Relationship between Beat-to-Beat Variability of RT-Peak and RT-End Intervals in Normal Controls, Patients with Anxiety, and Patients with Cardiovascular Disease

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Background: Some studies suggest that it is important to take the end of "T" wave to quantify QT-interval variability, which signifies cardiac repolarization lability, as there is substantial and important information beyond the peak of the T wave on the surface electrocardiogram.

Methods: In this study, we examined the relationship between the variability of beat-to-beat RTe (beginning of R-peak to T-end) and the variability of RTp (R-peak to T-peak) in the following groups: normal controls (n = 26), patients with anxiety (n = 26), and patients with cardiovascular disease with or without diabetes (n = 63). We obtained ECG sampled at 1024 Hz in lead II configuration in supine posture to obtain beat-to-beat interbeat interval (R-R) and RT-interval variability for 256 seconds.

Results: We found significant positive correlations ($r = 0.8$; $P < 0.00001$) in normal controls and patients with anxiety between the variability of RTeVI and RTpVI (RTe and RTp variability indices, respectively, corrected for the mean of RTe and RTp and the mean and the variance of R-R). These correlations were also statistically significant in the medically ill group but the r values were much smaller ($r = 0.45$ in various groups). The slopes were also significantly different between the two groups ($P < 0.001$). Bland-Altman plots also showed better agreement between the two measures in the controls and patients with anxiety compared to the group with cardiovascular disease.

Conclusions: These findings have methodological implications for studies comparing people with and without overt cardiovascular illness. While RTe or RTp variability index may be used interchangeably in normal controls and some patients with no overt cardiovascular problems, it may be more prudent to use both RTe and RTp variability indices in patients with cardiovascular illness. These indices, especially RTeVI, may provide different information about cardiac repolarization lability. Future studies should address the importance of the relative usefulness of these two measures especially in cardiac patients before and after successful treatment.

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QT variability; T-wave end; T-wave peak; normal controls; anxiety; cardiac disease; diabetes; mortality

Beat-to-beat heart rate (HR) or heart period (HP or R-R) variability is a useful noninvasive tool to study cardiac vagal function and decreased HR variability is associated with poor prognosis in several disease states.¹⁻³ Beat-to-beat QT-interval variability (QTV) obtained from the surface electrocardiogram

(ECG) is useful to study cardiac repolarization lability, and some recent studies have related this measure to significant cardiac mortality.⁴⁻⁶

Cardiac repolarization lability plays an important role in causing sudden death.⁷ An increase in sympathetic activity and a decrease in cardiac vagal

activity make the myocardium vulnerable to fatal arrhythmias.^{8,9} Beat-to-beat QTV appears to be an important and independent measure of cardiac mortality and severity of illness in patients with heart disease as well as in coronary patients with effort angina pectoris.^{4-6,10,11} We have found that beat-to-beat QTV significantly increases during challenges associated with an increase in cardiac sympathetic activity, including a change from supine to standing posture, administration of intravenous isoproterenol and pemoline, drugs that have sympathomimetic effects.¹²⁻¹⁴ A recent study has shown that cocaine also increases QTV.¹⁵ All these studies suggest an influence of sympathetic system on QTV. Patients with anxiety disorders are at a higher risk for cardiovascular mortality and sudden death,¹⁶ and our previous studies have shown a significantly higher QTV in patients with anxiety.^{17,18}

Several recent studies have examined beat-to-beat fluctuations in ventricular repolarization by using the interval from peak of the R wave to peak of the T wave (RTp interval).¹⁹⁻²¹ This approach can potentially ignore fluctuations in repolarization that principally influence the latter part of the T wave. This issue may be of lesser importance in studying repolarization lability in normal subjects but is likely to be a significant issue while considering individuals with structural heart disease or metabolic abnormalities, which are associated with after depolarization.²²

In all our previous studies, we used QT variability index (QTvi), which is derived as follows:

$QTvi = \log_{10}[(QTV/QTm^2)/(RRv/RRm^2)]$,
where QTV is detrended QT variance, QTm, mean QT interval; RRv, R-R interval detrended variance; and RRm, R-R interval mean.

