis of heart rate (HR) variability usually reveals three peaks in the following bands: very low frequency (VLF: 0–0.04 Hz), low frequency (LF: 0.04–0.15 Hz) and high frequency (HF: 0.015–0.5 Hz). VLF is related to peripheral vascular mechanisms, renin-angiotensin system and thermoregulatory mechanisms, LF power to baroreceptor mechanisms related to sympathetic as well as parasympathetic systems and HF power to respiratory sinus arrhythmia, which mainly reflects cardiac vagal function [1–3]. With increasing age, there is a decrease in heart period or HR variability, especially in the HF range [4–7]. QT interval on the surface electrocardiogram (ECG) reflects the time for repolarization of myocardium and prolongation of QTc is strongly associated with sudden cardiac death. Cardiac repolarization plays an important role in causing sudden death and an increase in sympathetic activity and a decrease in cardiac vagal activity makes the myocardium vulnerable to fatal arrhythmias [8–11].

As QT interval follows HR closely, and recent literature has shown the possible utility of QT variability as a noninvasive marker of cardiac repolarization, and a high-

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Prof. Dr. V.K. Yeragani
Wayne State University School of Medicine
Flat No 16, K.C.N. Mansion
Bangalore-560001 (India)
Tel. +91 80 2287715, E-Mail vikramyershr@yahoo.com

er QT variability is associated with sudden death in cardiac patients and also with coronary patients with effort angina pectoris, we have been investigating the diurnal changes in QT variability on short-term QT interval time series of 5-min ECG records in addition to several other studies on QT variability in supine and standing postures [12–19]. Also a decrease in heart period variability is associated with increased cardiac mortality in patients with cardiac disease as well as normal controls [20–24].

Several studies suggest an association between anxiety and increased cardiac mortality [25–28]. There is also strong support for decreased HR variability associated with certain conditions of anxiety [29–31]. QTvi is an index of QT variability corrected for mean QT interval divided by HR variability corrected for mean HR. Thus, an increase in QT variability and a decrease in HR variability make this statistic more sensitive to distinguish different groups in regard to ventricular repolarization lability [12]. In the present study, we have extended our investigation to QT interval variability (QTV) over 24 h to investigate if QT variability measures are significantly different in normal controls compared with patients with panic disorder using 24-hour ECG records.

Methods

Subjects

Thirty-three normal adults [11 males, 22 females; 34.3 ± 9.6 years (mean ± SD)] and 22 patients with panic disorder matched for gender (7 males and 15 females; 35.9 ± 7.9 years) participated in this study. We have used means and standard deviations throughout the text and tables of this paper. These studies were approved by the Institutional Review Boards at the Wayne State University School of Medicine, Detroit, Mich., and the Wright State University School of Medicine, Dayton, Ohio, USA. All subjects were healthy and informed consent was obtained prior to their participation in these studies. The subjects had no history of hypertension, and their routine blood chemistry and ECG were within normal limits. These subjects had not taken any medication for at least 2 weeks prior to the studies except for occasional nonopioid analgesics. Patients were diagnosed according to the DSM-II-R criteria [32] and were symptomatic at the time of recruitment. At the baseline evaluation, the subjects' severity of anxiety was rated using Spielberger's State Anxiety Inventory [33].

Twenty-four-hour ECG was recorded with Delmar Cardiocorders on microcassettes using standard procedures. The 5-min segments of ECG were digitized from the 24-hour ECG for each hour at 1,000 Hz at the beginning of each hour. These 5-min segments will provide more accuracy for the QT variability analyses, as the resolution for the QT intervals will be 1 ms. From these 20- to 24-hour segments, we chose 8 noise-free 5-min ECG segments every 3 h for QT analyses. The patients recorded when they went to sleep and woke up. Almost all records were begun between 8 and 11 a.m. and continued for 24 h.

QT Variability

All these analyses were conducted on 5-min segments of data sampled at 1,000 Hz. This QT variability algorithm has been described in detail by Berger et al. [12] and has been used by his and our groups in previous studies [13, 15–19]. It was performed on a PC using Solaris Desktop Unix software (Sunsoft, Mountainview, Calif., USA). It uses a graphical interface of digitized ECG where the time of the 'R' wave is obtained using a peak detection algorithm. Then, 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 using the time-stretch model. If the operator chooses a longer QT template, all the QT intervals will be biased accordingly. This algorithm should only be used to study QT variability and not the mean QT.

