A Quantitative QT Hysteresis Model

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Abstract

We report on a model of the QT/RR relationship using the preceding 255 RR intervals to predict the current QT interval. The parameters of the model are sufficiently stable across two study populations to suggest the possibility of a broadly applicable quantitative model. All data is from 12-lead 24-hour Holter recordings with a sampling rate of 1000 s/s. The study populations are 33 Mortara company employees and 383 recordings from the GISSI-HF study. Each hour of RR and QT interval data, measured by an automatic algorithm, was fitted to a linear QT/RR model. The model is the simple linear one, but with the preceding RR of each normal beat QT replaced by a weighted average (called the "corrected" RR, or RR_c) of the preceding 255 RR intervals. The parameters of the model are the slope, intercept, and weights applied to the prior RR intervals. Equal weights are used for successively doubled numbers of RR intervals, going backward in time from the current beat, resulting in 8 weights (with a sum of unity) for 255 beats. Hours with insufficient normal beats or rate variation were omitted. Of 9741 hours of data, 8114 were acceptable. Illustrating the importance of the RR history, the weighted RR improved QT prediction by reducing rms error to 2.94ms from 5.74ms using only the prior RR. A composite set of weights, taken from the average of all results, and applied to each hour resulted in an rms prediction error for QT of 3.12ms, suggesting that one universal set of RR weights may apply to a diverse population. Further, the largest mean difference (between universal and hourly optimized weights) of rms errors for any single recording was 1.0ms.

1. Introduction

entricular repolarization duration does not respond instantaneously to sudden heart rate changes. This phenomenon was first described on action potentials in a pioneer study published in 1988 by Franz [1] and it is commonly referred to as QT hysteresis. During exercise, the steady state QT interval following accelerations and decelerations of the heart rate has been observed to occur with a time lag of approximately 2 minutes [2]

Because of hysteresis, use of the immediately preceding RR interval to produce a normalized (heart-rate corrected) QT interval is inadequate. For example, in the QT/RR plane, even when considering relatively short time periods, a fixed heart-rate level would be associated with multiple QT intervals [3,4].

One of the first reported methods to compensate for hysteresis in continuous recordings generates and analyses averaged templates based on individual beats selectively pooled according to the preceding heart rate pattern [5]. This method (commonly referred to as "Holter bin") has been applied in different clinical contexts including normal subjects [6], LQTS patients [7] and in the study of drug-induced QT prolongation [8,9].More recently, Pueyo et al. modelled the QT-RR relationship as a time-variant system with both linear and non-linear components [10,11] An implementation of this model to assess QT prolongation in the context of pharmaceutical trials has been recently described [12]. However, the diagnostic capability of this approach, and consequently its clinical value, remains to be assessed.

2. Data acquisition and methods

All data used herein is from 12-lead, 24-hour Holter recordings (H12+, Mortara Instrument) with simultaneous sampling of all leads at 1000s/s. Two study populations are included. The largest population (G) consists of 383 recordings from the GISSI-HF heart failure study [13]. The second (C) consists of 33 Mortara company employees without known heart disease.

Data preprocessing included fully automatic beat detection and labeling, and depolarization and repolarization onset/offset detection by Mortara proprietary algorithms. Accurate QT measurement by these algorithms is a critical component for this study [14].

The resulting ensemble of QT and RR intervals are fitted to a linear model of QT dependence on RR, with

the modification that the RR interval to be used in the model is a weighted average of prior RR intervals. This weighted RR is dubbed the RR_c, or corrected RR. Beats with an abnormal QRS are not included in the ensemble of QT/RR_c pairs, though individual RR_c values may include abnormal RR intervals from prior beats. It makes little sense to have a unique weight for each prior RR interval involved in the makeup of RR_c when more than a few RR intervals are considered. Our resolution of this point is to use a single weight for a cluster of RR intervals, with the size of the cluster increasing two-fold for each cluster going into the past from the cycle with the measured QT. Our model looks like

$$RR_c = \sum (W_i \times RR_i), \quad QT_p = S_{QT/RR} \times RR_c + QT_0,$$

where QT_p is the predicted QT, $S_{QT/RR}$ is the QT/RR slope, W_i is the weight for RR cluster i, RR_i is the average RR of the cluster and QT_0 is the intercept. The summation is over a specific number of clusters, which we varied from 1 to 9 (1 to 511 beat history). The sum of the weights is unity. The independent parameters are determined by least squares fitting of QT_p to measured values of QT.

