ORIGINAL ARTICLES

A Novel Method for Patient-Specific QTc—Modeling QT-RR Hysteresis

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Background: Cardiac repolarization adaptation to cycle length change is patient dependent and results in complex QT-RR hysteresis. We hypothesize that accurate patient-specific QT-RR curves and rate corrected QT values (QTc) can be derived through patient-specific modeling of hysteresis.

Method and Results: Model development was supported by QT-RR observations from 1959 treadmill tests, allowing extensive exploration of the influences of autonomic function on QT adaptation to rate changes. The methodology quantifies and then removes patient-specific repolarization adaptation rates. The estimated average 95% QT confidence limit was approximately 1 msec for the studied population. The model was validated by comparing QT-RR curves derived from a submaximal exercise protocol with rapid exercise and recovery phases, characterized by high hysteresis, with QT-RR values derived from an incremental stepped protocol that held heart rate constant for 5 minutes at each stage of exercise and recovery.

Conclusions: The underlying physiologic changes affecting QT dynamics during the transitions from rest to exercise to recovery are quite complex. Nevertheless, a simple patient-specific model, comprising only three parameters and based solely on the preceding history of RR intervals and trend, is sufficient to accurately model QT hysteresis over an entire exercise test for a diverse population. A brief recording of a resting ECG, combined with a short period of submaximal exercise and recovery, provides sufficient information to derive an accurate patient-specific QT-RR curve, eliminating QTc bias inherent in population-based correction formulas.

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QT hysteresis; repolarization; corrected QT (QTc)

Numerous studies have quantified QT versus RR behavior in various populations.[1–9] The cumulative effect of these studies has been to highlight the tremendous variability in the QT-RR relationship. More recent studies[10,11] have shown that the QT-RR relationship is patient-specific; application of generalized population trends to correct QT to a standard heart rate, QTc, can produce erroneous results when applied to a specific subject.[12–15]

The patient-specific nature of the QT-RR relationship calls into question the validity of characterization by a single parameter (i.e., QTc). The QT-RR relationship is further complicated by the effects of delayed repolarization adaptation to changes in heart rate. While not widely recognized, changes in cycle length are not instantaneously reflected in changes in QT interval. During exercise QT lags behind as cycle length shortens, and during recovery QT remains short relative to the increasing cycle length. The lag in the heart's adaptation to changes in cycle length results in QT-RR hysteresis. QT duration reflects the cumulative effects of the preceding beat history and the patient-specific adaptation rate to change in heart rate.

Pueyo et al.[16] have modeled the effective cycle length associated with each QT observation, derived from 24-hour ambulatory ECG (Holter) records, as a sum of weighted RR intervals for the preceding approximately 150 beats. The method solves a system of equations where each preceding RR interval weight is an unknown—essentially a system of equations with approximately 150

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unknowns. This complex methodology is successful in modeling patient-specific QT-RR hysteresis.

Guided by the principle of Ockham's razor, surmising that the relationship between QT and the preceding intervals may be much less complex than Pueyo et al.'s model, we hypothesized that repolarization adapts at a patient-specific rate with each beat. This simple assumption leads to a model that captures much of the observed patient-specific QT-RR hysteresis. However, systematic residual error associated with this simple model occurs when the heart rate trend is rapidly changing (e.g., the transition from exercise to recovery), leading to an "overshoot" of the predicted QT. This observation led us to add model complexity that utilizes the trend or rate of change of cycle length, a characteristic not captured in models based only on a weighted sum of previous RR values.

This model of QT-RR hysteresis corrects for the influence of the cycle length history and trend on the QT observations and derives accurate patient-specific QT-RR curves that extend over a wide range of heart rates. We anticipate that such a simple approach for developing QT corrections for both heart rate and hysteresis will likely lead to significant improvements in studies of cardiac repolarization.[15]

METHODS

Study Population

Electrocardiogram (ECG) recordings were drawn from a study population of 1959 subjects referred for clinical treadmill testing in the Palo Alto Veterans Affairs Health Care System between 1997 and 2004. These represented approximately half of the initial tests referred to our Cardiology Service during this time period, with the choice of devices for testing made only by availability and convenience. Subjects were tested on a device (QUEST, Burdick Corp., Deerfield, WI) that permitted continuous 12-lead digital recording at 500 samples per second. The demographic profile of this population has been described in previous studies.[17] Fifteen additional ECG recordings in support of study-specific exercise profiles were obtained from five healthy volunteers from our lab using both the treadmill system and a 12-lead Holter recorder operating at 1024 samples per second (DL1200 by Braemar Inc., Eagan, MN). This study was approved by the Stanford University Institutional Review Board and each patient gave informed written consent.

QT and RR Estimation

About 760 QT-RR observations, distributed uniformly over the exercise and recovery phases, were derived from each ECG treadmill recording, resulting in about 1.5 million QT-RR observations. The large volume of observations required use of an automated method of measurement. Beat averaging was used to improve the signal-to-noise ratio. Each QT-RR estimate was derived from a continuous 15-beat ECG segment, using only the dominant beats in the segment and the eight independent leads I, II, V_1–V_6. The end of T was determined by a method similar to the steepest slope approach.[18] Each ECG lead was baseline-corrected, beat-averaged, and the waveform envelopes for the eight traces were summed to form a global estimate of the declining T-wave amplitude. The end of T was defined as the intersection of a line, fitted to a suite of points selected around the vicinity of the steepest descent, and the isoelectric baseline. The corresponding RR interval associated with the QT measurement was the simple RR average from the 15-beat segment. Beat averaging of exercise-derived data is necessary to improve signal quality and QT measurement accuracy but does preclude analysis of QT dynamics over beat intervals that are shorter than the averaging interval. The QT observations for each patient record were visually examined for consistency and accuracy and errors were deleted. Thirty-one tests from the 1959 population were excluded on the basis of unreliable estimates of QT associated with high noise, low T-wave amplitudes or ambiguous end of T.

