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Original article

QT/RR relation during atrial fibrillation based on a single beat analysis in 24-h Holter ECG: The role of the second and further preceding RR intervals in QT modification

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KEYWORDS
Antiarrhythmic drug;
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Summary
Background: During atrial fibrillation (AF) irregularity of RR intervals may modify QT/RR relation differently from sinus rhythm. The purpose of this study was to compare QT/RR relation based on a single-beat analysis using the first preceding RR interval with the modified RR interval reflecting not only the first preceding but also the second and further preceding RR intervals during AF.
Methods: QT and RR intervals were measured using an automatic QT analyzing system in 32 patients who had both AF and sinus rhythm on the same 24-h Holter ECG recording. In 12 patients antiarrhythmic drugs (AADs) were administered. To reflect irregularity of the preceding RR intervals during AF, a modified RR (mRR) using a weighted average of five successive RR intervals: $(5RR_1 + 2RR_2 + RR_3 + RR_4 + RR_5)/10$ was adopted. Linear regression analyses between QT and RR intervals were performed using the preceding RR_1 (QT/RR) and the modified RR (QT/mRR) during AF.
Results: During AF the slope of QT/RR was lower than that of QT/mRR and was also lower than that of QT/RR during sinus rhythm in patients with and without AAD. Slopes of regression line in QT/RR during sinus rhythm, QT/RR and QT/mRR during AF were steeper in patients with AAD than those in patients without. Slopes of QT/RR during sinus rhythm correlated with those of QT/mRR ($r = 0.79$, $p < 0.01$) better than those of QT/RR ($r = 0.64$, $p < 0.05$) during AF. QT interval at an RR interval of 1.20 s or 1.00 s obtained from QT/RR during AF was significantly smaller than that during sinus rhythm in patients with and without AAD.

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Conclusions: The slope of QT/mRR during AF became closer to that of QT/RR during sinus rhythm compared with that of QT/RR during AF. QT interval during sinus rhythm could be estimated better using QT/mRR than using QT/RR during AF.
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Introduction

The relationship between heart rate (RR interval) and QT interval during sinus rhythm has been studied intensively [1—3]. There are several formulae to correct for the heart rate but most of them have limitations especially during atrial fibrillation (AF). Analyses of automatic QT measurement using 24-h Holter electrocardiogram (ECG) recordings have shown that QT measurement is reliable and reproducible 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 AF, however, only a few reports have described different characteristics of QT/RR relation compared with sinus rhythm [7,8]. Variable RR intervals during AF modified QT interval differently from RR intervals during sinus rhythm.

We have previously studied the QT/RR relation during AF using a 15-s averaged beat analysis (QT/RR-average) and a single-beat analysis (QT/RR-single) in 24-h Holter ECG [9]. QT interval after sinus restoration could be estimated better using QT/RR-average than using QT/RR-single during AF [9]. Patients with AF are often treated with QT-prolonging antiarrhythmic drugs (AADs) and in some patients QT-prolonging effects of AAD become more remarkable after sinus restoration [10]. Hence, estimation of QT interval after sinus restoration should be done using QT/RR-average in patients with AAD therapy.

In a single-beat analysis it is possible that not only the first preceding RR interval but also the second and further preceding RR intervals during AF affect the QT interval. The aim of the present study was to compare QT/RR relation using the first preceding RR interval with the modified RR interval assessed by a weighted average method during AF.

Methods

This study consisted of 32 patients with paroxysmal AF. Patients were required to have episodes of both AF and sinus rhythm on the same 24-h Holter ECG and the duration of each AF episode was longer than 60 min. The subjects consisted of 20 patients without QT prolonging AAD and 12 patients with AADs (cibenzoline 4, bepridil 4, and amiodarone 4) (Table 1).

Table 1 Clinical characteristics.