We have always used the end of T wave (QTe) to calculate beat-to-beat QT variability in our previous studies.^{23,24} The main aim of this study was to systematically investigate the relationship between QTeVI (measured as RTeVI in this article) and QTpVI (measured as RTpVI) in normal controls, in patients with anxiety disorder (a condition associated with abnormal QT variability but no overt cardiac disease), and in patients with cardiovascular illness (with or without diabetes). In patients with heart failure, an increase in action potential duration in the M (mid myocardial) cells may result in transmural electrical heterogeneity, which may result in prolonged QT interval and an increased transmural dispersion of ventricular repolarization reflecting in

more heterogeneity in the terminal portion of the QT interval. Hence, we sought to test the hypothesis that the correlation between the above two indices would be less significant in patients with cardiac disease.

METHOD

Subjects: There were 26 normal controls (14 males and 12 females; age: 51 ± 11 years) and 26 patients (15 males and 11 females; age: 44 ± 11 years) with anxiety disorders, and 63 patients with cardiovascular illness (36 males and 27 females; age: 55 ± 10 years) in the patient group. All patients were of east Asian origin. Patients with anxiety were diagnosed according to the DSM III-R criteria.²⁵ Normal controls and patients with anxiety had no history of drug addiction, alcoholism or any significant medical illness, especially diabetes or hypertension, and these subjects were not on any medication except for occasional nonnarcotic analgesics. Patients with cardiovascular illness were outpatients who were consecutively recruited into the study with a diagnosis of hypertension ($n = 21$), coronary artery disease ($n = 25$) and congestive heart failure ($n = 17$). Diabetes was not an exclusion criterion. Most of the patients were on the following medications: atenolol, carvedilol, enalapril, lisinopril, ranitidine, perindopril, amlodipine, aspirin, antioxidants, clopidogrel, furosemide, losartan, and oral hypoglycemic drugs. However, 14 patients with hypertension were newly diagnosed and were not on any medication. These studies were approved by the ethics committee at the M.S. Ramaiah Hospital, Bangalore, India. The studies were explained to the patients and informed consent was obtained prior to their participation in the studies. The noninvasive nature of the studies was particularly stressed up on before the subjects' participation to alleviate any anxiety, especially in the patient group.

Beat-to-Beat R-R and QT-Interval Variability

Data Acquisition

ECG was continuously acquired in lead II configuration in a noise-free environment. The tests were performed while the patient lied down quietly on the bed. The ECG signal was digitized at 1024 Hz and the data were saved on a PC for later analyses. The subjects lied down quietly for at least 5 minutes before the supine data for 320 seconds

were acquired. We used 256 seconds of artifact-free data for the analysis of RT variability.

RT Variability

The QT-variability algorithm has been described by Berger and coworkers in detail and has been used by his and our groups in previous studies.^{4,5,17,18,23,24} Baseline wander is removed by digital filtering, using a pass band >0.3 Hz. This technique uses a graphical interface of digitized ECG (sampled at 1024 Hz, which gives a precision of 1 msec to measure the R-R and QT intervals), and 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. The actual variance of the QT interval is calculated from the R peak to the end of the T wave. We call this RTe in this study. The computer program also automatically identifies the peak of the T wave and writes the time of occurrence of these peaks. We calculated the distance from the peak of the R wave to the peak of the T wave and we call it RTp. The output of this algorithm contains beat-to-beat R-R intervals and RTe and RTp intervals.

The beat-to-beat R-R intervals in msec were sampled at 4 Hz using linear interpolation. The RTe and RTp intervals were similarly constructed at 4 Hz using linear interpolation. We used R-R time series free of ventricular premature beats and noise. The R-R and QT interval data were then detrended by using the best-fit line prior to the computation of the variability indices.