Effective Heart Rate

Figure 1, modeled from clinical pacing observations,[19] conceptually illustrates QT adaptation to changes in pacing rate for a range of rate adaptation parameters. Initially the patient was paced at a constant rate and then the pacing was abruptly increased to a higher rate. The observed QT did not instantaneously adjust to the shortened RR interval; rather, it slowly adapted to the new rate. The QT behavior reflected an effective RR interval influenced both by the most recent RR interval and by the rate history.

Our simple model that captures this heart-rate adaptation process assumes that the effective RR interval for the most recent beat is a rolling weighted average between the effective RR

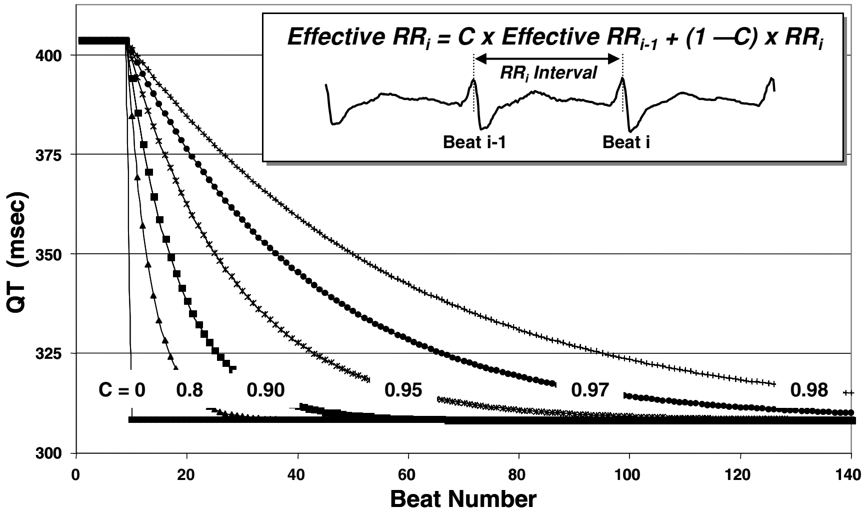

Figure 1. Model QT adaptation to a step change in heart rate. The effective RR interval is computed recursively from a rolling weighted average of the next RR interval and the last effective RR value. The parameter C, ranging from zero to one, controls the adaptation rate, with larger values of C associated with slower adaptation.

interval from the preceding beat and the most recent RR interval. With each new beat (i) the effective RR value is updated as a weighted average of the last computed effective RR value, associated with the previous beat ($i - 1$), and the RR value associated with the most recent beat (i)

$$EffectiveRR_i = C \times EffectiveRR_{i-1} + (1 - C) \times RR_i \quad [0 \leq C \leq 1] \tag{1}$$

The parameter C controls how fast the effective RR value adapts to changes in heart rate. In Figure 1, for $C = 0$ the effective RR value updates with each new beat to the most recent RR value, and QT fully adapts to each new RR interval; there is no weighted averaging. As C increases the associated effective RR curve adapts to the rate change over a progressively greater number of beats, and QT adapts more slowly. For the extreme case of $C = 1$, the effective RR value never adapts to change.

Recursively substituting $EffectiveRR_n$ in Equation 1 for n preceding RR intervals ($n = 0$ is the most recent RR interval, $n = 1$ is the preceding RR, etc.) leads to

$$EffectiveRR_i = \sum_n \{C^n \times [(1 - C) \times RR_i]\} \tag{2}$$

As beats progress each new RR value contributes to the effective RR value by the weighted average term

$$[(1 - C) \times RR_i] \tag{3}$$

The influence of each beat diminishes as beats progress, following the series C^1, C^2, C^3, ... C^n. Note that as n increases C^n approaches zero ($C < 1$) and the effects of beats older than n have negligible influence on the current effective RR value; that is, the heart has "forgotten" the influence of beats older than n. It is useful to define a beat half-life (HL) as being the number of beats that must occur before the influence of a particular beat has fallen by 50%, that is,

$$C^{HL} = 0.5 \quad \text{or} \quad HL = Log(0.5)/Log(C) \tag{4}$$

As an example, $C = 0.98$ implies a half-life of 34 beats; that is, after 34 beats the influence of one RR interval is half of its initial contribution.

