New quantitative methods for evaluation of dynamic changes in QT interval using 24-hour Holter ECG recordings: QT interval in idiopathic ventricular fibrillation and Long QT syndrome

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Running title: Nomogram of QT interval

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Abstract

Objectives: The aim of this study was to introduce a nomogram of normal QT interval at various heart rates measured from 24-hour Holter ECG recordings in healthy subjects with respect to age and gender. Using the nomogram, we characterized dynamic changes in QT interval in patients with idiopathic ventricular fibrillation (IVF) and long QT syndrome (LQT).

Methods: The study group consisted of 429 subjects: 249 healthy men ranging in age from 21 to 88 years (47 (20) years), 173 healthy women ranging in age from 21 to 85 years (47 (19) years), 7 men with IVF ranging in age from 33 to 53 years (43 (9) years) and 5 women with LQT ranging in age from 20 to 55 years (37 (14) years). In each subject, QT interval and heart rate were determined automatically from a 24-hour Holter ECG digital data. Namely QT interval was measured from signal-averaged ECG waves obtained by averaging consecutive sinus beats during each 15-sec period throughout 24 hours. Data were grouped and averaged at an interval of 5 beats/min for heart rates ranging from 46 to 120 beats/min.

Results: In both healthy subjects aged <50 years and >50 years QT intervals were longer in women than in men. Both men and women aged >50 years showed longer QT intervals than those ages <50 years. From these findings we determined a nomogram of QT interval at varying heart rates adjusted for age (younger group aged <50 years or elderly group aged >50 years) and gender. In IVF patients, QT intervals were significantly shorter at slower heart rates than normal values obtained from the nomogram. In LQT patients, QT intervals were significantly longer at both faster and slower heart rates than normal values.

Conclusions: Using the nomogram of QT interval at varying heart rates adjusted for gender and age, dynamic changes of QT interval of various pathologic conditions could be assessed. For instance, IVF patients had shorter QT interval at slower heart rates, a finding suggestive of arrhythmogenecity of this specific syndrome at night. LQT patients had prolonged QT interval at specific heart rates range depending on their genotype.

Key words: Nomogram of QT interval, Heart rate, Age, Gender, Ventricular fibrillation, Long QT syndrome
Introduction

In the clinical practice, QT interval is often measured to determine mechanisms of ventricular arrhythmias related to either QT prolongation[1][2] or shortening[3][4] and to evaluate effects of class III antiarrhythmic drugs[5] Diagnosis of QT interval abnormalities is currently based on the ECG record for about 10 seconds or more. To compare QT intervals at different heart rates, various correction formulas have been proposed.[6][7] Of these, Bazett’s formula is used most frequently because of its simplicity. However, Bazett’s equation has been criticized because of inaccuracy at both higher and lower heart rates. Recently, computer based QT interval measurement is available for Holter ECG records.[8][9] Hence, the aim of this study was to determine a nomogram of normal QT interval at various heart rates based on automatic measurements of 24-hour Holter ECG recordings in healthy subjects. Evaluation of QT interval without correction formula may become possible using the nomogram of normal QT interval at various heart rates. To validate the clinical implication of our new nomogram, heart rate dependent changes in QT interval of patients with idiopathic ventricular fibrillation (IVF) and long QT syndrome (LQT) were studied.

Method

Subjects

The study subjects to established a nomogram of normal, heart rate dependent QT intervals consisted of 422 healthy subjects (249 men, mean age of 47 (20) years; 173 women, mean age of 47 (19) years) (Table 1). They were obtained from 5433 consecutive patients undergoing a 24-hour Holter ECG examination in our university hospital between 1999 and 2003. All 422 subjects did not have cardiac disease and other morbid conditions known to affect QT interval. No subject was under treatment with any drugs affecting QT interval. Patients with IVF (7 men, mean age of 43 years) and LQT (5 women, mean age of 37 years) constituted the validation group to determine the usefulness of our new nomogram. All IVF patients (4 patients with Brugada type ECG and 3 patients with J wave in the inferior leads) had syncope and documented episodes of ventricular fibrillation (VF) with ECG recordings not related to reversible factors. All LQT patients had also a history of syncopal episodes.

QT interval measurement from 24-hour Holter ECG

Holter ECGs were recorded using NASA and CM5 leads for 24 hours, but only CM5 lead was used for automatic QT measurements. A digital ECG recording device (FM-100, Fukuda Denshi, Japan) with a sampling rate of 128/sec was used with an automatic measurement system (SCM-6000, Fukuda Denshi, Japan) and QT analyzing software (HPS-QTM, Fukuda Denshi, Japan). Signal-averaged QRST complexes from CM5 lead were obtained by summation of consecutive sinus beats of every 15-sec period over 24 hours. Therefore the total number of 5760 data points could be obtained for each subject.