The QT/RR slope is known to be dependent on autonomic conditions, and this motivated limiting the time scope of the blocks of data used in individual determinations of the independent parameters. We used one hour blocks of data for this purpose, yielding 24 separate determinations for the typical 24-hour recordings. The derived weights for computing RR_c become indeterminate when the heart rate is monotonic. In this study, we excluded from further analysis hours where the mean square difference of $RR_8 - RR_9$ was less than 9 ms-squared to avoid indeterminate results. Additional exclusion criteria included a minimum of 2000 normal beats, fewer than ¼ of all beats omitted for reasons of unmeasured QT or abnormal QRS, weights either > 1.0 or < -1.0, and rms deviation of QT_p from measured QT (QT-RMS) while using a 511 beat history > 6.0 ms.

3. Results

There were a total of 9741 usable hours of data, and 8114 of these qualified after exclusions for sufficient rate variation, etc. The average values of QT-RMS over these 8114 hours decline monotonically (from 5.74 to 2.86 ms) with increasing length of RR history used. A small part of this decrease can be attributed to the successive increases by one of the number of parameters. While there are technical methods to assess the worthiness/validity of increasing the length of the RR history that is to be used in QT prediction (which increases the number of parameters to be determined), we find that the dispersion of the weights for a given portion of the RR history to be a more intuitive method of assessment. Figure 1 has a graphic illustration of the weights when a 511-beat history is used. The weights shown include the average of all data and the average of the G and C data. Table 1 shows the mean and standard deviation of the mean for each of the same weights. From these data, it can be seen that the RR history up to 255 prior beats is important to prediction of the QT.

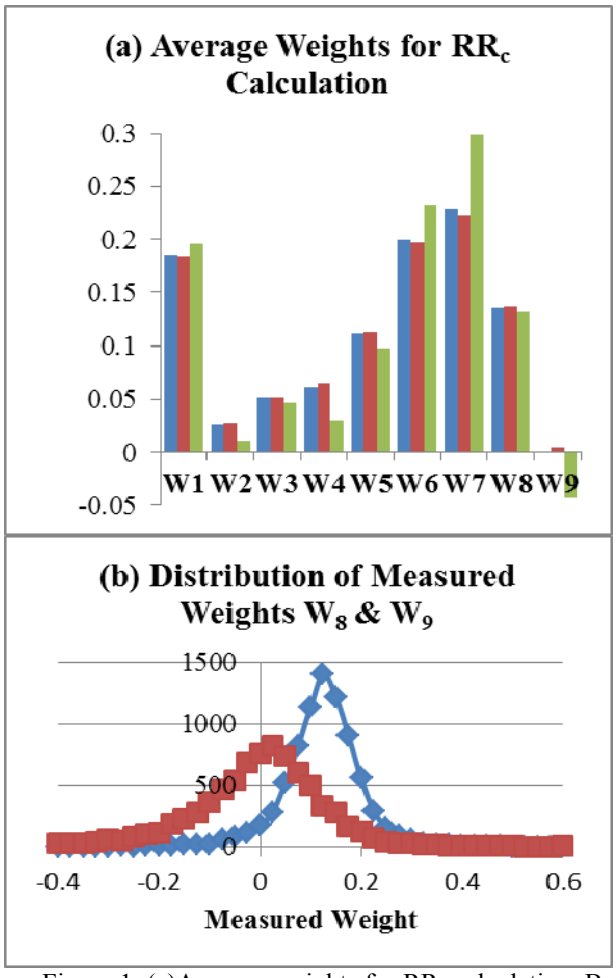

Figure 1. (a)Average weights for RR_c calculation. Bars are blue for all data (G+C), red for G, green for C. (b) Distribution of measured weights W_8 and W_9.

The relatively small standard deviations of the weights are implicit evidence of a low dispersion across the different hours and subjects included. This characteristic is illustrated in Figure 1(b) for the weights W8 and W9. The similarity of the weights from the heart failure and nominally normal databases explicitly suggests that a fixed set of weights may be applicable to a broad population. To test this hypothesis, the average weights in Table 1 were applied to the individual hours of each recording. The resulting average QT-RMS is

3.12ms, only 0.26ms greater than the result of applying unique weights to each hour. A test for the existence of outliers masked by the averages was performed by looking for the largest deviation between the subject-and-hour-specific QT-RMS and average weight QT-RMS in any single subject with at least nine hours of qualifying data. The maximum difference found was 1.0ms. We conclude that the average weights may be considered a universal set.

