Beat-to-Beat QT Interval Variability Is Primarily Affected by the Autonomic Nervous System

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Background: Beat-to-beat QT interval variability is associated with life-threatening arrhythmias and sudden death, however, its precious mechanism and the autonomic modulation on it remains unclear. The purpose of this study was to determine the effect of drugs that modulate the autonomic nervous system on beat-to-beat QT interval.

Method: RR and QT intervals were determined for 512 consecutive beats during fixed atrial pacing with and without propranolol and automatic blockade (propranolol plus atropine) in 11 patients without structural heart disease. Studied parameters included: RR, QTpeak (QRS onset to the peak of T wave), QTend (QRS onset to the end of T wave) interval, standard deviation (SD) of the RR, QTpeak, and QTend (RR-SD, QTpeak-SD, and QTend-SD), coefficients of variation (RR-CV, QTpeak-CV, and QTend-CV) from time domain analysis, total power (TP; RR-TP, QTpeak-TP, and QTend-TP), and power spectral density of the low-frequency band (LF; RR-LF, QTpeak-LF, and QTend-LF) and the high-frequency band (HF; RR-HF, QTpeak-HF and QTend-HF).

Results: Administration of propranolol and infusion of atropine resulted in the reduction of SD, CV, TP, and HF of the QTend interval when compared to controlled atrial pacing (3.7 ± 0.6 and 3.5 ± 0.5 vs 4.8 ± 1.4 ms, 0.9 ± 0.1 and 0.9 ± 0.1 vs $1.2 \pm 0.3\%$, 7.0 ± 2.2 and 7.0 ± 2.2 vs 13.4 ± 8.1 ms², 4.2 ± 1.4 and 4.2 ± 1.2 vs 8.4 ± 4.9 ms², respectively). Administration of propranolol and atropine did not affect RR interval or QTpeak interval indices during controlled atrial pacing.

Conclusions: Beat-to-beat QT interval variability is affected by drugs that modulate the autonomic nervous system.

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QT interval; QT interval variability; autonomic nervous system

Prolongation of QT interval is implicated in the pathogenesis of cardiac arrhythmias and sudden death.¹ Beat-to-beat QT interval variability has also been reported to be increased in patients with dilated cardiomyopathy,² coronary artery disease³ or in those presenting with sudden cardiac death.⁴ Therefore, QT interval variability could be a useful parameter to study these disease states and the ensuing complications.

The autonomic nervous system also influences the QT interval, either by altering the preceding

RR interval or via direct effects on the QT interval itself. Murakawa et al. demonstrated that QT interval reduction that occurs during the daytime was potentiated by increased sympathetic activity.⁵ Browne et al. reported that drugs that modulate the autonomic nervous system modulate the QT interval independent of rate.⁶ These studies indicate that the autonomic nervous system plays a role in controlling the absolute value of the QT interval, however, it is unclear whether they also may affect QT interval variability. Therefore, the goal of the

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current study is to determine whether modulators of the autonomic nervous system affect beat-to-beat QT interval variability.

METHODS

Patients

The study population included 11 patients (6 men, mean age 59 ± 14 years) without structural heart disease or ECG abnormalities. Five patients had paroxysmal supraventricular tachycardia, three patients had sick sinus syndrome, and three patients had paroxysmal atrial flutter. All medications were discontinued for ≥ 5 half-lives before initiation of the study after signing a written informed consent. Patients who had premature beats $\geq 2\%$ of total beats were excluded from analysis.

Protocol

Electrophysiological study to assess for presence of supraventricular arrhythmias or electrophysiologic abnormalities was performed. A standard 6-French quadripolar catheter was placed in the right atrium, and constant atrial pacing was achieved. The pacing rate was 80/min in all patients, except for three patients with sinus rhythm rate >80 /min in which atrial pacing was performed at 90 or 100/min. Propranolol (0.2 mg/kg IV, at 2 mg/min) was administered. Next, atropine (0.04 mg/kg IV, over 2 minutes) was administered. Before and 15 minutes after the start of propranolol administration and after atropine addition, ECGs were recorded with an FDX-6531 electrocardiograph (Fukuda Denshi Co., Tokyo, Japan), which simultaneously acquires 12 standard leads (6 precordial and 6 limb leads).

Measurements Density of RR Interval, QT Peak Interval, and QT End Interval

A sequence of 10 minutes of ECG data was stored on a PC card (20MB) in digitized format. These data were transferred to a personal computer (PC-9821 FA, NEC, Tokyo, Japan) for RR interval and QT interval analysis and automatic measurement of RR, QT peak, and QT end interval by the computer. QT peak interval was measured from the onset of QRS complex to the apex of T wave, and QT end interval was measured from the onset of QRS complex to the end of T wave. The differential of T wave was rearranged to the absolute value, and the threshold

levels were defined as the mean level from the second T peak in the dV/dt absolute value to the peak plus 104 ms. The end of T wave was determined as the interception of a threshold level with the differential of T wave. QT peak, QT end, and RR intervals for 512 consecutive beats were assessed in V₄ lead. If U wave was present in V₄ lead recordings, measurements were performed using V₃ or V₅ lead.⁷ If premature beats were present, these values of premature beat were altered to the mean values of the preceding and subsequent beats.

