Slow QT Interval Adaptation to Heart Rate Changes in Normal Ambulatory Subjects

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Background: Clinical formulas for QT correction utilize instantaneous HR. We showed previously that longer-term HR affects QT duration. We extend these findings, identifying more accurate models of QT behavior.

Method: Multiple models of QT dependence on HR were tested in 2 independent populations. Holter recordings were analyzed in population A (healthy volunteers, $n = 14$, 6 males, age 26.9 ± 12.3 yr). The hypotheses generated in population A were tested in an independent group population B, healthy volunteers, $n = 15$, 9 males, age 52.9 ± 15.6 yr). Linear models of QT interval dependence on a weighted average of RR intervals in the preceding 3 minutes were compared to models based on the immediately preceding RR interval (instantaneous HR).

Results: In population A, linear models based on RR intervals over the preceding minute performed better than the best nonlinear model based on the single RR interval immediately preceding the QT interval. Linear models including HR values preceding the QT interval by more than 60 s further improved model fit. This model hierarchy was confirmed in population B. Linear formula for QT correction based on exponential decay of HR effect with 60 s time constant outperformed Bazett and Fridericia formulas in both populations.

Conclusions: QT duration in normal ambulatory subjects is affected by noninstantaneous HR, including HR history dating back more than 60 s. Exponential decay of this “memory effect” with time constant of 1 minute provides an accurate description of QT adaptation. This may be of clinical importance when HR is not steady.

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INTRODUCTION

HR plays a crucial role in determining the duration of ventricular repolarization. In order to identify repolarization impairment, HR correction of QT interval duration is necessary to allow comparison with established norms. Clinical formulas for QT interval correction utilize the RR interval immediately preceding the QT interval, equivalent to instantaneous HR. However, adaptation of QT interval to change in pacing rate occurs more gradually. Experiments using pacing to cause sudden HR

change showed that QT value reach a new steady state after 1–3 minutes.^{1–3}

We⁴ and others^{5,6} have shown recently that noninstantaneous HR importantly affects QT duration in normal ambulatory subjects and LQT1 patients. This study was performed to identify more accurate and physiologically plausible models of QT behavior than a linear function of average HR over 60s reported previously, and to confirm the results in an independent population monitored over full 24 hrs to capture full circadian range of QT/RR relationship.

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METHODS

Ambulatory ECG recordings from two distinct populations (population A and B) of healthy subjects were analyzed. Population A was used to generate hypotheses on QT behavior, which were then tested in population B. Ambulatory ECG monitoring for both populations was approved by IRB in their respective institutions.

Population A consisted of 14 healthy volunteers, 6 males, age 26.9 ± 12.3 yr, recruited at the Mayo Clinic, with no known cardiovascular disease. In this population, ambulatory ECG signal using CardioCorder (Del Mar Avionics, Irvine, CA) from the CM5 lead was digitized at 128 Hz with 16-bit precision. Analysis was limited to data acquired between 4 a.m. and 10 a.m. Only subjects with at least 200 minutes of acceptable quality data were included; most of the subjects were included in a previous report.⁴

Population B consisted of 15 healthy volunteers, 9 males, age 52.9 ± 15.6 yr, recruited at Yale University, with no known cardiovascular disease. In population B, ambulatory ECGs were recorded on GE Medical Marquette Series 8500 (GE Healthcare, Little Chalfont, United Kingdom). ECG signals from 3 modified precordial leads obtained over 24 hr periods were digitized at 125 Hz with 12-bit precision; the channel providing the best data quality was used for analysis in each subject.

The signal was automatically annotated with previously validated⁷ custom software (created in Microsoft Visual C++ v 6.0, Redwood, CA, by one of the investigators [JN]) for onset of QRS complex, peak of the R wave and end of the T wave. All the recordings were manually reviewed by one of the investigators (ER, MB). Data of inadequate quality were rejected. Only QT intervals preceded by 3 minutes of uninterrupted signal of acceptable quality were included in the analysis. The quality of the ambulatory ECG signal was better in population A than in population B, with a lower proportion of manually rejected segments in population A ($19.8 \pm 14.1\%$) than in population B ($56.6 \pm 23.4\%$; $P < 10^{-4}$ by nonpaired *t*-test).