	W1	W2	W3	W4	W5	W6	W7	W8	W9
RR Span	1	2-3	4-7	8-15	16-31	32-63	64-127	128-255	256-511
Mean G+C	0.1847	0.0258	0.0517	0.0618	0.1110	0.2000	0.2291	0.1357	0.0003
SD G+C	0.0010	0.0008	0.0006	0.0006	0.0007	0.0008	0.0009	0.0010	0.0018
Mean G	0.184	0.027	0.052	0.065	0.112	0.200	0.222	0.136	0.004
Mean C	0.196	0.010	0.046	0.029	0.097	0.232	0.298	0.132	-0.042

Table 1. Prior RR interval span and numerical values of average weights for the combined data (Mean G+C), and their standard deviations (SD G+C). Also included are the average weights for the separate databases (Mean G = GISSI-HF, Mean C = Company Employees).

Atrial fibrillation often produces marked rate variation, and thus can be considered a paradigm of QT hysteresis. Indeed, for a given preceding RR interval, a wide range of QT intervals are typically observed. This is the case in the left panel of Figure 2 where three distinct clusters of QT values (430, 405, and 370ms) at an RR of 1000ms can be seen. The right panel shows the same data, with RR replaced by RR_c as calculated from the universal weight coefficients from Table 1. To be noted in this panel is the reduced QT variation at any given RR, the linearity of the QT/RR relationship over a range of RR from 750 to 1400ms, and the increase of apparent QT/RR slope. The increase of QT/RR slope is not confined to cases of atrial fibrillation. The average increase over the combined dataset is 0.087.

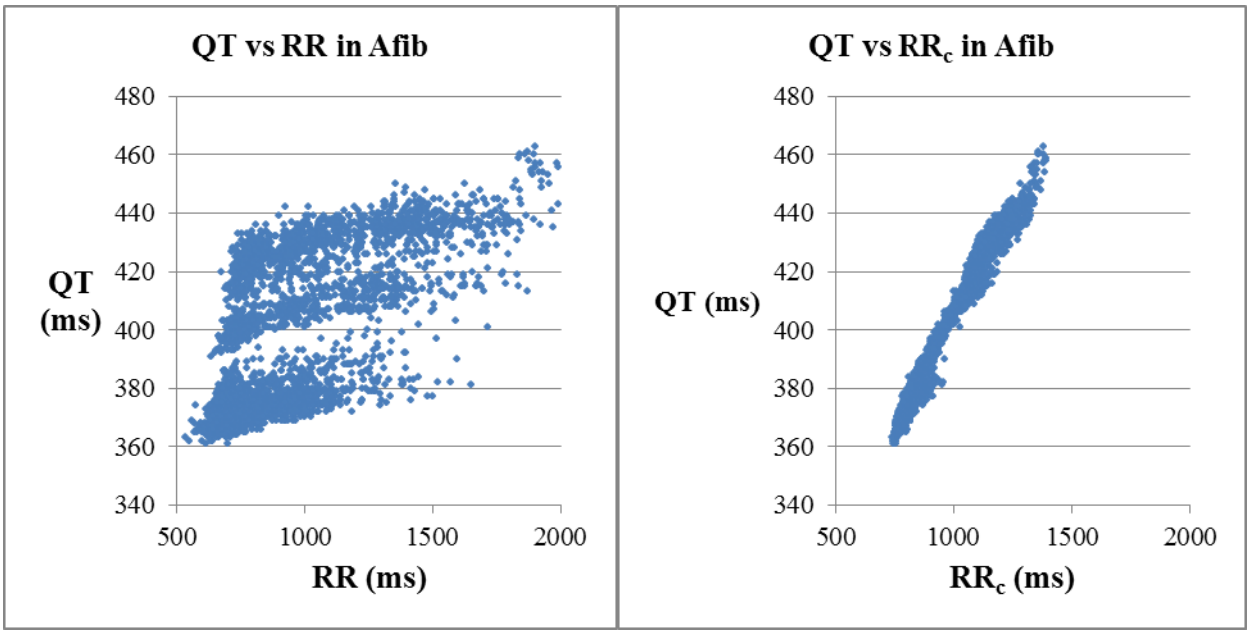

Figure 2. Illustration of the difference between QT/RR and QT/RRc scatterplots for a case of atrial fibrillation. Each panel has the identical QT data. Approximately 1 hour of data is included.

4. Discussion

A diverse set of recordings with more than 9000 hours of data reveals a consistent quantitative model of QT adaptation/hysteresis. These data show that > 13% of the QT adaptation to heart rate change occurs 128-255 beats after the change. When the model is applied to a sample of atrial fibrillation data, a remarkable improvement in ability to predict the QT is evidenced, demonstrating that QT assessment/correction in atrial fibrillation is possible. This same data also shows QT/RR linearity over a wide RR range, showing that any discussion of non-linearity of

the QT/RR response should include an accounting for QT hysteresis. Finally, QT/RR slopes show dramatic increases when hysteresis is accounted for. Future work will include testing QT prediction using the hysteresis model in stress testing and in pediatric ECGs.

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