Time and Frequency Domain Analysis of RR Interval, QT Peak Interval, and QT End Interval

The RR, QT peak, and QT end interval variability were analyzed with a microcomputer (PC-9821, NEC Co., Tokyo, Japan) using commercial software (Fukuda Denshi Co., Tokyo, Japan). The standard deviation of RR, QT peak and QT end intervals over 512 consecutive beats were estimated (RR-SD, QT peak-SD and QT end-SD). The coefficients of each interval variation (CV) were obtained (RR-CV, QT peak-CV, and QT end-CV). The CV was determined by the following formula: CV = the standard deviation of interval/mean interval $\times 100$. Frequency domain measures of variability were estimated in the range of frequencies from 0.01 to 0.5 cycle/beat with fast Fourier transforms. The total power (TP) and the power spectral density of the low-frequency band (LF) (0.04–0.15 Hz, in ms²) and the high-frequency band (HF) (0.15–0.40 Hz, in ms²) were obtained (RR-TP, QT peak-TP, QT end-TP, RR-LF, QT peak-LF, QT end-LF, RR-HF, QT peak-HF, and QT end-HF).

Statistical Analysis

Values are expressed as mean $\pm$ standard deviation. Repeated measures analysis of variance was used to determine differences in RR, QT peak, and QT end intervals. The significance of intergroup differences was assessed using the Scheffé's criterion and F test. Statistical significance was set at $P < 0.05$.

Reproducibility of QT interval measurement was calculated from two ECG recordings at constant atrial pacing (the first ECG recording and the second ECG recording at 1 hour after the first ECG recording) by using these 11 patients. Correlation between QT peak and QT end measured by the same

method was evaluated using both linear regression analysis expressed as the correlation of coefficient (r) and the Bland-Altman method for assessing the limits of agreement between the repeated measurements.⁸

RESULTS

QT_e interval data from a representative patient is illustrated in Figure 1. Administration of propranolol and atropine resulted in shorter QT_{end} interval and a decreased distribution of QT_{end} interval values.

Administration of propranolol and atropine did not affect RR interval or QT_{peak} interval indices by time and frequency domain analysis during control atrial pacing, but did result in decreased SD and CV of QT_{end} interval and decreased TP and HF of QT_{end} interval. Propranolol administration decreased all QT_{end} interval indices, but did not affect RR interval or QT_{peak} interval (Table 1).

QT Measurement and QT Measurement Reproducibility

RR, QT_{peak}, and QT_{end} were checked visually on the monitor; however, we did not need any corrections except few premature beats. Reproducibility of QT_{peak} and QT_{end} measurement was extremely high (r = 0.99, r = 0.99) (Fig. 2). The mean

differences (d) and the standard deviation of the differences (s) of QT_{peak} and QT_{end} were calculated. For QT_{peak} and QT_{end}, each the upper and lower limits of agreement were +3.37 ms and -3.35 ms, +2.95 and -2.65 ms, respectively.

DISCUSSION

The present study demonstrated that drugs that modulate the autonomic nervous system result in alterations in QT interval variability. Propranolol decreased QT interval variability, but did not affect RR interval or QT_{peak} interval during constant atrial pacing. Therefore, the effect of the sympathetic nervous system on QT interval variability does not require changes in RR interval and may occur by an alternate, more direct mechanism.

Autonomic Tone Effects on QT Interval and QT Interval Variability

It is known that autonomic tone contributes to modulations of the QT interval directly through it influence on the ion channel made of myocardial action potential, and indirectly through it influence on heart rate. Browne KF et al. showed that atropine administration resulted in decreased QT interval during atrial constant pacing⁶ and that QT interval was prolonged during sleep when compared to awake states with identical heart rates.⁹

QT end interval

Figure 1. Data of QT end interval from a representative patient. Left panel represents during control atrial pacing. Middle panel represents after propranolol administration. Right panel represents after atropine administration.

Table 1. Time Domain Analysis and Frequency Domain Analysis of RR, QT Peak, and QT End Interval Variability at Control Pacing and after Administration of Propranolol and Atropine