The HR (beats per minute: bpm) time series were sampled at 4 Hz using the technique of Berger et al. [34]. The amplitude spectrum of this HR signal more closely matches that of the input signal to an integral pulse frequency modulation model of the heart's pacemaker than do the spectra of other ECG-derived HR signals. The HR signal produced by this algorithm is like a stepwise continuous instantaneous HR signal convolved with a rectangular (boxcar) window. This signal maintains amplitude equal to the reciprocal of the current R-R interval, for the duration of that R-R interval. It also works as an antialiasing filter. It behaves as a low-pass filter, passes very little power beyond the Nyquist rate. It preserves all the frequencies up to 1/4th of the sampling rate. The way we use it in all our studies including this one, it does not affect the information up to 1 Hz as we sample the signal at 4 Hz. We used HR time series free of ventricular premature beats and noise. The data were then detrended by using the best-fit line prior to the computation of spectral analyses.

The mean HR (HRm), detrended HR variance (HRv), mean QT interval (QTm), detrended QT variance (QTv) and QTvm, QTv corrected for QTm (QTv/QTm squared) were calculated from the instantaneous HR and QT time series of 1,024 points (256 s).

A normalized QTvi was calculated as suggested by Berger et al. [12].

$$QTvi = \log_{10} [(QTv/QTm^2)/(HRv/HRm^2)]$$

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

Spectral Analyses

HR time series (256 s at 4 Hz = 1,024 points) was subjected to spectral analyses and the power spectrum was computed with the Blackman-Tukey method [35]. The powers were integrated in the bands of VLF, LF and HF regions. HR and QT interval time series were subjected to spectral analysis and the cross-spectrum between the two time series was computed from 256 s with the Blackman-Tukey method [35].

Statistical Analysis

Analysis of variance for repeated measures was used for all 8 epochs of HR and QT variables. Significant effects were followed up by individual comparisons (two-tailed t tests) for variables of interest. Twenty-four-hour means were also compared using two-tailed t tests. Significance level was set at $p \leq 0.05$. Subjects with missing data points were excluded from the analyses.

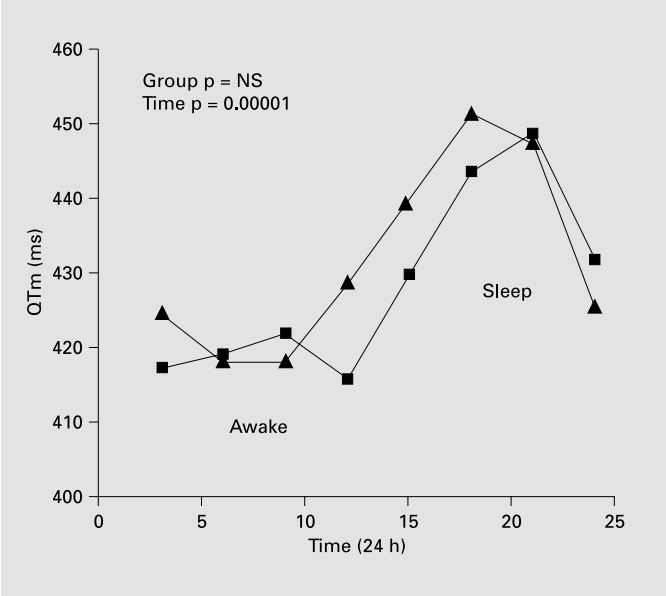

Fig. 1. Mean QT interval in milliseconds over the 24-hour period illustrating significant diurnal differences in both groups. ▲ = Patients; ■ = controls.