Patients/women	32/4
Age (years)	62.0 ± 13.7
Ischemic heart disease	3
Hypertension	9
Diabetes mellitus	1
Bisoprolol	5
Verapamil	5
QT prolonging antiarrhythmic drugs	12

Holter ECGs were recorded using NASA and CM5 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). The analyzing system determined the top and the end of T wave automatically, according to the following algorithm. The top of T wave was determined as the point where the first derivative (dv/dt) of the T wave polarity changed from positive to negative or negative to positive. The end point of T wave was determined as the point where the first derivative of T wave became undetectable after the top of T wave. In each case, detection level of the first derivative of T wave was set as the average level of ST segment to overcome the background noise.

The recordings with periods of AF and sinus rhythm after termination of AF were analyzed separately. Representative automatic measurements of QT and RR intervals based on a single beat analysis during AF are shown in Fig. 1. Variability of QT interval was remarkable due to the changes in RR interval during AF. To correct for variability of RR intervals during AF, a weighted average method was adopted [8]. Modified RR (mRR) = $(5RR_1 + 2RR_2 + RR_3 + RR_4 + RR_5)/10$, where RR_1 is the RR interval just previous to the measured QT, RR_2 the second previous interval, RR_3 the third previous interval, and so forth. This method demonstrates that the first preceding RR has the highest weight in QT adaptation and then the weight of the preceding RR gradually declines according to the distance from the measured QT. During AF, the slope and intercept of the QT/RR relation were obtained with the preceding RR (QT/RR) and with the modified RR (QT/mRR).

Statistical analysis

Results are presented as mean ± SD. The dependence of 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). Relations between QT/RR during sinus rhythm and AF were evaluated with Spearman rank correlation coefficient. 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. Statistical significance was set at $p < 0.05$.

Results

Clinical characteristics of patients are summarized in Table 1. Representative QT/RR relationships using the preceding RR interval and the modified RR interval (QT/RR and QT/mRR) during AF and that (QT/RR) during sinus rhythm are shown in Fig. 2 (without AAD) and Fig. 3 (with AAD). During AF the slope of QT/RR was lower than that of QT/mRR and was also lower than that of QT/RR during sinus rhythm in patients with and without AAD (Table 2). Slopes of regres-

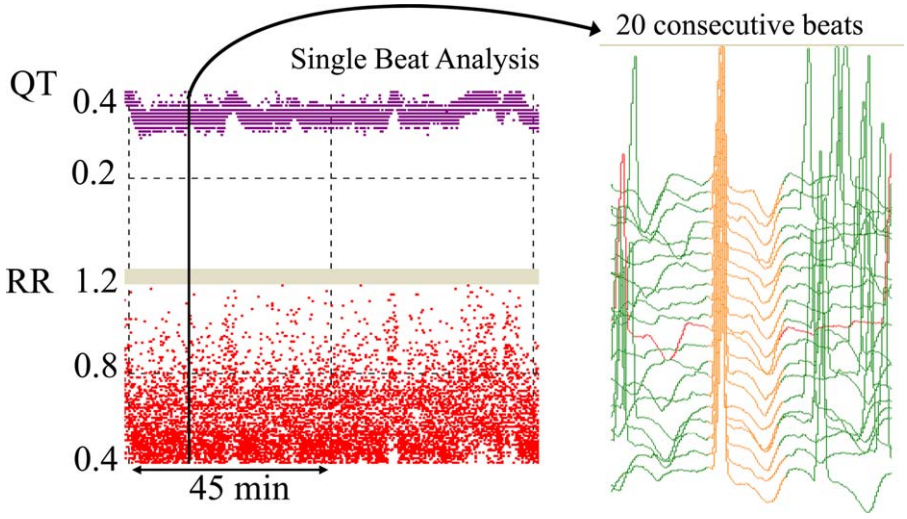

Figure 1 QT and RR intervals based on a single-beat analysis during atrial fibrillation (AF). Panels show representative 20 consecutive beats of QRS-T complex during AF based on a single-beat analysis. Orange line indicates automatically determined QT interval.

