Comparison of QT/RR Relation Based on a 15-s Averaged ECG and a Single Beat ECG During Atrial Fibrillation

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Background: The aim of this study was to compare QT/RR relation based on a 15-s averaged beat ECG with a single beat ECG during atrial fibrillation (AF) and to determine which was better to estimate the QT interval after sinus restoration.

Methods and Results: QT and RR intervals were measured using an automatic QT analyzing system in 33 patients who had both AF and sinus rhythm on the same 24-h Holter ECG recording. In 14 patients, antiarrhythmic drugs (AAD) were administered. QT/RR relations were analyzed from ECG waves obtained by the summation of consecutive QRS-T complexes during each 15-s period (QT/RR-average) and a single beat QRS-T (QT/RR-single). During sinus rhythm, the slope of QT/RR-average did not differ from that of QT/RR-single in patients with and without AAD. On the other hand, during AF, the slope of QT/RR-average was significantly greater than that of QT/RR-single (without AAD: 0.12 ± 0.06 vs. 0.06 ± 0.03 , $P < 0.001$; with AAD: 0.15 ± 0.05 vs. 0.08 ± 0.04 , $P < 0.001$). During AF, the QT interval at an RR interval of 1.2-s (QT-1.2) determined from QT/RR-average was significantly greater than QT-1.2 from QT/RR-single in patients with and without AAD. QT-1.2 in QT/RR-single during AF was significantly smaller than that during sinus rhythm but QT-1.2 in QT/RR-average during AF was not.

Conclusions: The QT interval after sinus restoration could be estimated better using QT/RR-average than using QT/RR-single during AF. (*Circ J* 2011; **75**: 274–279)

Key Words: Antiarrhythmic drug; Atrial fibrillation; Holter ECG; QT/RR relation

The relationship between QT and RR intervals during sinus rhythm has been studied intensively.^{1–3} Analyses of automatic QT measurement using 24-h Holter electrocardiogram (ECG) recordings have shown that QT measurement is reliable and reproducible during sinus rhythm and adaptation of ventricular repolarization to heart rate could be assessed by the slope and intercept of the linear regression line of QT/RR relation.^{4–6} During sinus rhythm QT/RR relation was assessed by 2 different methods: (1) based on an averaged beat ECG and (2) based on a single beat ECG using 24-h Holter ECG.

During atrial fibrillation (AF), however, only a few reports have described different characteristics of QT/RR relation compared with sinus rhythm.^{7,8} Patients with AF are often treated with QT-prolonging antiarrhythmic drugs (AAD) and in some patients the QT-prolonging effects of AAD become more remarkable after sinus restoration.⁹ A recent study confirmed that patients with AAD therapy are more likely to develop torsades de pointes when the underlying rhythm is a sinus rhythm compared with AF.¹⁰ Hence, reliable methods for assessing QT/RR relation during AF are of clinical importance especially in patients with AAD therapy. The aim of

the present study was to compare QT/RR relation based on an averaged beat ECG with a single beat ECG during AF using Holter ECG and to find out which method was better for estimation of QT interval after sinus restoration.

Methods

This study consisted of 33 patients with paroxysmal AF (Table 1). Patients were required to have episodes of both

Table 1. Clinical Characteristics

Patients/women	33/9
Age (years)	67.2±13.3
Ischemic heart disease	5
Hypertension	9
Hypertrophic cardiomyopathy	2
β-blocker	5
Calcium antagonist	5
Antiarrhythmic drug	14

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AF and sinus rhythm after AF termination on the same 24-h Holter ECG, where the duration of each AF episode was longer than at least 60 min. The subjects consisted of 19 patients without AAD and 14 patients with QT-prolonging AADs (cibenzoline 3, sotalol 3, bepridil 4 and amiodarone 4).

Holter ECGs were recorded using NASA (the bipolar lead between the superior and inferior edge of the sternum, used by the National Aeronautics and Space Administration) and CM5 (the modified chest lead V_s) leads for 24 h, and CM5 lead was used for automatic QT measurements. A digital ECG recording device (FM-180, Fukuda Denshi, Tokyo, Japan) with a sampling rate of 128/s was used with an automatic measurement system (SCM-6600, Fukuda Denshi) and QT analyzing software (HPS-QTM, Fukuda Denshi). The analyzing system determined the top and the end of the T wave automatically, according to the following algorithm. The top of the T wave was determined as the point where the first derivative (dv/dt) of the T wave polarity changed. The end point of the T wave was determined as the point where the first derivative of the T wave became undetectable after the top of the T wave. In each case, the detection level of the first derivative of the T wave was set as the average level of the ST segment to overcome the background noise.