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 (d v/d t) of the T wave changed from positive to negative. 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.

All measured QT interval data were obtained as a text file from a Holter ECG analyzer, which classified the heart rate in steps of 5 beats/min ranging from 41 to 120 beats/min (see below); it also calculated means and standard deviations (SD) of the QT
interval for each of the heart rate ranges.

The reliability of QT interval measurements might depend on the shape of T wave. In this study, we therefore selected subjects according to the following criteria: 1) availability of more than 4000 data points during 24 hours, and 2) a correlation coefficient ($R^2$) $\geq$ 0.5 of the regression line between QT interval and heart rate as shown in Figure 1. During 24-hour Holter ECG recordings, inaccuracies of automatic measurements due to changes in T wave morphology scattered plots of QT interval with heart rate and decreased $R^2$ value of regression line.

Nomogram of normal QT interval in healthy subjects classified by age and gender

The healthy subjects were divided by age 50 years into two groups; younger group (<50 years) and elderly group ($\geq$50 years) to evaluate aging effect. We selected 50 years of age as a dividing line because the median age of men was 49 years and that of women was 51 years. They were also grouped into heart rate categories in steps of 5 beats/min from 46 beats/min to 120 beats/min. We made a nomogram of QT interval of healthy subjects with reference to age and gender. Comparison of circadian change (diurnal time vs. nocturnal time) was carried out for each heart rate range. Diurnal time was arbitrary defined as from 6 am to 6 pm, and nocturnal time was from 6 pm to 6 am.

QT dynamics in IVF and LQT patients

In each patient, Holter ECGs were recorded without drug therapy. We compared QT intervals in IVF and LQT patients with those obtained from the nomogram adjusted for age and gender and calculated difference between them (QT deviation).

Statistical analysis

Continuous variables are presented as mean values (SD). Comparison with mean values between two groups was analyzed by an unpaired two-tailed Student’s t test. Statistical significance was defined as p<0.05.

Results

1. QT interval in healthy subjects in relation to age and gender (Figure 2) and circadian rhythm (Figure 3)

   In men, QT interval of elderly group was significantly longer than that of younger group at heart rates ranging from 46 to 90 beats/min. In women, QT interval was also significantly longer in elderly group than in younger group at heart rates from 46 to 100 beats/min. Women had longer QT intervals than men at heart rates under 110 beats/min in younger group and under 105 beats/min in elderly group. Nocturnal QT intervals had a tendency to be longer than diurnal QT intervals at heart rates under 80 beats/min in both men and women.

2. Nomogram of normal QT intervals adjusted for age and gender (Table 2)

   From 422 healthy subjects, averages and SD of QT intervals for each heart rate range were determined with respect to gender and age.

3. QT intervals in IVF patients

   In Figure 4, a representative QT-heart rate relationship obtained from a 49-year-old man with Brugada syndrome is shown. Measured QT intervals at slower heart rates were located around the lower range of normal QT interval (mean-2SD) for men aged <50 years. In 7 men with IVF, averaged QT intervals were significantly shorter at heart rates under 80 beats/min compared with the nomogram and the QT deviation ranged from -11 to -20 msec (Table 3).

4. QT interval in LQT patients

   In Figure 5, a representative QT-heart rate relationship obtained from a 37-year-old
woman with LQT is shown. Measured QT intervals were located above the upper range of normal QT interval (mean+2SD) for women aged <50 years at all heart rate ranges. All 5 LQT patients had syncopal episodes during physical exercise and broad-based T wave suggesting LQT1. Averaged QT intervals were significantly longer at all heart rate ranges compared with the nomogram for healthy subjects and QT deviation ranged from 58 to 76 msec (Table 3).

**Discussion**

The major findings of the present study were as follows: (1) Women had longer QT intervals than men for each corresponding heart rate. (2) Older subjects had longer QT intervals than younger subjects for both men and women. (3) Using the nomogram of QT interval for each heart rate category adjusted for gender and age, deviation of QT interval could be determined in patients with ventricular arrhythmias. (4) For instance, IVF patients had shorter QT interval and LQT patients had longer QT interval compared with healthy subject at particular heart rate ranges.