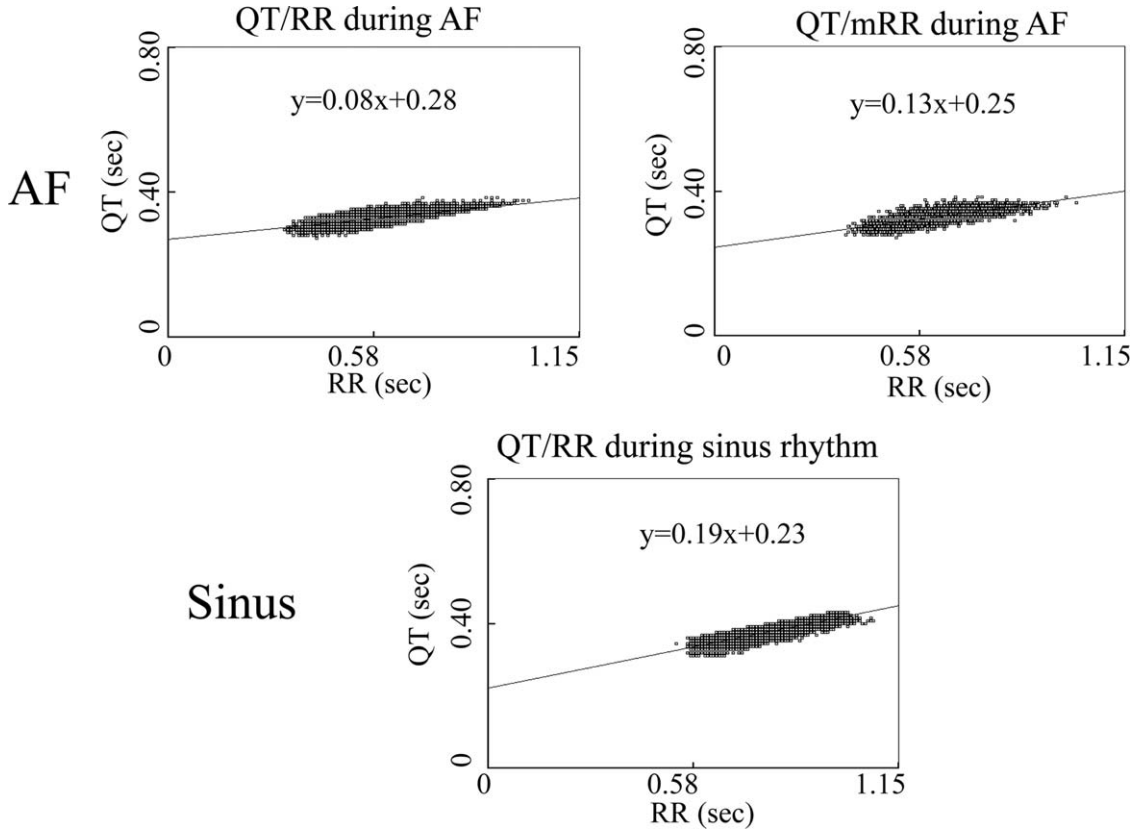

Figure 2 QT/RR relations during atrial fibrillation (AF) and sinus rhythm in a patient without antiarrhythmic drug therapy. Upper panels show QT/RR (left) and QT/mRR (right) during AF and a lower panel shows QT/RR during sinus rhythm.

sion line in QT/RR during sinus rhythm, QT/RR, and QT/mRR during AF were steeper in patients with AAD than those in patients without (Table 2). In Fig. 4, correlation coefficient of QT/RR during sinus rhythm with QT/RR during AF ($r = 0.64$, $p < 0.05$) was smaller than that with QT/mRR during AF ($r = 0.79$, $p < 0.01$).