Given a continuous RR interval time series, including ectopy if present, and a trial value of C, recursive application of Equation 1 to the RR time series results in an associated effective RR interval time series. The initial value for the first effective RR interval is set to the first RR interval, and the effective RR interval time series is considered valid after n beats have passed, where n is large relative to the half-life for the associated value of C—i.e., the influence of unknown beats that

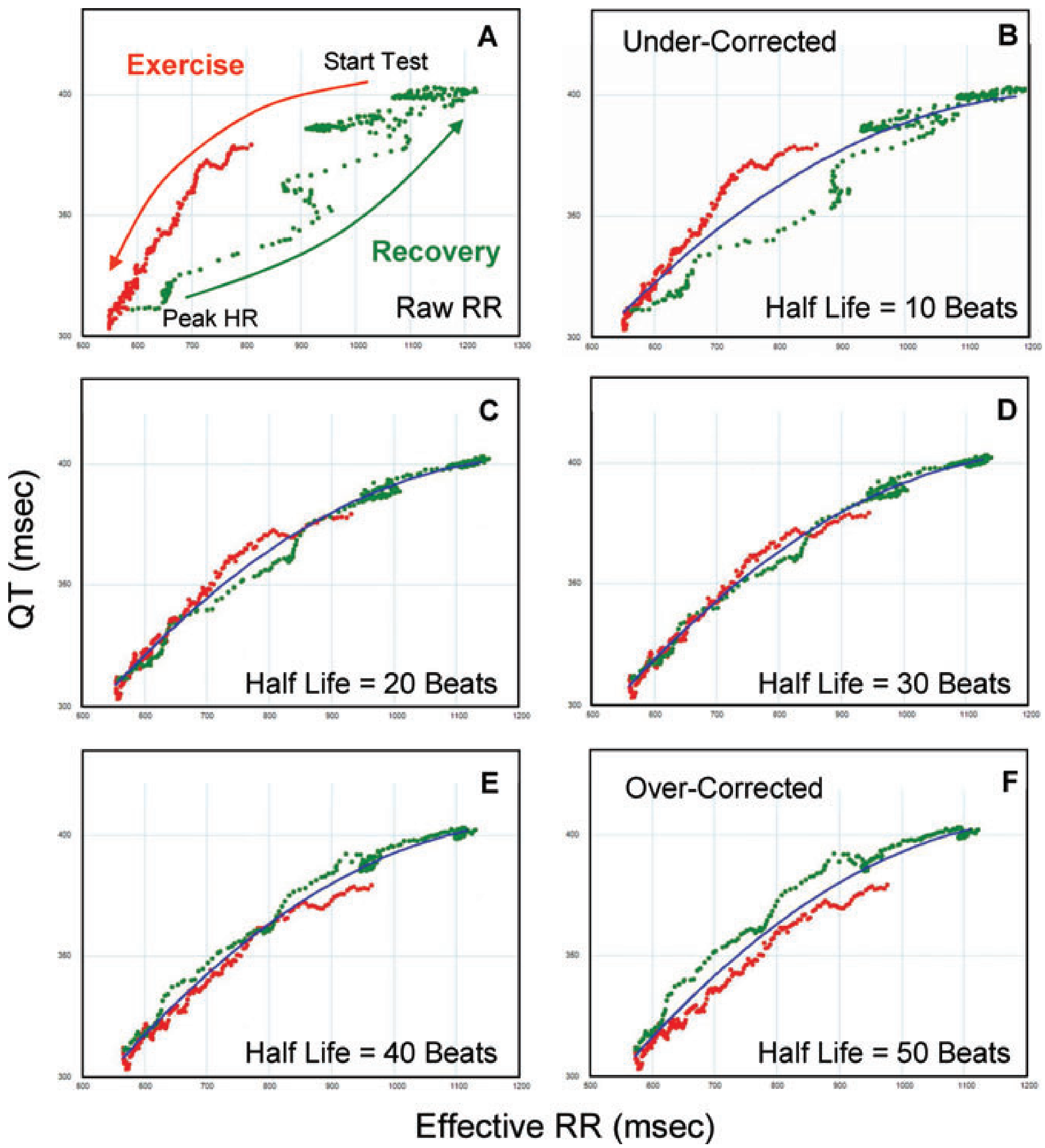

Figure 2. Example of observed QT-RR hysteresis associated with a standard treadmill stress test (A). Examples B–F show progressively greater effective RR corrections associated with increasing C and beat half-life. The complex multivalued hysteresis exhibited in (A) resolves into a simple QT-RR curve in (D). Further increases in beat half-life (F) result in overcorrection and overmigration of the exercise and recovery QT values. A key strength of the method derives from the simultaneous migration of the exercise and recovery QT values to a common curve.

occurred before the onset of the ECG recording has faded. In practice, for ECG records that begin with low and stable heart rates, the effective RR series is valid after about 100 beats. Finally, for each QT-RR measurement pair, the RR value is replaced by the effective RR value associated with the measurement (i.e., the effective RR value associated with the beat in the middle of the 15-beat segment associated with the measured QT value). Figure 2 shows a suite of QT versus effective RR plots for an exercise test for various values of C. Plot A is the raw uncorrected QT-RR data, showing substantial hysteresis. The red and green QT values represent the exercise and recovery phases respectively. As C and the associated half-life increase, the hysteresis and scatter collapse (plots B, C)

until plot D, where the exercise phase QT values comingle with the recovery phase values. In plots E and F the effective RR intervals have been overcorrected and the exercise and recovery data have migrated through each other; the red exercise QT values are systematically less than the green recovery values.