Different models of QT dependence on HR were tested in each subject and compared to each other. Most of them were linear models, describing QT interval as a linear function of weighted average of RR intervals over preceding 3 minutes. The performance of the models was assessed by comparing the QT intervals predicted by the model with the measured values. The value of "residuals," de-

finer as root-mean-square of differences between measured and predicted QT values in a given recording, was used to assess the model fit; lower residuals signify a better model performance. The hypotheses generated in population A were tested in population B. In order to consider model X better than model Y, we required that the values of residuals be significantly lower for model X than for model Y (as assessed by paired *t*-test) in both population A and population B. For clarity, only selected models are discussed in the text.

In each linear model, regression lines and residuals were calculated for every subject. Linear models with either exponential or linear weight function were evaluated. For example, **LMwexp60** denotes a linear model with an exponential weight function with a time constant of 60 s; **LMwlin120** denotes a linear model with a linear weight function decreasing to zero over 120 s (Fig. 1). Models describing QT as a linear function of the RR interval immediately preceding QT (**LM0**) or of the average RR interval of preceding 60 s (**LMm60**) were also studied. These linear models were compared to the optimal *nonlinear* model based on the instantaneous RR interval. In this model (**N0**), the predicted QT interval for each RR interval value is calculated as an average of all measured QT intervals preceded by this RR value. Only RR bins containing at least 10 beats were analyzed in the **N0** model. An example QT-RR data from a single subject fit with different models is shown in Figure 2.

We also compared the performance of **LMwexp60** (the model with best overall performance) with Bazett and Fridericia formulas. In contrast to the standard linear model, which has 2 free parameters (slope and intercept of the regression line), Bazett and Fridericia formulas estimate the QT interval duration as a function of the preceding RR interval, using only one free parameter (QTc). To derive a corresponding formula for **LMwexp60**, we used a fixed slope of the regression line. This was set to 0.19, based on the average slope of linear regression of QT vs weighted RR interval for the **LMwexp60** model (0.1904 ± 0.0529) in population A.

Therefore, the formula corresponding to Bazett or Fridericia for **LMwexp60** is

$$QT = QTc + 0.19(RRwexp60 - 1,000) \quad (1),$$

where **RRwexp60** (in milliseconds) denotes the weighted average of RR intervals over preceding

Figure 1. Examples of weight functions discussed in the text. Time (in seconds) is shown on the abscissa, while the relative weight assigned to an RR interval preceding QT by this time is plotted on the ordinate. **(A)** LMwexp60, a linear model with an exponential weight function with a time constant of 60 s, is represented by the solid curve. Dashed line represents LMm60, a linear model of QT interval dependence on average of RR interval over preceding 60 s. **(B)** Solid line represents LMwlin120, a linear model with a linear weight function decreasing to zero over 120 s. Dashed line represents LMwlin60, a linear model with a linear weight function decreasing to zero over 60 s.

3 minutes, using an exponential weight function with 60 s time constant.

The values of model parameters are given as average $\pm$ standard deviation. Unless stated otherwise, 2-tailed Student's paired *t*-test was used to test for differences of the means. $P < 0.05$ was considered statistically significant. Data analysis was performed in Excel 2007 (Microsoft).

RESULTS

Population A

Linear model based on average RR interval over the preceding minute (LMm60) performed better than linear model based on the single RR interval immediately preceding QT (LM0). This difference was highly significant (6.76 ± 1.59 vs 9.44 ± 3.00 ms; $P < 0.0002$). The best *nonlinear* model based on this RR interval (N0) performed better than LM0 as expected (8.36 ± 2.11 vs 9.19 ± 2.58 ms; $P < 0.005$), but both LMm60 and LMwlin60 models were superior to N0 (6.72 ± 1.55 vs 8.36 ± 2.11 ms; $P < 0.005$ and 6.66 ± 1.51 vs 8.36 ± 2.11 ms; $P < 0.005$, respectively).

Use of linear model based on linear weight function decreasing to zero over 2 minutes (LMwlin-

120) further improved the model fit as compared to linear model based on average RR interval over the preceding 1 minute (LMm60: 6.40 ± 1.61 vs 6.76 ± 1.60 ms; $P < 0.0002$). LMwlin120 was also better than a similar model based on linear weight function decreasing to zero over 1 minute (LMwlin60: 6.40 ± 1.61 vs 6.67 ± 1.57 ms; $P < 0.05$).

Linear model with exponential weight function with time constant of 1 minute (LMwexp60) likewise improved the model fit as compared to linear model based on average RR interval over the preceding minute (LMm60: 6.32 ± 1.61 vs 6.76 ± 1.59 ms; $P < 0.001$). LMwexp60 also performed better than LMwlin60 (6.32 ± 1.61 vs 6.67 ± 1.57 ms; $P < 0.02$). The results are summarized in Table 1.