**Nomogram of QT interval for healthy subjects**

Recently the method for QT interval evaluation is roughly divided into two kinds. The one is using Bazett’s formula, and the other is determining formula for each subject’s QT/RR relation such as linear regression formula and the exponential formula. However, it is impossible to make the single formula of QT/RR relation applied to every subject.[10] Correction of QT interval by any rate adjustment methods might have some limitations and the relationship between QT interval and heart rate could have inter-subject variability.[11] In the clinical practice, any formulas for heart rate correction can be used only for a narrow rage of heart rates, i.e., between 50 and 70 beats/min.[7]

On the other hand, evaluation of QT interval without a correction formula has been reported by Viitasalo and Karjalainen.[12] For every heart rate a nomogram provides the deviation of QT interval from the QT interval at 60 beats/min.[13] They constructed standard values for QT intervals in healthy young men; however, it is well known that age and gender significantly affect QT interval.[14] Hence, in the present study, we measured QT interval not only in men but also in women with wider age ranges, using an automatic QT measurement system for 24-hour Holter ECG. For this purpose, subjects who have not taken the medicine which would influence QT interval and who did not have any structural heart disease were selected. Compared with the nomogram by Viitasalo, [12] the mean QT interval in the young men group is slightly longer at heart rates over 80 beats/min (20 msec longer, at 90 beats/min).

**Effects of Gender and Age on QT interval**

Previous studies demonstrated that women had similar QT intervals to men, but women had faster mean heart rates than men.[15] Consequently, the corrected QT intervals for heart rate in women became longer than in men. Merri et al reported that normal QT intervals were 0.392 (0.027) sec for men, and 0.397 (0.030) sec for women from 423 healthy subjects.[15] These values are very similar to those of the specific age group and at the specific range of heart rate in the present study (Table 1). Merri et al included subjects with the median age of 35 years and the RR interval was longer in men than in women, thus QTc was significantly longer in women (0.421 (0.018)) than in men (0.409 (0.014)). The mean differences of QT interval between men and women in different studies have been reported to be 2 to 6 % [15][16] and the present study revealed mean differences of 4%. This gender based QT interval differences became more
pronounced as cycle length increases because women showed a greater increase in QT interval at slow heart rates.[16] The autonomic nervous system also affects QT interval greatly, and QT-heart rate relations differ in daytime and nighttime as reported previously.[17] Those findings clearly indicate that it would be impossible to determine the normal QT interval that could be applied to every subject with different gender, ages and heart rates.

Gender-related differences in QT interval seems to be related to different sex hormones blood levels since it is not present at birth and appears only after puberty.[18] Mangoni et al. observed no difference in QT interval between males and females in elderly subjects and supported the hormone-mediated theory.[19] In the present study both younger and elderly (postmenopausal) women demonstrated longer QT interval than age-adjusted men for every heart rate category and suggested that not only gonadal hormones but also extragonadal factors could influence the gender differences in QT interval.

Irrespective of gender, QT interval prolonged along with an increase in age, especially at ages ≥ 50 years in both women and men. Several studies have revealed the relation between QT interval and age.[14][19] Mangoni et al demonstrated that aging and body mass index related to prolongation of QTc interval.[19] The underlying mechanism of QT prolongation in older subjects still remains unknown but several factors including cardiac hypertrophy, increased vascular stiffness and increased aortic impedance are proposed. Women are at risk of drug-induced QT prolongation and especially elderly postmenopausal women are more risky than younger women. These observations also support importance of aging for QT prolongation and arrhythmogenecity.

**QT interval in IVF**

Recent studies suggested that the presence of a prominent transient outward current (Ito) in the right ventricular epicardial layer and genetic abnormalities of the sodium channel gene (SCN5A) may play a role for the characteristic ECG pattern in Brugada syndrome.[20][21][22] Experiment using wedge preparation of canine heart revealed that a down-sloping ST-segment elevation may be due to an earlier repolarization of the epicardial action potential due to a more intense Ito.[23][24] Na channel blocking agents induced coved type of ST elevation in the precordial leads because they accentuated Ito-mediated notch and failed to develop the action potential plateau (loss of dome). We hypothesized that these abnormalities of ionic currents may affect not only configuration of ST segment pattern but also ventricular repolarization dynamics.

In patients with IVF who had a history of recent episodes of VF, QT intervals for slower heart rates were shorter than normal QT intervals at the corresponding heart rates. A shorter QT interval might represent shorter refractoriness of the ventricle suggesting enhanced vulnerability of the ventricle.[3] Slower heart rates and increased vagal activity at night increase Ito and decrease ICa. These changes in ionic currents may reduce the prolongation of QT interval at night, possibly resulting in the nocturnal occurrence of cardiac arrest in IVF patients.[4][25]

Either reduction of inward currents (INa or ICa) or increase in outward currents (IK or Ito) causes early repolarization resulting in shortening of QT interval. In IVF patients, an increase in Ito may limit the prolongation of action potential duration especially at slower heart rates and also produce prominent J wave in surface ECG. During sinus tachycardia, both faster heart rates and an increase in adrenergic tone may offset the excessive Ito current and make a difference in QT interval insignificant compared with
A new genetic disease (gain of function of IK channels) characterized by a short QT interval, familiar sudden death and inducible VF has been described.[3] Patients have a short QT interval (<300msec) with slight modification with heart rate changes. The tall symmetrical T wave may depend on increased phase 2 and 3 outward K currents linked to mutation in the KCNH2 gene.[26] In our IVF patients, the degree of QT shortening is smaller than in genetically identified short QT syndrome. However, we can easily identify short QT intervals in IVF patients using the nomogram obtained from the present study.