Curve Fitting—QT versus RR

The optimal value for the parameter C is chosen as the value that minimizes the scatter between the QT values for the exercise and recovery phases. Quantifying the degree of scatter is aided by fitting a curve that is representative of the QT-RR relationship to the corrected data and computing the associated standard deviation. Previous investigators have proposed many different functional forms.[16] We have found that a simple second-order polynomial [$QT = a \times RR^2 + b \times RR + c$] provides sufficient flexibility to encompass both the characteristics of previously reported functional forms over the RR range of interest and the substantial patient-specific diversity reflected in this study's population. Testing with a third order polynomial did not improve the statistical fit and was rejected as adding unwarranted complexity. For each value of C the polynomial is fitted to the QT versus effective RR data. Equal weight is given to the exercise and recovery sides of the QT data, eliminating potential bias associated with disparate numbers of QT measurements from the two phases. The C value that minimizes the standard deviation of the fitted curve is chosen as the patient-specific best average value for the test, and the associated curve is identified as the optimal patient-specific QT-RR relationship. Uncertainty in the model's predicted QT value for any RR value along the derived polynomial curve (e.g., QT at 1000 msec, a patient-specific QTc) can be estimated using a bootstrap procedure with 100% replacement.[20]

Heart Rate Trending

The above-described method has been found to model much of the observed hysteresis in the diverse study population. However, observed systematic discrepancies between the model and the data suggest a model extension. Figure 3A provides a good representative example from one

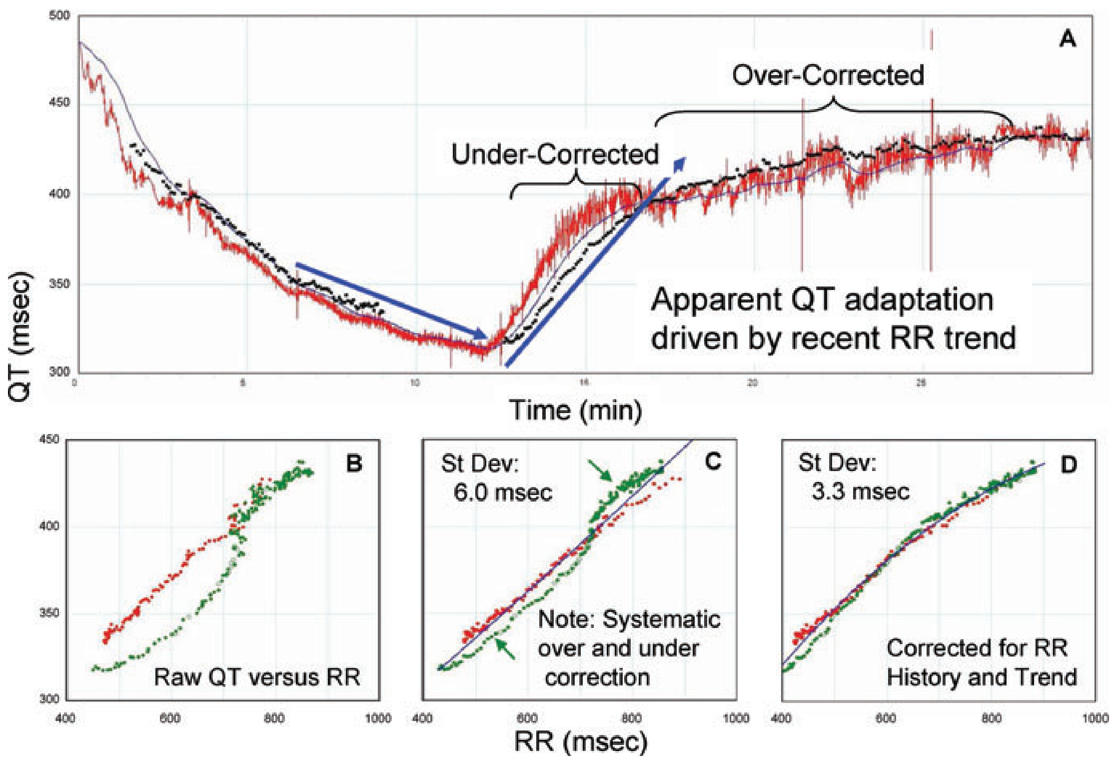

Figure 3. QT sensitivity associated with RR trends. The best-fitting effective RR model (blue line in A) systematically fails to capture QT trends in the presence of rapid RR trend changes. Addition of a linear RR trend term to the effective RR model reduces systematic error and standard deviation (C).

test that characterizes the systematic discrepancies observed in tests from about half of the population. The observed QT values are plotted as black squares. The QT-RR polynomial relationship from the best-fitting model is used to transform both the raw and effective RR time histories into equivalent QT units, red and blue curves, respectively. Note that the effective RR curve always lags the actual RR observation, reflecting the running weighted average of the previous beat history. If the model were perfect then the effective RR blue curve would pass through all of the QT black square values. The observed QT and raw RR pairs are also plotted in Figure 3B, showing the hysteresis between the exercise (red) and recovery (green) phases. The best-fitting value of C, associated with the fitted QT-RR curve (blue line), reduces the standard deviation to 6 msec, Figure 3C. However, during the start of recovery, following peak heart rate (minimum RR, Fig. 3A and C), the observed QT values overshoot the best-fitting model and remain depressed, relative to the model, for several minutes; the effective RR values are under-corrected. Then, several minutes into recovery, as the RR recovery curve rapidly flattens, the QT values appear to overshoot the model again; the effective RR values are overcorrected. The weighted averaging method is not capable of modeling the observed transitions from under to overcorrected.