Single-parameter correction formulas (Bazett, Fridericia and formula (1), derived from model LMwexp60 as detailed above) resulted in similar estimates of QTc (417.9 ± 20.5 ms, 415.0 ± 17.0 ms, 417.6 ± 18.6 ms, respectively; NS). However, Fridericia formula provided better data fit than Bazett (11.19 ± 2.28 ms vs 15.41 ± 3.32 ms; $P < 10^{-4}$), though it was inferior to formula (1) (11.19 ± 2.28 ms vs 7.22 ± 2.11 ms; $P < 10^{-4}$).

Figure 2. Examples of QT-RR data scatter plots from a single subject. QT duration is plotted on the ordinate, while the abscissa plots the RR interval immediately preceding QT (**A**; model **LM0**), average RR interval over the preceding minute (**B**; model **LMm60**), or RR interval weighted with a linear function decreasing to zero over 120s (**D**; model **LMwlin120**). The regression lines (blue), their equations and residual values (indicating the spread of QT/RR points from the regression lines) are also included. Model **N0** (**C**) uses the best nonlinear function of the RR intervals immediately preceding QT intervals (green). For this subject, model **LMwlin120** provides a better description of QT behavior (lower residuals) than the alternatives.

Population B

The results described above for population A were confirmed in population B. Models **LMm60** and **LMwlin60** both performed better than best "instantaneous" nonlinear model **N0** (**LMm60**: 9.20 ± 2.61 vs 9.95 ± 2.52 ms; $P < 0.005$, **LMwlin60**: 9.19 ± 2.61 vs 9.95 ± 2.52 ms; $P < 0.005$). Model **LMwlin120** resulted in better fit than **LMm60** (9.14 ± 2.54 vs 9.31 ± 2.59 ms; $P < 10^{-4}$). It was also superior to **LMwlin60** (9.14 ± 2.54 vs 9.30 ± 2.59 ms; $P < 0.0005$). Model

LMwexp60 performed better than both **LMm60** (9.07 ± 2.52 vs 9.31 ± 2.59 ms; $P < 10^{-4}$) and **LMwlin60** (9.07 ± 2.52 vs 9.30 ± 2.59 ms; $P < 0.0005$). Similar to population A, formula (1) derived from **LMwexp60** model performed better than Fridericia (9.94 ± 2.71 vs 11.45 ± 2.55 ms; $P < 0.0005$), while Bazett formula was inferior to Fridericia (13.43 ± 2.24 vs 11.45 ± 2.55 ms; $P < 0.002$). The QTc values estimated by Bazett and formula (1) were similar (414.1 ± 14.4 vs 414.9 ± 12.9 ms; NS), but QTc values derived from Fridericia formula (409.7 ± 11.9 ms) were significantly lower

Table 1. Table Summarizing Comparison of Different Linear Models. Italicized Values (below diagonal) Represent Population B, While the Values in Standard Font (above diagonal) Contain Data from Population A. The Marginal Cells Contain the Residuals Values (mean $\pm$ standard deviation, in ms) for the Indicated Models. The Other Cells Contain P Values Derived from Comparisons of the Models Indicated in the Corresponding Column and Row