In patients with and without AAD, QT at an RR of 1.20 s or 1.00 s obtained from QT/RR relation during AF was significantly smaller than that obtained from QT/RR during sinus rhythm (Fig. 5). In patients without AAD, QT at an RR of 1.20 s or 1.00 s obtained from QT/mRR during AF was significantly smaller than that obtained from QT/RR during sinus

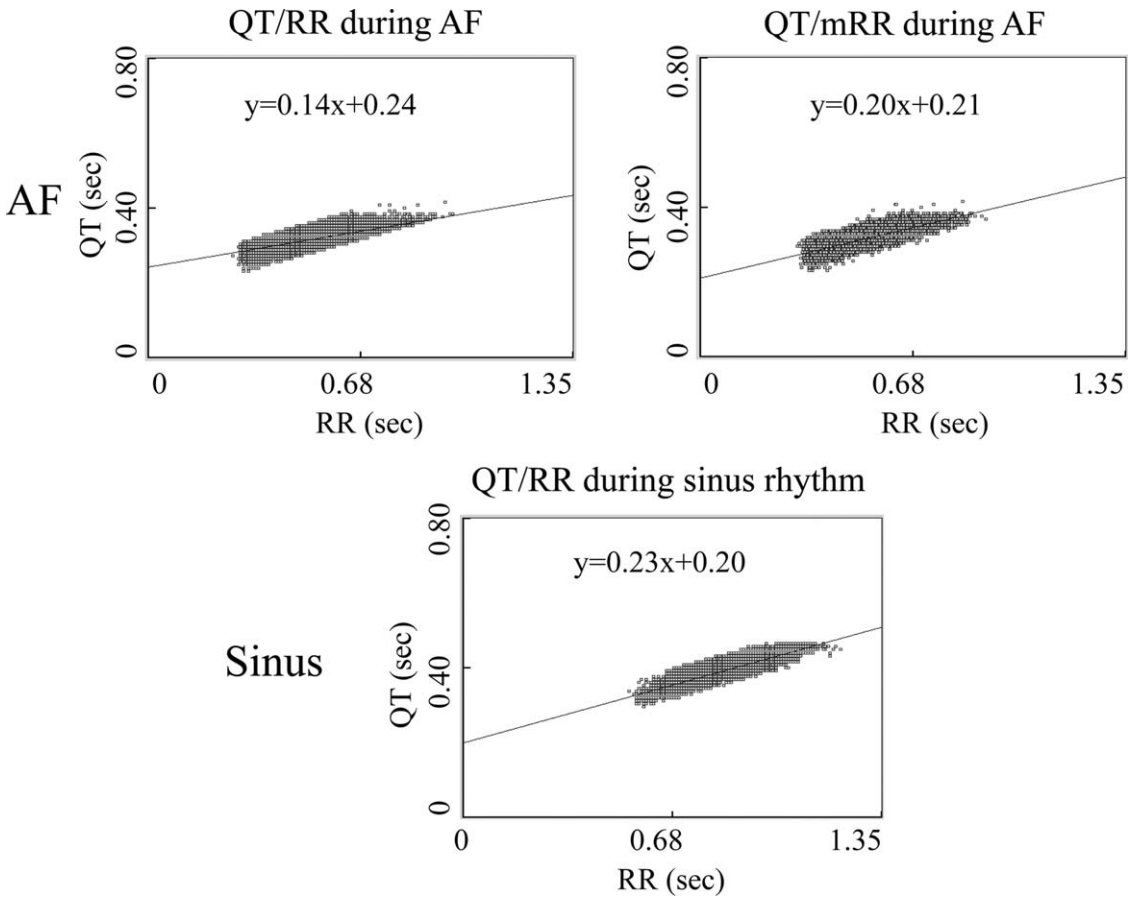

Figure 3 QT/RR relations during atrial fibrillation (AF) and sinus rhythm in a patient with antiarrhythmic drug therapy (amiodarone 200 mg/day). Upper panels show QT/RR (left) and QT/mRR (right) during AF and a lower panel shows QT/RR during sinus rhythm.

Table 2 Slope and intercept of QT/RR relation in patients with and without antiarrhythmic drugs.