This systematic QT behavior over the course of the treadmill test suggests that the heart adapts to a heart rate trend and adapts QT in anticipation of a continuation of the trend. To accommodate this observation a trending term is added to Equation 1. For each beat the preceding effective RR values are fitted to a trend line, with the contribution or weight of each preceding value decreasing with RR age as L^n, with $0 < L < 1$, and n is the associated RR interval number before the current interval. The derived weighted trend line is used to predict the next effective RR value, and a weighted average between the observed RR interval and the predicted effective RR interval is computed

$$(RR_i + W \times PredictedRR_i)/(1 + W) \quad \text{where } W \geq 0. \tag{5}$$

This term is used to replace the term [RRi] in Equation 1, forming

$$\text{Effective}RR_i = C \times \text{Effective}RR_{i-1} + (1 - C) \times [(RR_i + W \times PredictedRR_i)/(1 + W)] \tag{6}$$

Thus, the primary model parameters are as follows

- C (Decay rate of an RR interval, $0 \leq C \leq 1$)
- L (Decay rate of previous *EffectiveRR* values in linear trend prediction, $0 < L < 1$)
- W (relative averaging weight between the observed RR and *PredictedRR* values, $W \geq 0$. Note: $W = 0$ reverts to Equation 1)

The optimal model for the patient-specific QT-RR data is found by searching the three-parameter model space for the values that minimize the standard deviation of the best-fit QT-RR curve. Figure 3D illustrates the improvement in the model obtained by adding the heart rate trending term. The systematic bias is nearly eliminated and the standard deviation is reduced by almost 50%.

The algorithm is readily implemented on a standard desktop computer and executes in 10–15 seconds for a treadmill test that includes 9 minutes of exercise and 5 minutes of recovery, comprising roughly 1500 heart beats (i.e., 500–1000 QT-RR observations).

Model Testing

The model development was driven by the goal of accounting for and removing hysteresis in observed ECG records associated with increasing and decreasing heart rate, and thus recovering patient-specific QT-RR curves. The study population was analyzed extensively both to gain insights into QT dynamics for a wide range of patient conditions and to drive the model development. However, the possibility remains that the derived patient-specific QT-RR curve is contaminated by unknown or inadequately modeled phenomena and does not truly reflect the patient QT-RR curve that would be observed if hysteresis were not present. To investigate this potential issue a new test protocol was developed. Starting from a resting stage, the protocol next exercised each subject over a 5-minute period at a constant speed and grade to achieve approximately 80% of the age-predicted maximum heart rate, followed by about 10 minutes of standing recovery. This element of the protocol was designed to maximize the observed hysteresis over the initial exercise and recovery phases. The subject then continued on the treadmill with speed and grade designed to stair-step heart rate in about 20 beats/minute increments to 80% of predicted

maximum heart rate, and returned in similar stair-steps to standing recovery. Each stage was maintained for about 5 minutes, allowing the heart rate and QT values to stabilize. Measurements of the stable QT values for each stable heart rate define the patient-specific QT curve and should be equivalent to the model-derived QT-RR curve from the short five-minute test exhibiting high hysteresis. This protocol was repeated 15 times with the assistance of 5 volunteers from our lab, ranging in age from 16 to 59, and included ECGs with numerous premature atrial and ventricular beats. To assess consistency one of the volunteers performed the protocol 7 times over the course of 2 weeks; model parameters derived from the first test were used to assess model stability in the subsequent tests.

A statistical comparison between the observed QT-RR data and the computed model results for the 1959 treadmill tests was also conducted in a search for systematic error or bias. Model error (observation – model-predicted QT) was examined for heart rate ranges in 15 beats/minute bins (e.g., 45–60, 60–75, etc) and for tertile ranges of heart-rate (i.e., the model error for the lower, mid, and upper thirds of the heart rate range associated with each test). The standard deviation of the model fit for each test was examined for correlations with observed T-wave amplitude, heart rate range, peak heart rate, ST depression, age, and ectopy rates.

RESULTS

The 1959 Study Population: The developed dynamic QT model was applied to the patient population data from 1959 treadmill tests, comprising approximately 1.5 million QT-RR pairs. The median model error (the median of the standard deviation of the hysteresis corrected QT-RR values relative to the best-fitting patient-specific curve) for the population was 3.9 ± 2.4 msec, reflecting good model performance over a broad range of ages, heart-rates, and patient health. The estimated average 95% QT confidence limit, derived using a bootstrap method with 100% replacement, was approximately 1 msec for the studied population.

Table 1 examines the model error as a function of heart rate ranges. Overall, the model errors appear to be small. For heart rates lower than 150 beats/minute, the average model errors are less than 1 msec, growing to approximately 3 msec at the highest heart rate. The model error standard deviation trends to larger values at higher heart rates (~2.5 msec growing to ~4.5 msec), probably due to increased noise at higher levels of physical exertion that decreases the reliability of picking the end of T. The correlation coefficients between the standard deviation of the model fit for each test and observed heart rate range, peak heart rate, ST depression, age, and ectopy rates are all less than 0.1, suggesting that the model efficacy is not biased by normal clinical variations in these characteristics. However, the correlation with T-wave amplitude is somewhat larger and inversely correlated with the standard deviation (r = −0.44), consistent with greater uncertainty in picking end of T in lower amplitude signals.