The recordings with periods of AF and sinus rhythm after

AF conversion were analyzed separately and the slope and intercept of QT/RR relation were obtained using 2 different methods. One method plotted the QT interval against the RR interval from averaged ECG waves obtained by the summation of consecutive QRS-T complexes during each 15-s period over several hours (QT/RR-average). QT and RR intervals based on a 15-s averaged beat analysis are shown in **Figure 1 (Upper panels)**. Averaging the time series of 15-s segments during AF decreased the variability of QT and RR intervals. The other method plotted the QT interval of each single beat against the previous RR interval and correlated without any preprocessing for several hours (QT/RR-single). QT and RR intervals based on a single beat analysis are shown in **Figure 1 (Lower panels)**. The variability of QT intervals was remarkable due to changes in RR intervals during AF.

Statistical Analysis

Results are presented as mean $\pm$ standard deviation (SD). The dependence of the QT interval on the RR interval was analyzed by linear regression in each patient ($QT = A[RR] + B$; where A is the slope and B is the intercept). Unpaired and paired data were analyzed by Student's t-test. Comparisons of multiple groups were obtained by ANOVA with Fisher's protected least significant difference. Yates 2 $\times$ 2 chi-square

Figure 2. QT/RR relations during sinus rhythm and atrial fibrillation (AF) in a patient without antiarrhythmic drug therapy. (Upper) QT/RR-average; (Lower) QT/RR-single.

Figure 3. QT/RR relations during sinus rhythm and atrial fibrillation (AF) in a patient with antiarrhythmic drug therapy (amiodarone 200mg/day). (Upper) QT/RR-average; (Lower) QT/RR-single.

Table 2. Slope and Intercept of QT/RR Relation in Patients With and Without Antiarrhythmic Drugs				
	No antiarrhythmic drugs (n=19)		Antiarrhythmic drugs (n=14)	
	Slope	Intercept	Slope	Intercept
Sinus rhythm				
QT/RR-average	0.13±0.04*	0.28±0.04	0.20±0.05*,#	0.27±0.09
QT/RR-single	0.12±0.05*	0.29±0.04	0.18±0.05*,#	0.29±0.07
AF				
QT/RR-average	0.12±0.06*	0.27±0.04	0.15±0.05*	0.28±0.06
QT/RR-single	0.06±0.03	0.31±0.02	0.08±0.04	0.32±0.04

Values are mean±SD.
*P<0.001 vs. QT/RR-single during AF, #P<0.001 vs. no antiarrhythmic drug group.
AF, atrial fibrillation.

Figure 4. QT interval at an RR interval of 1.2s in QT/RR-average and QT/RR-single during sinus rhythm and atrial fibrillation (AF) in patients with and without antiarrhythmic drug (AAD) therapy. *P<0.001 vs. QT/RR-single during AF; #P<0.01 vs. no AAD.

Figure 5. Relationship between QT interval at an RR interval of 1.2s (QT-1.2) in QT/RR-average (Left) or QT/RR-single (Right) during atrial fibrillation (AF) and during post cardioversion sinus rhythm. Prolonged QT-1.2 during post cardioversion sinus rhythm (≥ 0.45 s) could be better estimated using QT/RR-average ($\chi^2=8.19$, $P<0.01$) than using QT/RR-single.

test was used to compare the categorical variables between groups. Statistical significance was set at $P<0.05$.

Results

The clinical characteristics of patients are summarized in

Table 1. Representative QT/RR-average and QT/RR-single during sinus rhythm and during AF are shown in **Figure 2** (without AAD) and **Figure 3** (with amiodarone). In 19 patients without AAD, during sinus rhythm, the slope of QT/RR-average did not differ from that of QT/RR-single (**Table 2**). During AF, the slope of QT/RR-average (0.12 ± 0.06) was

significantly greater than that of QT/RR-single (0.06 ± 0.03 , $P < 0.001$). The slope of QT/RR-single during AF (0.06 ± 0.03) was significantly smaller than that during sinus rhythm (0.12 ± 0.05 , $P < 0.001$).

In 14 patients with AAD therapy, the slopes of regression line in QT/RR-average and QT/RR-single during sinus rhythm were steeper compared with those in 19 patients without AAD therapy (Table 2). During AF, the slope of QT/RR-average (0.15 ± 0.05) was significantly greater than that of QT/RR-single (0.08 ± 0.04 , $P < 0.001$). The slope of QT/RR-single during AF (0.08 ± 0.04) was significantly smaller than that during sinus rhythm (0.18 ± 0.05 , $P < 0.001$). The slope of QT/RR-average during AF had a tendency to be smaller than that during sinus rhythm but the difference was statistically insignificant.

During AF or sinus rhythm, the QT interval at an RR interval of 1.2-s (QT-1.2) in QT/RR-average or QT/RR-single was significantly greater in patients with AAD compared with those without AAD except QT-1.2 in QT/RR-single during AF (Figure 4). In patients with and without AAD, QT-1.2 during AF was significantly smaller in QT/RR-single than in QT/RR-average. QT-1.2 in QT/RR-single was significantly smaller during AF than during sinus rhythm.