The mean R-R (RRm), detrended R-R variance (RRv), mean RT interval (RTm), and detrended RT variance (RTv) were calculated from the instantaneous RR and RT time series of 1024 points (256 seconds). Mean R-R and mean RT intervals are in milliseconds (ms).

A normalized RT variability index (for both RTe and RTp) was calculated as suggested by Berger et al.^{4,5,23,24}

$$RTvi = \text{Log}_{10}[(RTv/RTm^2)/(RRv/RRm^2)]$$

We used R-R mean R-R variance instead of HR as the denominator in the equation unlike in our

previous studies. This index represents the log-ratio between the RT interval and the R-R variabilities (detrended), each normalized for the corresponding mean.

Statistical Analysis

We used BMDP statistical software to perform the analyses. All tests were two-tailed and a probability value of <0.05 was accepted as significant. We used Pearson Product-Moment Correlation statistic to examine the relationship between the variability indices of RTeVI and RTpVI among the three groups of subjects. We also compared the slopes for the above correlations between patients with cardiovascular disease and the other two groups. In addition to the regression plots, we also used Bland-Altman plots for the two groups to examine the agreement of the two measures, RTeVI and RTpVI.^{26,27}

RESULTS

Table 1 shows the mean $\pm$ SD of age, R-R and RT interval measures for the three groups of subjects. Figure 1 illustrates the significant positive correlation between RTpVI and RTeVI in the two groups with and without cardiac disease ($r = 0.4-0.8$). However, the relationship was much more significant in the subjects without cardiac disease ($r = 0.7-0.8$) compared to those with cardiac disease ($r = 0.4$), and there was a significant difference between the slopes in the two groups ($F = 7.9$; $df = 111$; $P < 0.0005$).

The r values between RTpVI and RTeVI were very similar between the control subjects and patients with anxiety and also males and females in these groups ($r = 0.7-0.8$). The r values ranged from 0.35 to 0.45 among different patient groups (those with hypertension, coronary artery disease with or without diabetes) and males and females. Of particular note is that the patients with newly diagnosed hypertension, who were not on any medication ($n = 14$), also had an r value of 0.45 between RTpVI and RTeVI. The slopes were significantly different even when we compared normal controls or the patients with anxiety to the patients with cardiac illness separately ($P < 0.02$).

In addition to the regression plots (Fig. 1), Bland-Altman plots (Fig. 2) also showed that the agreement between RTeVI and RTpVI were much more

Table 1. RTp, RTe, and R-R Interval Measures of the Three Groups of Subjects (mean $\pm$ SD)

Variable	Normal Controls (n = 26)	Patients with Panic Disorder (n = 26)	Patients with Cardiovascular Disease (n = 63)
Age (years)	51 $\pm$ 11	44 $\pm$ 11	55 $\pm$ 10
R-R interval mean $\pm$ SD (ms)	855 $\pm$ 135	788 $\pm$ 95	796 $\pm$ 132
R-R Detr Var (ms ²)	1083 $\pm$ 954	1153 $\pm$ 1293	758 $\pm$ 591
RTe mean (ms)	366 $\pm$ 51	350 $\pm$ 60	367 $\pm$ 52
RTe Detr Var (ms ²)	20 $\pm$ 22	18 $\pm$ 30	50 $\pm$ 63
RTp mean (ms)	254 $\pm$ 45	240 $\pm$ 53	229 $\pm$ 38
RTp Detr Var (ms ²)	18 $\pm$ 12	17 $\pm$ 20	46 $\pm$ 56
RTeVI	-1.50 $\pm$ 0.50	-1.41 $\pm$ 0.40	-1.10 $\pm$ 0.50
RTpVI	-0.62 $\pm$ 0.42	-0.55 $\pm$ 0.40	-0.25 $\pm$ 0.54

Detr Var = detrended variance; ms = milliseconds.

significant in the control group compared to patients with cardiac disease.