Table 1. Model Performance over a Range of Heart Rate Bins

HR Range	# Tests	Ave Error (msec)	StDev (msec)
45–60	93	0.73	2.56
60–75	563	0.16	2.95
75–90	1276	0.11	3.28
90–105	1760	−0.01	3.81
105–120	1790	−0.04	4.24
120–135	1580	0.29	4.13
135–150	1231	0.09	3.99
150–165	811	−1.14	4.02
165–180	381	−1.70	3.88
180–195	75	−3.21	3.58
Lower tertile		0.05	3.62
Middle tertile		−0.03	4.05
High tertile		0.00	4.62

The model appears to be insensitive to the presence of premature atrial and ventricular contractions. The effective RR interval computation averages the short RR interval associated with the premature beat with the longer RR interval associated with the following compensating pause, resulting in a model prediction for little net change in QT. Figure 4 compares the effective RR (blue line) with the observed RR (red line) intervals; the abrupt jumps in RR associated with rhythm disturbances are smoothed in the predicted curve. The QT observations, which reflect 15-beat averages, do not show any systematic jumps associated with rhythm disturbance. If QT duration is changed by rhythm disturbances, the duration of the impact is short relative to the 15-beat QT averaging used in this study. Low noise, high-resolution ECG recordings, where beat-by-beat analysis could be conducted, might provide insights into very short-term QT dynamics.

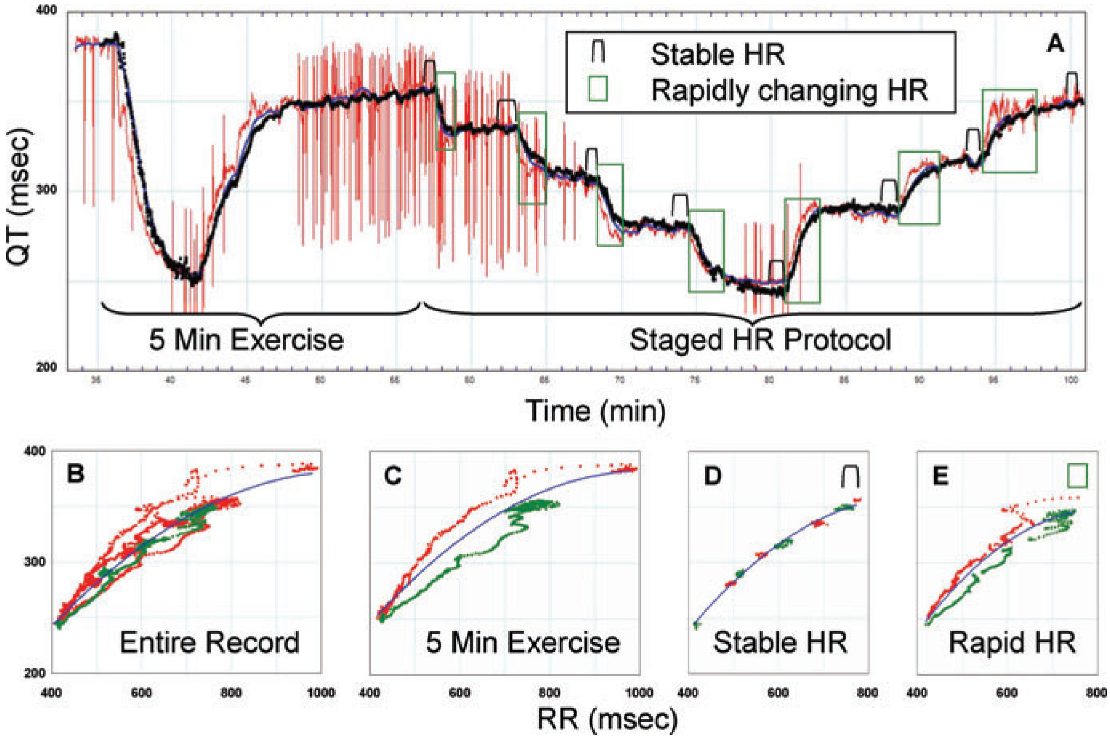

Figure 4. Model testing—rapid and staged heart rate protocol. The raw QT-RR observations for the entire record are shown in A and B. Selected subsets of the record are highlighted: (C) five minute exercise followed by 10 minutes of recovery; (D) QT-RR values derived from the end of the approximately 5 minute stable heart rate segments; and (E) QT-RR values from the rapidly changing heart rate segments.