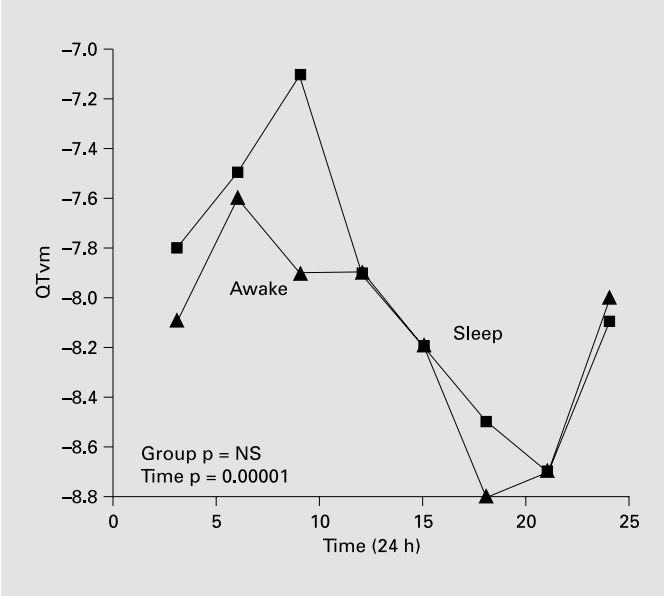

Fig. 2. QTvm, which is Ln of QT interval, detrended variability divided by mean QT squared over the 24-hour period illustrating significant diurnal differences in both groups. ▲ = Patients; ■ = controls.

Results

The graphs represent 8 points, the first 3 during awake period, the 4th just before sleep, 5–6 during sleep and the last 2 in the morning.

Patients were significantly more anxious than controls on the State Anxiety Inventory ($p < 0.0001$). There were significant increases in QTm ($F = 11.2$; d.f. = 7,343; $p < 0.00001$) and significant decreases in QTvm ($F = 4.9$; d.f. = 7,343; $p < 0.00001$) and QTvi ($F = 6.7$; d.f. = 7,315; $p < 0.00001$) during sleep in either group ($p < 0.00001$), but the decrease in QTvi was more pronounced in the control group (fig. 1–3). There was also a significant group difference for QTvi showing higher values for patients, especially at nighttime ($F = 5.0$; d.f. = 1,49; $p < 0.03$). Comparing the sleep values showed that for the 7th epoch, QTvi as well as QTvm were significantly higher in patients ($p < 0.0001$ and $p < 0.04$, respectively). QT-LF power was lower during sleep in both groups ($F = 5.0$; d.f. = 7,343; $p < 0.00001$). The HF power was significantly lower during sleep only in normal controls ($F = 7.5$; d.f. = 7,259; $p < 0.00001$). This diurnal change was not significant in the patient group (fig. 4, 5). There was also an increase in coherence in the band of 0–0.5 Hz during sleep in either group ($F = 7.6$; d.f. = 7,343; $p < 0.00001$) (fig. 6).

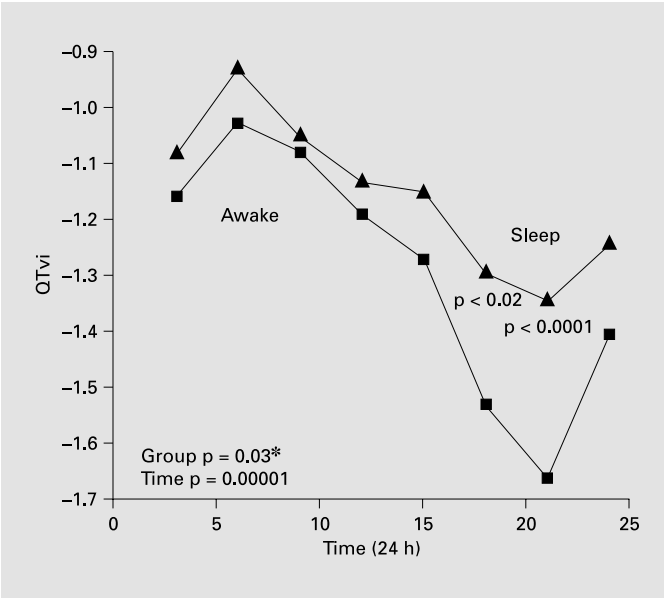

Fig. 3. Values of QTvi over the 24-hour period illustrating significant diurnal differences in both groups. Sleep QTvi was significantly higher in patients and the diurnal changes were more pronounced in controls. ▲ = Patients; ■ = controls.