	CONT	PROP	PROP+ ATRO
Mean RR (ms)	721 ± 52	721 ± 52	721 ± 52
Mean QTpeak (ms)	292 ± 35	293 ± 39	288 ± 34
Man QTend (ms)	397 ± 28	395 ± 30	392 ± 28
RR-SD (ms)	3.0 ± 1.5	2.7 ± 0.6	2.4 ± 0.4
QTpeak-SD (ms)	2.6 ± 0.6	2.4 ± 0.7	2.1 ± 0.5
QTend-SD (ms)	4.8 ± 1.4	3.7 ± 0.6*	3.5 ± 0.6**
RR-CV (%)	0.4 ± 0.2	0.4 ± 0.1	0.3 ± 0.1
QTpeak-CV (%)	0.9 ± 0.2	0.8 ± 0.2	0.7 ± 0.1
QTend-CV (%)	1.2 ± 0.3	0.9 ± 0.1*	0.3 ± 0.1**
RR-TP (ms ²)	6.0 ± 6.3	3.6 ± 2.1	3.0 ± 1.9
QTpeak-TP (ms ²)	7.4 ± 8.8	3.0 ± 2.4	2.4 ± 1.3
QTend-TP (ms ²)	13.4 ± 8.1	7.0 ± 2.2*	7.0 ± 2.2*
RR-LF (ms ²)	0.7 ± 1.2	0.4 ± 0.5	0.3 ± 0.5
QTpeak-LF (ms ²)	1.5 ± 1.4	0.7 ± 0.5	0.6 ± 0.3
QTend-LF (ms ²)	2.8 ± 2.3	1.9 ± 0.6	2.0 ± 0.9
RR-HF (ms ²)	5.1 ± 5.3	3.1 ± 1.7	2.4 ± 1.2
QTpeak-HF (ms ²)	4.3 ± 6.7	1.8 ± 1.5	1.4 ± 0.8
QTend-HF (ms ²)	8.4 ± 4.9	4.2 ± 1.4*	4.2 ± 1.2*

CONT = control atrial pacing; PROP = after the administration of propranolol; PROP + ATRO = after the administration of propranolol-atropine; RR = RR interval; QTpeak = QTpeak interval; QTend = QTend interval; SD = standard deviation; CV = coefficient variation; TP = total power; LF = low-frequency power; HF = high-frequency power. Data presented are mean ± SD. *P < 0.05, **P < 0.05 versus control.

Magnano AR. et al. reported that isoproterenol was associated with much less QT shortening as HR increases and with complex morphological changes of the U-wave, which contribute to prolongation of the QT at high heart rates. They concluded that autonomic tone directly affect the ventricular myocardium causing differences in QT that are independent of heart rate.¹⁰ On the other hand, there are a few studies about autonomic tone effect on QT interval variability. Emori and Ohe reported that during atrial pacing, mean total power of the RTp (from the R wave peak to the T wave peak) variability decreased from during sinus rhythm, but autonomic blockade gave no additional change to the RTp variability.¹¹ Lombardi et al. reported that RTp variability was extremely low and only a respiration-related high-frequency component was recognizable in spectral analysis of it.¹² However, they did not analyze the variability of the QTend although QTend interval represented total ventric-

ular repolarization time, and it is not clear whether observed changes QTend interval variability are a primary result of neural modulation or whether they may be a secondary effect of RR interval modulation. The present study showed the QT interval variability exists during the fixed atrial pacing and reduced by beta-blocker, but was not changed by atropine. These findings indicated that the parasympathetic system may act preferentially on the QT interval itself, while the sympathetic system appears to affect QT interval variability.

Clinical Implication

Beta-blocker therapy improved survival and decreased sudden deaths in heart failure patients^{13–15} by mechanisms that may include protection against catecholamines, antifibrillatory effects, minimizing hypokalemia and improvement in QT dispersion.^{16–19} Berger et al. demonstrated that patients with dilated cardiomyopathy had greater QT variance than control subjects despite reduced heart rate variance, and the QT interval variability increases with worsening New York Heart Association functional class but is independent of ejection fraction.² Atiga et al. further demonstrated that QTVI could be used to identify patients with sudden cardiac death and to predict arrhythmia-free survival.⁴ The current data also demonstrate that administration of beta-blockers resulted in decrease of QTend interval variability during constant atrial pacing. Therefore, reduction in QTend interval variability with propranolol may contribute to lower rates of sudden cardiac death in patients with heart failure. The measurement of QT interval variability might be useful to predict sudden cardiac death and effects of beta-blocker therapy in patients with heart failure.

Limitation

The present study possesses two notable limitations. First, atropine was only administered in the context of propranolol treatment because treatment with atropine alone increased sinus heart rate above constant atrial pacing. As a result, the effects of the parasympathetic system on QT interval variability remain unclear. Second, propranolol affects cardiac function and may alter the beat-to-beat left ventricular stroke volume, which, in turn, may influence QT interval variability in term of contraction excitation coupling.

Figure 2. Scattergram (left panel) showing the relation between QT peak (upper) and QT end (lower) interval obtained the same method 1 hour apart. Lines of equality and correlation (continuous line) are shown. Plot of the difference between the two QT peak (upper) and QT end (lower) interval measurements against their mean are shown. (right panel) Lines represent boundaries of mean $\pm$ 2SD.

CONCLUSION

Beat-to-beat QT interval variability is affected by drugs that modulate the autonomic nervous system. These findings indicated that the parasympathetic system may act preferentially on the QT interval itself, while the sympathetic system appears to affect QT interval variability. These effects appear to be dependent on changes in the terminal element of T wave.

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