The determined beat half-life of both the individual RR intervals and the trend continuation of the effective RR rate, corresponding to the parameters C and L, ranged from near zero to well over 100 beats, confirming previous observations that QT dynamics are highly variable among subjects.[20]

Model Testing Protocol: An example of data derived from the 5-minute and incrementally stepped exercise protocol is shown in Figure 4. Figure 4A shows the time history of the protocol and is formatted the same as Figure 3A described above. Note the close correspondence between the model (blue line) and the observed QT values (black squares). The RR "spikes" in this test are associated with premature atrial contractions. Figures 4B–E show the raw QT-RR data collected over the protocol, where 4B shows the entire protocol, 4C shows the 5-minute exercise phase, 4D shows raw QT-RR values from the end of each stable heart rate phase of the protocol, and 4E shows the QR-RR values while heart rate is rapidly changing during stage changes. The stable raw QT-RR values, shown with the associated best-fit QT-RR curve in Figure 4D, should be good estimates of the true QT-RR relationship. There does not appear to be any systematic bias between the QT values obtained during the increasing heart rate phase of the stepped protocol and those from the decreasing phase; data from both phases cluster around a single QT curve in Figure 4D. Figure 5 illustrates the QT-RR curves derived from application of the dynamic QT model to the various data groupings shown in Figure 4, along with the stable raw QT-RR values, marked Stable HR (Raw). The average scatter (maximum–minimum) across all the derived QT-RR curves is less than 4 msec and is very consistent with the stable raw QT values. Similar results were obtained from all 15 tests. The dynamic QT model appears to do a good job of removing hysteresis and recovering a patient-specific QT-RR curve in agreement with values derived from measurements at stable heartrates. The first part of this protocol, composed of an initial resting period, followed by submaximal exercise lasting about 5 minutes, plus the recovery period, is sufficient to define an accurate subject-specific QT-RR curve.

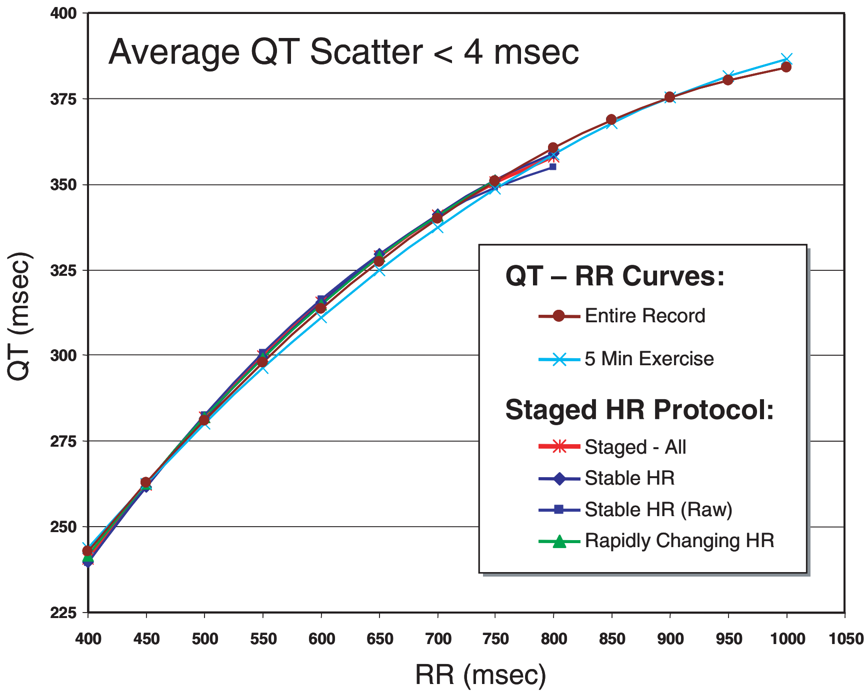

Figure 5. QT-RR curves derived using the dynamic QT model compared with the stable heart rate QT-RR values from the raw data presented in Figure 5. The Stable HR (Raw) curve reflects the observed QT-RR values obtained following approximately 5 minutes of stable heart rate at different RR values. Note that the model-derived curves are in good agreement with the stable heart rate QT values.

To gain some insight into model stability and predictability, one test subject performed the protocol 7 times over the course of 2 weeks. Each test averaged nearly 2 hours in ECG recording duration and resulted in approximately 6,700 QT-RR observations. The optimal model parameters *C*, *L,* and *W*, and the associated standard deviation between the observed and predicted QT values, were computed for each test. The average standard deviation for all seven tests was 4.44 ± 0.43 msec. The optimal model parameters from the first test were then used to analyze the subsequent 6 tests. The average standard deviation increased by 3.0 ± 2.4% , or about 0.13 msec, relative to the test-specific optimal model solutions. The average difference in the derived QT-RR curves was 0.06 ± 0.26 msec.

DISCUSSION

The underlying physiologic changes affecting QT-RR dynamics that occur over the transitions from rest to exercise to recovery are quite complex. The behavior is further complicated by disease state, sex, and age. Nevertheless, this study has found that a simple patient-specific model, comprising only three parameters and based solely on the preceding history of RR intervals and trend, is sufficient to accurately model QT hysteresis over an entire exercise test for a diverse population. The observed hysteresis can be routinely modeled to within a few milliseconds, comparable to the underlying QT measurement uncertainty. The strength of the model derives from its joint analysis of the exercise and recovery phases, which simultaneously corrects both phases to a single QT-RR curve. The QT-RR data collected from an incrementally stepped heart rate protocol, providing QT measurements associated with stable heart rates, are in agreement with the QT-RR curves derived from a brief exercise protocol exhibiting significant hysteresis. We believe the method is recovering true patient-specific QT-RR curves.

We speculate that the linear trend component of the model may be related to the buildup and subsequent metabolism of catecholamines. Future studies that measure catecholamines over the course of

the test may help develop insights into the underlying physiology. Alternatively, comparing QT dynamics for the same patient between exercise and pacing protocols may help improve the connection between model elements and autonomic function.