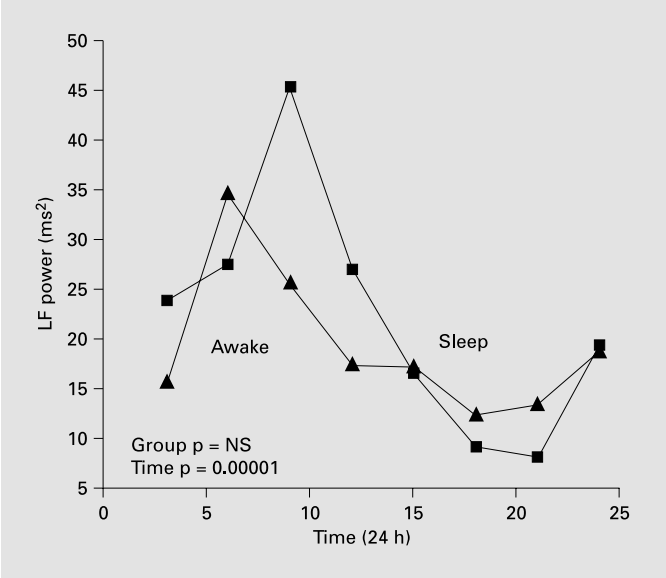

Fig. 4. Means LF power of QT in milliseconds squared over the 24-hour period illustrating significant diurnal differences in both groups. The diurnal changes were more pronounced in controls. ▲ = Patients; ■ = controls.

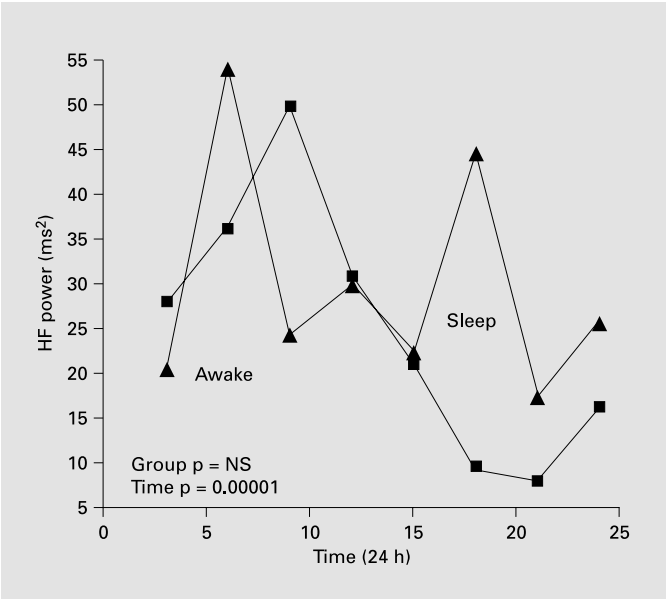

Fig. 5. Means of HF power of QT in milliseconds squared over the 24-hour period illustrating significant diurnal differences in both groups. The diurnal changes were not significant in the patient group. ▲ = Patients; ■ = controls.

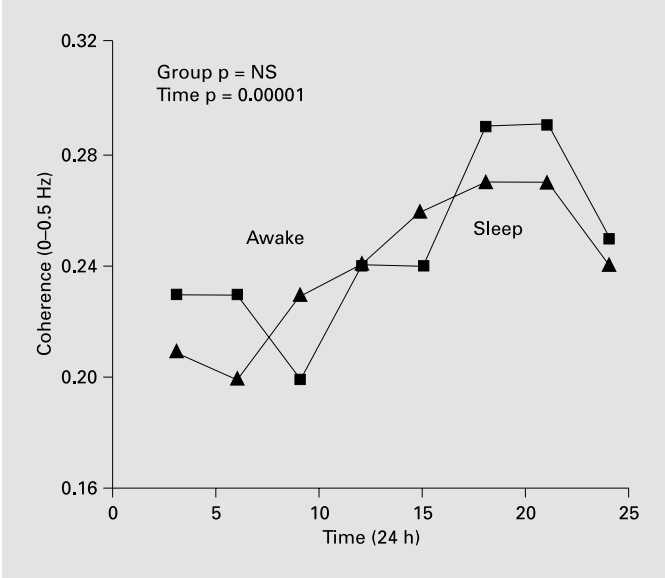

Fig. 6. Coherence in the band of 0.0–0.5 Hz between QT interval and HR from cross-spectral analysis over the 24-hour period illustrating significant diurnal differences in both groups. ▲ = Patients; ■ = controls.