In patients with or without AAD, QT-1.2 during AF determined from QT/RR-average (Figure 5 Left) and from QT/RR-single (Figure 5 Right) correlated positively with QT-1.2 during sinus rhythm. In 23 patients, QT-1.2 after sinus restoration showed ≥ 0.45 s and, in 12 of these patients, QT-1.2 determined from QT/RR-average during AF showed ≥ 0.45 s (Figure 5 Left). On the other hand, QT-1.2 determined from QT/RR-single during AF showed ≥ 0.45 s in only 4 patients (Figure 5 Right). Prolonged QT-1.2 (≥ 0.45 s) during post cardioversion sinus rhythm could be identified better using QT/RR-average ($\chi^2 = 8.19$, $P < 0.01$) than using QT/RR-single.

Discussion

During AF, the slope of QT/RR-average was significantly greater than that of QT/RR-single in patients with and without AAD therapy. The slope of QT/RR-single was significantly smaller during AF than during sinus rhythm. During AF, QT-1.2 in QT/RR-average was significantly greater than QT-1.2 in QT/RR-single in patients with and without AAD. QT-1.2 in QT/RR-single was significantly greater during sinus rhythm than during AF but QT-1.2 in QT/RR-average during sinus rhythm was similar to that during AF. The QT interval after sinus restoration could be estimated better using QT/RR-average than QT/RR-single during AF.

QT/RR During AF

The QT interval changes along with the heart rate and it is corrected using several formulae, such as Bazett and Fridericia.¹¹ However, standard "rate-correction" formulae underestimate the change in QT at slower heart rates during sinus rhythm.^{12,13} Furthermore, there are no established methods for evaluating QT intervals during AF. A new approach to analyze QT intervals during AF was proposed by Darbar et al.¹⁴ Sorting raw QT data into "bins", which are determined by the preceding RR intervals permits assessment of QT/RR relationships over a broad RR range during AF. The authors revealed that cardioversion of AF acutely prolonged the QT interval and increased the steepness of the QT/RR slope.

During AF, the second and further preceding RR intervals before the preceding RR interval may play an important role for the regulation of the QT interval. Larroude et al demonstrated that QT dynamics could be reliably measured in AF

and were comparable with sinus rhythm when several preceding RR intervals were included in the analysis.¹⁵ Adaptation of the QT interval to changes in the preceding RR interval consists of 2 components: the fast component (non-steady state adaptation) and the slow component (steady state adaptation).¹⁶ In the present study, we adopted the single beat (QT/RR-single) and the 15-s averaged ECG (QT/RR-average) during AF and found that the slope of QT/RR-average was greater than that of QT/RR-single during AF and was closer to that of QT/RR during sinus rhythm. Hysteresis of paced QT interval in response to abrupt changes in pacing rate was studied by Lau et al.¹⁷ The time constant of QT adaptation was 60.4 s when the rate was decreasing, which may be related to the steeper slope of QT/RR based on the 15-s averaged ECG wave during AF compared with QT/RR based on a single beat. Our findings suggest that QT/RR during sinus rhythm could be estimated better using QT/RR-average than using QT/RR-single during AF.

QT/RR and AAD

Drugs that prolong the action potential duration of the atrial myocardium can suppress AF, but they have the possibility to cause excessive QT prolongation leading to torsades de pointes.^{18,19} Although the risk of proarrhythmia is higher after sinus restoration compared with during AF,¹⁰ it is sometimes difficult to estimate the degree of QT prolongation after sinus restoration. During sinus bradycardia, an increase in IKr may prevent the excessive QT prolongation after a long RR interval and also may prevent a steeper slope of QT/RR relation. AADs with an IKr blocking effect could cancel these protective effects and increase the slope of QT/RR.

In patients with and without AAD, the QT interval after sinus conversion could be better estimated by analyzing QT/RR-average rather than QT/RR-single during AF. In patients with QT-prolonging AAD therapy for AF, not only QT morphology including notched T waves,²⁰ but a steeper slope of QT/RR-average during AF may indicate risks of the exaggerated prolongation of the QT interval after sinus restoration.

Study Limitations

This study was performed in a limited number of patients who had no episode of torsades de pointes. The precise effects of AAD on QT/RR relation during AF require evaluation in future studies with a much larger number of patients. The different autonomic nerve activity between sinus rhythm and AF may affect QT-RR relation differently. The linear regression line of QT/RR was obtained from relations between QT and RR during AF and sinus rhythm but the actual sampling range of the heart rate (RR intervals) was limited in each subject. In most patients, we could estimate QT/RR relation using the linear regression line within the physiological range of RR intervals.

Conclusions

The slope of QT/RR-average during AF was greater than that of QT/RR-single during AF and was not different from that of QT/RR after sinus rhythm restoration. The QT interval during sinus rhythm could be estimated better using QT/RR-average compared with QT/RR-single during AF.

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