Analysis of the study population confirms that QT corrections for heart rate are highly individual. The degree of observed hysteresis is dependent upon both patient physiology and the details of heart rate history over the course of the test. Current standard methods for correcting QT for heart-rate, QTc, introduce noise, and contribute to the observed scatter. Our experience with the model testing protocol suggests that a brief ECG recording that includes modest exercise and recovery is sufficient to determine an accurate patient-specific QT-RR curve and an associated QTc value. An appropriate protocol would include 10–15 minutes of initial rest followed by 4–5 minutes of modest exercise and continued recording of 10–15 minutes of recovery.

The model is based upon the assumption that the inherent patient-specific QT-RR curve and the associated model parameters are approximately stable over the duration of the test. As noted by previous investigators, many other physiologic changes impact QT, and the hysteresis model parameters may well follow longer-term changing conditions.[21] Comparing repeated exercise protocols for a single patient, as well as their 24-hour ambulatory records—although typified by limited heart rate range—would be helpful in assessing the stability over time of the patient-specific hysteresis model. Our limited experience with repeat testing with the stair-stepped protocol is encouraging; the model derived from the first test adequately explained the subsequent tests.

Improved resolution of patient-specific QTc and QT-RR curves may be helpful in future studies of adverse repolarization dynamics, potentially including patients with long QT syndrome, exercise-induced ischemia, or in studies assessing the impact of new therapeutic agents on QT dynamics over a broad range of heart rates.

REFERENCES

1. Bazett JC. An analysis of time relation of electrocardiograms. Heart 1920;7:353–367.
2. Fridericia LS. Dir Systolendaeur in Elektrokardiogram bei normalen menchen und bei herzkranken. Acta Med Scand 1920;53:469–486.
3. Funck-Brentano C, Jaillon P. Rate-corrected QT interval: Technique and limitations. Am J Cardiol 1993;72:17B–22B.
4. Hodges M, Salerno Q, Erlien D. Bazett's QT correction reviewed. Evidence that a linear QT correction for heart rate is better. J Am Coll Cardiol 1983;1:694.
5. Karjalainen J, Viitasalo M, Mänttäri M, et al. Relation between QT interval and heart rates from 40 to 120 beats/min in rest electrocardiograms of men and a simple method to adjust QT interval values. J Am Coll Cardiol 1994;23:1547–1553.
6. Kawataki M, Kashima T, Toda H, et al. Relation between QT interval and heart rate. Applications and limitations of Bazett's formula. J Electrocardiol 1984;17:371–375.
7. Klingfield P, Lax K, Okin P. QT Interval-Heart Rate relation during exercise in normal men and women: Definition by linear regression analysis. J Am Coll Cardiol 1996;28:1547–1555.
8. Malfatto G, Facchini M, Zaza A. Characterization of the non-linear rate-dependency of QT interval in humans. Europace 2003;5:163–170.
9. Sagie A, Larson MG, Goldberg RJ, et al. An improved method for adjusting the QT interval for heart rate (the Framingham Heart Study). Am J Cardiol 1992;70:797–801.
10. Malik M, Färbom P, Batchvarov V, et al. Relation between QT and RR intervals is highly individual among healthy subjects: Implications for heart rate correction of the QT interval. Heart 2002;87:220–228.
11. Pueyo E, Smetana P, Laguna P, et al. Estimation of the QT/RR hysteresis lag. J Electrocardiol 2003;36:187–490.
12. Batchvarov VN, Ghuran A, Smetana P, et al. QT-RR relationship in healthy subjects exhibits substantial intersubject variability and high intrasubject stability. Am J Physiol Heart Circ Physiol 2002;282:H2356–H2363.
13. Benatar A, Decraene T. Comparison of formulae for heart rate correction of QT interval in exercise ECGs from healthy children. Heart 2001;86:199–202.
14. Davey P. How to correct the QT interval for the effects of heart rate in clinical studies. J Pharmacol Toxicol Methods 2002;48:3–9.
15. Malik M, Hnatkova K, Novotny T, et al. Subject-specific profiles of QT/RR hysteresis. Am J Physiol Heart Circ Physiol 2008;295:H2356–H2363.
16. Pueyo E, Smetana P, Caminal P, et al. Characterization of QT interval adaptation to RR interval changes and its use as a risk-stratifier of arrhythmic mortality in amiodarone-treated survivors of acute myocardial infarction. IEEE Trans Biomed Eng 2004;9:1511–1520.
17. Hadley D, Dewey F, Freeman J, et al. Prediction of cardiovascular death using a novel heart rate recovery parameter. Med Sci Sports Exercise 2008;40:1072–1079.
18. Malik M, Batchvarov VN. Measurement, interpretation and clinical potential of QT dispersion. J Am Coll Cardiol 2000;36:1749–1766.
19. Lau CP, Freedman AR, Fleming S, et al. Hysteresis of the ventricular paced QT interval in response to abrupt changes in pacing rate. Cardiovasc Res 1988;22:67–672.
20. Sohn RA, Menke W. Application of maximum likelihood and bootstrap methods to nonlinear curve-fit problems in geochemistry. Geochem Geophys Geosyst 2002;3:1–17.
21. Extramiana F, Maison-Blanche P, Badilini F, et al. Individual QT-R-R relationship: Average stability over time does not rule out an individual residual variability: Implication for the assessment of drug effects on the QT interval. A.N.E. 2005;10:169–178.