Table 1 shows the mean values for 24-hour records for all the variables. Only QTvi was significantly different between the two groups ($p < 0.03$). There were no significant correlations between QTvi and any of the anxiety measures.

Discussion

To our knowledge, this is the first report on diurnal changes in QT variability measures in patients with panic disorder. However, one should note that we used only 8 segments of 256 s of ECG every 3 h rather than the whole 24-hour record due to the labor-intensive nature of the study of using a 1,000-Hz sampling rate and to have relatively stationary segments. These findings are in agreement with our earlier findings of increased QTvi in patients with panic disorder compared with normal controls [16].

These findings have important implications to use QTV as a noninvasive tool to study cardiac repolarization lability in relation to any conditions that are known to be associated with increased cardiac mortality, and also to investigate the effects of certain drugs on cardiac repolarization. This is especially important in children, as drugs such as tricyclic antidepressants are associated with sever-

Table 1. Twenty-four-hour mean ± SD of QT variability measures of controls and patients (average of 8 epochs over 24 h

	Controls (n = 32)	Patients (n = 20)	t	p
QT mean, ms	428 ± 20	432 ± 22	0.66	NS
QTv, ms^2	115 ± 54	99 ± 60	0.32	NS
QTvi	−1.28 ± 0.19	−1.15 ± 0.26	2.04	0.03
LF power (0.04–0.15 Hz), ms^2	39.3 ± 25.4	30.0 ± 14.5	1.4	NS
HF power (0.15–0.5 Hz), ms^2	34.2 ± 20.0	24.1 ± 12.3	1.9	NS
Total coherence (0–0.5 Hz)	0.27 ± 0.06	0.24 ± 0.06	1.38	NS

Degrees of freedom for the analyses = 50.

al sudden deaths [36]. Berger et al. [12] have reported that there was a significantly decreased coherence in the 0- to 0.2-Hz range in patients with dilated cardiomyopathy (0.39 vs. 0.28; $p < 0.0001$). Our previous values of coherence from laboratory records of subjects in supine posture for the 0- to 0.5-Hz range were 0.32 and 0.35 for normal adults and patients with panic disorder are much higher than the mean values of coherence for the 24-hour records (0.27 and 0.24 for normal controls and patients). This could be due to the difference between the laboratory records and the 24-hour ambulatory records. One should also note that the mean coherence as used in this study is simply the arithmetic mean of all the values in a particular frequency band and were not weighted. Hence the coherence values are low.

Our previous reports showed that enhanced sympathetic activity is associated with an increased QTvi and that patients with panic disorder and depression have higher QTvi at baseline [15, 16]. Sympathetic as well as parasympathetic systems influence the QT interval and the enhanced sympathetic drive may be responsible for the circadian variation of the QT interval [37–41]. Beta-blockers are associated with a decrease in QT variability [42]. Kostis and Belina [43] have shown that though there was an increase in the mean QT interval at nighttime, beat-to-beat QT variability was significantly lower ($p = 0.0005$). They attributed these changes to a higher vagal activity at nighttime. Our findings are essentially similar and QTvm as well as QTvi were significantly lower during sleep and increased again in the morning. It is also important to note that autonomic modulation of sinus node and ventricular myocardium are independent to a certain extent, and this might be exaggerated in cardiac conditions resulting in decreased coherence between HR and QT interval fluctuations [12, 43–45]. This again underscores the importance of QT variability as a novel measure of ventricular repolarization, which might yield additional information to that of HR or QT variability alone. These findings are also important as two previous reports suggested a possible increase in left ventricular mass in patients with panic disorder [46, 47].

The present investigation demonstrates blunted diurnal fluctuations in QTv measures in patients with panic disorder. This probably reflects in the higher QTvi values at nighttime in the patient group. We speculate that these effects may relate to changes in cardiac autonomic function, and may contribute to the well-known diurnal variation in the incidence of ventricular arrhythmias. This may also partly be due to a relative increase in cardiac sympathetic function in this group of patients. These findings may have implications for evaluating the risk for significant cardiac events in vulnerable populations, and also to evaluate the safety of certain medications such as antidepressants in these vulnerable populations.

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