**QT interval in LQT**

In the present study, surface ECG patterns of 5 females with LQT had broad-based T wave and episodes of syncope during physical stress suggesting LQT1 genotype and no patient had bifid T wave morphology or episodes of syncope during bradycardia. In LQT patients, QT interval prolonged from normal values not only at slower heart rates but also at faster heart rates depending on their genotype. Although the present study was limited in the absence of gene analysis of LQT patients, the nomogram provides an accurate relationship of measured QT interval with heart rate adjusted normal QT interval.

**Limitations**

The present study is limited for several reasons. First, artifacts could effect automatic analysis of the 24-hour Holter ECG. A beat-to-beat noise effect could be canceled by signal-averaged ECG measurements over 15 seconds. However, there is a possibility that QT interval changes during respiratory sinus arrhythmia might disappear during the averaging. Second, we did not find apparent changes in T wave configuration in healthy subjects, but T wave could change in the morphology and the polarity in patients with structural heart diseases or receiving cardiovascular drugs. Automatic measurement of the QT interval could not be applied to some patients with heart diseases. Third, the CM5 lead resembling V5 lead was used in the present study because of the stability and the accuracy of automatic measurement. Therefore, the present nomogram might not be applied to QT intervals in other leads, e.g., the right precordial leads. Although limited for these reasons, we believe the present study provides an alternative method for evaluation of QT interval without correction of heart rate in the clinical practice.

**Acknowledgments**

We gratefully acknowledge the technical assistance of Dr. Shiro Hayashi in The Central Laboratory, Toyama Medical and Pharmaceutical University.
Figure legends

Figure 1. A representative relationship of QT interval to heart rate (HR) during 24-hour Holter ECG recordings in a 50-year-old healthy man.

Total data number was 5701 and correlation coefficient ($R^2$) was 0.57. The dotted lines indicate the upper and lower limits of the normal QT interval (mean ± 2SD) obtained from the nomogram (Table II). Almost all data points fell into the normal range.

Figure 2. Influence of age and gender on QT interval at various heart rates

In men, the QT interval of the elderly group was longer than that of the younger group at heart rates ranging from 46 - 90 beats/min. In women, the QT interval was longer in the elderly group than in the younger group at heart rates from 46 - 100 beats/min. Women had longer QT intervals than men at heart rates under 110 beats/min in the younger group and under 105 beats/min in the elderly group.

* p<0.05, ** p<0.01 and *** p<0.001 vs. men<50 years old
† p<0.05, †† p<0.01 and ††† p<0.001 vs. women<50 years old
‡ p<0.05, ‡‡ p<0.01, and ‡‡‡ p<0.001 vs. men>50 years old

Figure 3. Influence of circadian rhythm on QT interval at various heart rates

Nocturnal QT intervals were longer than diurnal QT intervals at heart rates under 80 beats/min in both men and women.

* p<0.05, vs. daytime

Figure 4. A representative surface ECG and the relationship of QT interval to heart rate (HR) in a 49-year-old man with idiopathic ventricular fibrillation.

The coved type elevation of the ST segment in lead V1 after an episode of ventricular fibrillation suggested this patient had Brugada syndrome. In scatter plots of the relationship between QT interval and HR, most of the data points fell around the lower limit of the normal QT interval (mean –2SD).

Figure 5. A representative surface ECG and the relationship of QT interval to heart rate (HR) in a 37-year-old woman with long QT syndrome

The broad-based T wave and syncope during physical exercise suggested this patient had LQT1. In scatter plots of the relationship between QT interval and HR, most of the data points fell above the upper limit of the normal QT interval (mean +2SD).
References
Table 1. Age distribution of healthy subjects

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Table 2. Nomogram of normal QT interval obtained from 422 healthy subjects.

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* p<0.05, ** p<0.01 and *** p<0.001 vs. men<50 years old
† p<0.05, †† p<0.01 and ††† p<0.001 vs. men>50 years old
‡ p<0.05, ‡‡ p<0.01, and ‡‡‡ p<0.001 vs. men<50 years old
Table 3. Averaged QT intervals in 7 men with idiopathic ventricular fibrillation (IVF) and 5 women with long QT syndrome

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* p<0.01 and ** p<0.001 vs. Normal group shown in table 2
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