	No antiarrhythmic drug	$N = 20$	Antiarrhythmic drug	$N = 12$
	Slope	Intercept	Slope	Intercept
AF				
QT/RR	0.08 ± 0.03	0.31 ± 0.03	0.13 ± 0.05**	0.29 ± 0.05
QT/mRR	0.11 ± 0.04#	0.29 ± 0.03	0.17 ± 0.04**,#	0.26 ± 0.05
Sinus rhythm				
QT/RR	0.13 ± 0.04#	0.28 ± 0.04	0.17 ± 0.06*,#	0.29 ± 0.07

Values are mean ± SD.
QT/RR, relation between QT and RR using the preceding RR interval. QT/mRR, relation between QT and RR using the modified RR interval calculated from a weighted average of five successive RR intervals.
* $p < 0.05$ vs. no antiarrhythmic drug group.
** $p < 0.01$ vs. no antiarrhythmic drug group.
\# $p < 0.05$ vs. QT/RR during atrial fibrillation (AF).

rhythm but in patients with AAD there was no difference between them.

Discussion

Major findings

Variable RR intervals during AF modified QT interval differently from RR intervals during sinus rhythm and slope of QT/RR during AF became shallower than that during sinus rhythm. In other words, for any given increment in RR interval the QT interval increases more during sinus rhythm than during AF. With the addition of the preceding five RR intervals, slope of QT/mRR during AF became closer to that during sinus rhythm. QT at an RR of 1.2 s or 1.0 s obtained from QT/RR during AF was significantly smaller than that obtained from QT/RR during sinus rhythm, but that obtained from QT/mRR during AF did not differ in patients with AAD.

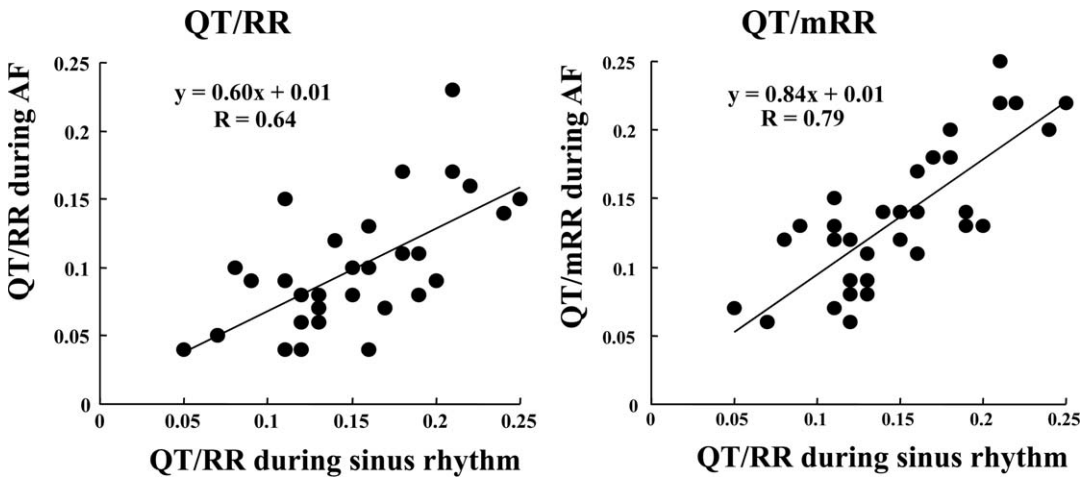

Figure 4 Correlation of slopes between QT/RR during sinus rhythm and QT/RR during atrial fibrillation (AF) (left) and correlation of slopes between QT/RR during sinus rhythm and QT/mRR during AF (right).