	LM0	LMm60	LMwlin60	LMwlin120	LMwlin180	LMwexp15	LMwexp30	LMwexp60	Popul. (A)
	9.44 $\pm$ 3.00	6.76 $\pm$ 1.59	6.66 $\pm$ 1.51	6.40 $\pm$ 1.61	6.43 $\pm$ 1.62	6.86 $\pm$ 1.71	6.40 $\pm$ 1.59	6.32 $\pm$ 1.61	
LM0 10.58 $\pm$ 3.13		P < 0.0002	P < 0.0002	P < 0.0002	P < 0.0002	P < 0.0002	P < 0.0002	P < 0.0002	LM0
LMm60 9.31 $\pm$ 2.59	P < 0.0002		P > 0.1	P < 0.0002	P < 0.005	P > 0.1	P < 0.0002	P < 0.001	LMm60
LMwlin60 9.30 $\pm$ 2.59	P < 10 ⁻⁴	P > 0.5		P < 0.05	P > 0.1	P < 0.01	P < 0.005	P < 0.02	LMwlin60
LMwlin120 9.14 $\pm$ 2.54	P < 10 ⁻⁴	P < 10 ⁻⁴	P < 0.0005		P > 0.5	P < 0.01	P > 0.5	P = 0.08	LMwlin120
LMwlin180 9.08 $\pm$ 2.51	P < 10 ⁻⁴	P < 0.0001	P < 0.0005	P < 0.05		P < 0.05	P > 0.5	P < 0.05	LMwlin180
LMwexp15 9.38 $\pm$ 2.64	P < 10 ⁻⁴	P > 0.1	P < 0.05	P < 0.002	P < 0.001		P < 0.005	P < 0.01	LMwexp15
LMwexp30 9.18 $\pm$ 2.56	P < 10 ⁻⁴	P < 0.0002	P < 10 ⁻⁴	P < 0.05	P < 0.01	P < 0.001		P > 0.1	LMwexp30
LMwexp60 9.07 $\pm$ 2.52	P < 10 ⁻⁴	P < 10 ⁻⁴	P < 0.0002	P < 0.005	P > 0.1	P < 0.0005	P < 0.001		LMwexp60
Popul. (B)	LM0	LMm60	LMwlin60	LMwlin120	LMwlin180	LMwexp15	LMwexp30	LMwexp60	

(P < 0.05 in both cases). The relationships between models present in both populations are illustrated in **Figure 3**.

DISCUSSION

Marked prolongation of ventricular repolarization—reflected clinically as prolongation of QT interval—frequently leads to a characteristic form of polymorphic ventricular tachycardia known as *torsades de pointes*. Even minor degrees of QT interval prolongation, associated with use of many noncardiac medications, can result in a small but measurable increase in risk of cardiac arrest.^{8–10} Extensive preclinical testing of newly introduced medications is required with respect to their effect on ventricular repolarization to minimize the risk of lethal arrhythmias. Identification of patients with QT interval prolongation is thus clinically important. Major changes in QT interval duration occur in normal subjects due to HR adaptation. In most cases, QT interval needs to be corrected for HR value in order to be compared with established norms. Several formulas for the correction have been proposed for clinical use, although only Bazett and Fridericia are widely employed in clinical practice. All of them use the duration of the RR interval preceding the QT interval—equivalent to instantaneous HR—to correct the QT duration. Nevertheless, it is known from pacing experiments that adaptation of action potential duration (APD) and QT interval to a

sudden change in pacing rate takes approximately 1 minute.^{1–3}

We⁴ and other groups^{5,6} have shown that non-instantaneous HR exerts an important effect on QT duration during ambulatory ECG monitoring. Specifically, we reported that a linear function of average HR over preceding 1 minute provides better prediction of QT duration than any function of instantaneous HR in normal subjects and LQT1 patients. In this study, we prospectively tested physiologically more plausible models of QT dependence on HR.

The findings in this report confirm and extend our previous results. The superiority of linear fit of QT/RR relationship using average HR over preceding 60 s to the best nonlinear model based on instantaneous HR which was derived in population A was confirmed in population B. Moreover, linear models including HR history older than 1 minute further improved the model fit in both populations, despite differences between the 2 populations in age, data acquisition system and signal quality (population B recordings having an inferior signal to noise ratio, which is reflected by systematically higher residuals). The linear model with an exponential decline of the “memory effect” of preceding HR with 60 s time constant provided the best prediction of actual QT interval behavior (lowest residuals) in both populations. Similarly, a linear formula for QT interval correction derived from this model performed significantly better than Bazett and Fridericia formulas.

Figure 3. Diagram depicting the order of selected models with respect to data fit. Arrows indicate a significant difference in performance in both population (A and B). The arrow points to the model providing better prediction of QT behavior (i.e., lower residuals). Models **LM0** and **NO** are based on instantaneous heart rate, models **LMwlin60** and **LMm60** are based on HR in the preceding minute, while QT duration is affected by HR as old as 2 minutes in model **LMwlin120**, and 3 minutes in **LMwexp60**.

The reports by Malik et al., who studied the lag between HR and QT change ("hysteresis") in normal subjects, address a similar question.^{5,6} These investigators used a somewhat different method, appropriate for a thorough study of drug effects on QT duration. Their analysis involved shorter ECG segments preceded by relatively stable HR to evaluate the drug effect, but pretreatment ECGs obtained during graded bicycle exercise were also included. Interestingly, these authors reported a substantially shorter time constant (approximately 5 times cardiac cycle lengths) when fitting their data with an exponential decay model. In contrast, we found that exponential decay model with 60 s time constant (**LMwexp60**) was significantly better in both populations than the equivalent model with 15 s time constant. It also provided significantly better fit than the model with 30 s time constant in population B, though the difference was not significant in population A (see **Table 1**).