The main aim was not the comparison of the three groups for the mean values of RTeVI and RTpVI. However, both measures were significantly higher in patients with cardiovascular disease than in the control and anxiety groups after adjusting for age ($P < 0.01$). Both measures were also significantly higher in patients with anxiety disorder compared to normal controls after adjusting for age ($P < 0.05$).

DISCUSSION

The main finding of this study is that there is a less significant relationship between RTp and RTe interval variability indices in patients with cardiovascular disease compared to normal controls or patients with anxiety with no overt cardiac disease. Even in subjects with no overt cardiac disease, the r values were only up to 0.8, which means 64% of the variance can be explained between the two measures. This is about 16% in patients with cardiac disease, a substantial difference. Similarly Bland-Altman plots also show that the agreements between RTeVI and RTpVI were much more significant in the control group. Figure 2 illustrates the larger standard deviation of the differences between RTpVI and RTeVI in patients with cardiac disease compared to the control group. This again suggests a better agreement of RTpVI and RTeVI in controls compared to patients with cardiac disease.

Hence, studies using cardiac repolarization lability should preferably use RTeVI. However, we do not know if RTpVI is independently important. Future studies should address these issues keeping in mind the difficulties associated with different techniques to identify the peak or the end of the T wave. This study also shows higher RTpVI and RTeVI in patients with cardiac disease, which is in agreement with the previous reports^{4,6}. However, this was not the objective of this study. In a recent study,²⁸ Berger and coworkers have shown that biventricular pacing caused a significant reduction of measures of ventricular dispersion of repolarization using T-peak and T-end intervals. In patients with heart failure, an increase in action potential duration in the M (mid myocardial) cells may result in transmural electrical heterogeneity,

Figure 1. Positive correlation of RTeVI (y-axis) and RTpVI (x-axis) in normal controls and patients with anxiety (upper panel) and patients with cardiac disease (lower panel). There was a significant difference of the slopes between the two groups.

Figure 2. Bland–Altman plots of the two groups. The upper panel shows the plot of the patients with cardiac disease and the lower panel shows the plot of normal controls and patients with anxiety disorder. The x-axis represents the average values of RTeVI and RTpVI, and the y-axis the difference between these two values. The lines above and below the mean difference represent 95% confidence interval limits. The graphs show that while one subject's values are out of the 95% confidence limits in the controls group, there are five such subjects in the group with cardiac disease. The graphs illustrate higher standard deviation (SD) of this difference in patients with cardiac disease. There is also more dispersion of the values of difference around the mean in the group with cardiac disease compared with controls.

which may result in prolonged QT interval and an increased transmural dispersion of ventricular repolarization.²⁹ This may, in turn, result in intramural conduction block and reentrant polymorphic arrhythmias.³⁰ The T-peak to T-end interval, in particular can contain information of transmural dispersion of repolarization in a wedge of myocardium, which could be related to the risk of arrhythmias.^{31,32} In fact one study suggests that the T-peak to T-end interval may be a valuable predictor of arrhythmogenicity in congenital long QT syndrome.³³

Reproducibility and Precision of RTe and RTp Measurements

Measurement of the peak of the R wave to peak of the T wave is more reliable than the end of the T wave even when we use the template-matching techniques.³⁴ Any kind of noise would decrease the accuracy of detecting the end of the T wave. This is especially true in patients with atrial fibrillation, bundle branch blocks, and paced rhythms. However, all our subjects were in sinus rhythm during the tests. It is also important to note that we have little information available as to the effects of drugs on RTe detection. However, our findings remained the same even when we examined the hypertensive patients, who were not on any medication. Future studies should particularly examine the validity of the RTe intervals in particular in various disease conditions and also the effects of medications on this measure.

Limitations and Future Directions

This study has included patients with cardiac disease who had different grades of physical symptoms and we do not have data on adequately treated asymptomatic patients in this study. It will be important to examine the relationship between RTp and RTe intervals in larger samples of patients with different cardiac diseases. This is a preliminary study comparing subjects with no apparent heart disease compared to those with a diagnosed cardiac condition.

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