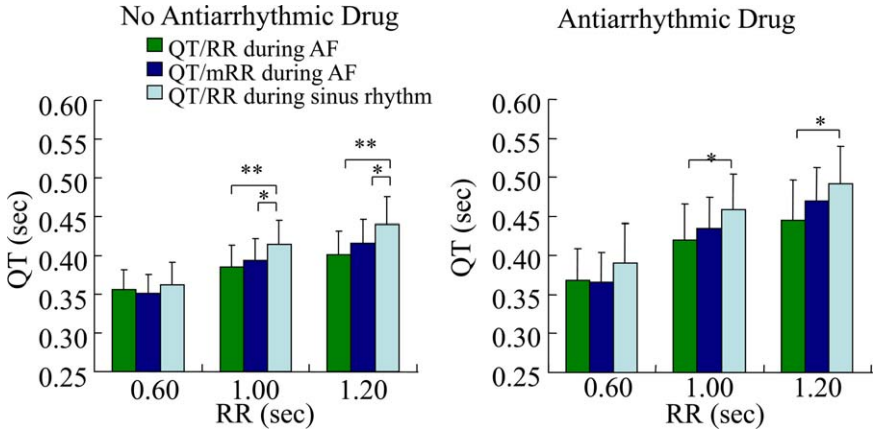

Figure 5 QT at RR of 0.60 s, 1.00 s, 1.20 s in QT/RR during atrial fibrillation (AF), QT/mRR during AF, and QT/RR during sinus rhythm in patients with and without antiarrhythmic drug therapy. Values are mean ± SD. $*p < 0.05$, $**p < 0.01$.

QT/RR during AF based on a single beat analysis

Standard ''rate-correction'' formulae such as Bazett and Fridericia [11] overestimate the change in QT interval at faster heart rates and underestimate at slower heart rates during sinus rhythm [1]. To overcome these limitations we have previously determined grouped and averaged QT at an interval of 5 beats/min for heart rates ranging from 46 to 120 beats/min using 24-h Holter ECG recordings during sinus rhythm [12]. But there are no established methods for evaluating QT during AF. Darbar et al. reported that sorting raw QT data into ''bins'' which were determined by the preceding RR during AF made assessment of QT/RR relationships over a broad RR range possible [13]. They 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 just preceding RR interval may play a role for the regulation of the QT interval. Larroude et al. reported that QT dynamics in AF were comparable with sinus rhythm when several preceding RR intervals are included in the analysis [14]. In the present study, we adopted the modified RR (mRR) reflecting not only the preceding RR, but also the second and further preceding RR intervals using a weighted average method during AF for the analysis of QT/RR relation [8]. We found that slopes of QT/RR during sinus rhythm correlated with those of QT/mRR better than those of QT/RR during AF. These findings suggest that QT interval during AF is affected by not only the immediately preceding RR interval but also the second and further preceding RR intervals.

Our previous study demonstrated that slope of QT/RR-average (using a 15-s averaged beat analysis) during AF was significantly greater than that of QT/RR-single (using a single beat analysis) during AF in patients with and without AAD therapy [9]. Slope of QT/RR-single was significantly smaller during AF than during sinus rhythm. During AF, QT at an RR of 1.2 s in QT/RR-average was significantly greater than that in QT/RR-single in patients with and without AAD. QT at an RR of 1.2 s in QT/RR-single during sinus rhythm was significantly greater than that in QT/RR-single during AF but was similar to that in QT/RR-average during AF. Hence, QT after sinus restoration could be estimated better using QT/RR-average than using QT/RR-single during AF.

Most of QT-prolonging drugs effective for AF suppression have the possibility to cause excessive QT prolongation leading to torsades de pointes [15]. Although the risk of

proarrhythmia is higher after sinus restoration compared with during persistent AF, it is sometimes difficult to estimate the degree of QT prolongation after sinus restoration [14]. In patients with AAD therapy, QT/mRR during AF showed similar tendency to QT/RR-average during AF, but in patients without AAD QT/RR-average seems to be better than QT/mRR to estimate QT during sinus rhythm.

Study limitations

This study was performed in a limited number of patients who had no episode of torsades de pointes. Patients with AAD therapy had several different AADs including class Ia and class III. The precise effects of AAD on QT/RR relation during AF require evaluation in future studies with much larger numbers of patients. The different autonomic nerve activity between sinus rhythm after conversion and AF may affect QT/RR relation differently. The sampling range of RR intervals for the analysis of QT/RR relation during sinus rhythm was different in each patient.

Conclusions

Based on a single-beat analysis the slope of QT/mRR during AF became closer to that of QT/RR during sinus rhythm than that of QT/RR during AF. QT during sinus rhythm could be estimated better using QT/mRR than using QT/RR during AF.

Acknowledgment

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