The reason for this difference is not completely clear, but could be related to the fact that our data are derived from ambulatory ECG monitoring during unsupervised activity, while some of the papers referred to above fit data from a graded bicycle exercise test. Some^{1,2} (though not all³) papers on

rate of QT interval change during sudden change in atrial pacing rate describe a biphasic response, with a quick change (within 1–2 beats), followed by slower drift (over more than 1 minute) to a new steady state. If the true QT adaptation in ambulatory setting is also best described by both a fast (1–2 s) and a slow (minutes) time constant, the effect of the fast time constant may not be apparent during relatively slow and smooth HR changes expected during unsupervised activity. On the other hand, the fast QT changes may become apparent during the more rapid HR changes expected with stepwise change in exercise intensity. If such data are fitted with a single exponential model, an intermediate value might provide the best fit.

Our data are supported by the results of Pueyo et al.,¹¹ who evaluated QT/RR relationship in ambulatory patients after myocardial infarction, randomized to placebo or amiodarone (EMIAT trial). Using a related, but more complex mathematical approach, they concluded that approximately 2.5 minute of HR history is needed to adequately describe QT behavior in this population.

The slow adaptation of QT interval may be of importance in a situation when the HR is not steady, such as atrial fibrillation, exercise-induced

HR changes or marked sinus arrhythmia. The standard 12-lead ECG may not be long enough to take longer-term HR effect on QT interval into account, but this effect will likely play a role when longer ECG tracings are studied, as is common during evaluation of drug effects on QT duration,^{5,12–14} or when abnormal QT/RR relationship is investigated as a marker of arrhythmic propensity.^{15–22}

The slow response of QT interval to HR change also puts certain constraints on plausible hypotheses concerning molecular mechanisms responsible for APD adaptation. For example, incomplete deactivation of the IKs current during rapid HR has been proposed as a mechanism of APD shortening.²³ However, the time constant of IKs response is approximately 1 s,²⁴ and this mechanism is unlikely to explain the slow QT interval response. In contrast, modulation of ICaL current by cytoplasmic Ca²⁺ concentration is affected by the Ca²⁺ content of sarcoplasmic reticulum; this could be a potential mechanism of the slowly changing QT interval behavior.^{25–27}

Limitations

There are several limitations to this study. Due to the use of clinical ambulatory ECG monitoring equipment, the sampling frequency of the ECG signal was only 125 or 128 Hz; higher sampling frequency would be desirable for research purposes and would likely increase the precision of QT interval measurement. On the other hand, it is important that our data were recorded by standard Holter systems, which are widely used in a clinical setting. Only data from a single ambulatory ECG lead were analyzed. Since only QT intervals preceded by 3 minutes of clean data were included, a selection bias cannot be ruled out. Approximately one third ($28.4 \pm 17.0\%$ and $29.7 \pm 20.9\%$ in populations A and B, respectively) of QRS complexes of acceptable quality were used to evaluate model performance, since the remainder contained poor-quality data in the preceding 3 minutes.

CONCLUSION

In normal ambulatory subjects, QT interval duration is strongly affected by noninstantaneous HR.

Measurable HR effect on QT duration persists for more than 60 s. Linear model of QT dependence on preceding RR intervals assuming an exponential decay of this "memory effect" with a time constant

of 60 s provides a good description of QT interval adaptation. The slow QT interval adaptation may be of clinical importance for QT correction in the setting of changing HR. It also has implications regarding plausible hypotheses concerning molecular mechanisms of APD shortening following HR increase.

List of Abbreviations Used in the Article

- HR** – heart rate
LQTS – Long QT syndrome
LM0 – Linear model of QT interval dependence on the immediately preceding RR interval
LMm60 – Linear model of QT interval dependence on average of RR interval over preceding 60 seconds
LMwlin120 – Linear model of QT interval dependence on average RR interval with linear weight function decreasing to zero over 120 seconds
LMwlin60 – Linear model of QT interval dependence on average RR interval with linear weight function decreasing to zero over 60 seconds
LMwexp60 – Linear model of QT interval dependence on average RR interval with exponential weight function with time constant 60 seconds
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