Evaluation of a subject-specific transfer-function-based nonlinear QT interval rate-correction method

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Abstract. The QT interval in the electrocardiogram (ECG) is a measure of total duration of depolarization and repolarization. Correction for heart rate is necessary to provide a single intrinsic physiological value that can be compared between subjects and within the same subject under different conditions. Standard formulas for the corrected QT (QTc) do not fully reproduce the complexity of the dependence in the preceding interbeat intervals (RR) and inter-subject variability. In this paper, a subject-specific, nonlinear, transfer function-based correction method is formulated to compute the QTc from Holter ECG recordings. The model includes 5 parameters: 3 describing the static QT-RR relationship and 2 representing memory/hysteresis effects that intervene in the calculation of effective RR values. Parameters identification procedure is designed to minimize QTc fluctuations and enforce zero correlation between QTc and effective RR. Weighted regression is used to better handle unbalanced or skewed RR distributions. The proposed optimization approach provides a general mathematical framework for further extensions of the model. Validation, robustness evaluation and comparison with existing QT correction formulas is performed on ECG signals recorded during sinus rhythm, atrial pacing, tilt-table tests, stress tests and atrial flutter (29 subjects in total). The resulting average modeling error on the QTc is 4.9±1.1 ms with a sampling interval of 2 ms, which outperforms correction formulas currently used. The results demonstrate the benefits of subject-specific rate correction and hysteresis reduction.

1. Introduction

The T wave on the surface electrocardiogram (ECG) is associated with repolarization gradients in the ventricles (Antzelevich 2004). The duration of the interval between the onset of the Q wave and the end of the T wave, known as the QT interval, is a measure of total duration of ventricular depolarization and repolarization. Because the QT interval is heart rate-dependent, further processing is required to extract a single intrinsic physiological value representing the duration of depolarization and repolarization in each subject. The resulting rate-corrected QT, denoted by QTc, is defined as the QT interval that would be measured at a regular rate of 60 bpm (Bazett 1920, Fridericia 1920). The problem is to design a signal processing technique for estimating the QTc from ECG recordings.

The QTc can be inferred from the relationship between QT and the preceding beat-to-beat interval (RR). Simple QT correction formulas have been proposed (Bazett 1920, Fridericia 1920, Hodges et al. 1983, Sagie et al. 1992). These formulas assume a unique static QT-RR relationship for all subjects, which facilitates its application to manually-measured QT and RR intervals extracted from short-duration ECGs. These definitions of QTc have shown their limitations in terms of residual rate-dependence of the QTc (Luo et al. 2004, Chiladakis et al. 2010). Indeed, the QT-RR relationship is nonlinear, subject-specific (Malik et al. 2002) and not instantaneous. The QT interval depends on the history of previous RR intervals, *i.e.*, it exhibits hysteresis (Lau et al. 1988, Pueyo et al. 2003, Halamek et al. 2007, Malik et al. 2008), which complicates QT correction.

Holter monitoring and automatic computer-based ECG analysis opened the way to more sophisticated approaches by processing longer time series. The linear correction model (Sagie et al. 1992) was extended to include a subject-specific slope computed by linear regression (Karjalainen et al. 1994). A set of two-parameter non-linear functions has been proposed to better reproduce observed QT-RR relationships (Malik et al. 2002, Pueyo et al. 2004). To account for slow adaptation of QT following an abrupt change in heart rhythm, methods based on transfer function were developed (Pueyo et al. 2004, Halamek et al. 2010). In these methods, the QT is expressed as a function of the effective RR defined as a weighted linear combination of previous RR intervals.

In this paper, existing QT-RR models are generalized and combined to define a new QT correction method. A computational framework is formulated to identify model parameters and extract the QTc. Weighted regression is used to better handle cases of skewed RR distribution. Validation and robustness evaluation is performed using Holter ECG data recorded during sinus rhythm, atrial pacing, tilt-table tests, stress tests and atrial flutter. Comparison with previous approaches is finally presented.

2. Data collection

2.1. Clinical protocol

Sixteen normal subjects, a patient with an atrial pacemaker and nine patients with atrial flutter were selected for ECG Holter monitoring.

Twelve of the normal subjects underwent a tilt-table test protocol and four underwent a stress test. The tilt-table test protocol, 70 min in duration, consisted in four 10-min periods in supine position separated by three 10-min periods in orthostatic positions at 90°, 70° and 45° successively (Hamidi et al. 1997). The treadmill stress test was performed according to the Bruce protocol (approx. 10 min) and was followed by 15–20 min recovery in supine position, 5 min sitting, 5 min standing, and 5 min lying again in supine position.

The patient with an atrial pacemaker was at rest during the recording. As part of pacemaker parameter adjustment protocol, the pacemaker was set up to deliver stimuli through an electrode located in the right atrium at the rate of 60 bpm for 8 min, 80 bpm for 4 min and 100 bpm for 8 min.

The patients in atrial flutter were recorded during an electrophysiological study. In four of them, catheter ablation was performed and sinus rhythm was restored. ECGs were recorded for several hours before, during and after the intervention.

In all subjects, three-lead ECGs were continuously recorded at 500 samples per sec. during the whole protocol using a Holter monitoring system (Burdick, Model 6632). Electrode configuration was designed to generate 3 pseudo-orthogonal leads X, Y and Z (X = V5 vs V6R; Y = S vs LL; Z = E vs V9), as in (Jacquemet et al. 2011). Sternal electrodes (E and S) come from the EASI lead system (Dower et al. 1988); LL is the left leg electrode; V6R and V9 are extended precordial electrodes.

2.2. Preprocessing and QT extraction

All ECG signals were band-pass filtered (0.01–100 Hz). In signals recorded during atrial flutter, the atrial contribution to the ECG was suppressed using a recently-developed dedicated method (Jacquemet et al. 2011). An ECG fiducial point detector (Dubé et al. 1988) was applied to the vector magnitude signal (root mean square of the 3 ECG leads) to identify the markers R, $\mathrm{Q_{on}}$ and $\mathrm{T_{off}}$. The marker R was defined as the location of the center of gravity of the QRS complex. The marker $\mathrm{Q_{on}}$ was defined as the position corresponding to 2% of the maximum of the R wave (and preceding the R peak). The marker $\mathrm{T_{off}}$ was defined as the intersection between the baseline and the tangent at the steepest negative slope of the lowpass-filtered T wave (15-Hz cutoff frequency) (Xue & Reddy 1998). These definitions are illustrated in Fig. 1. QT intervals were defined as $\mathrm{T_{off}}-\mathrm{Q_{on}}$ and RR intervals by the period between two successive R waves. The QT interval of the n-th beat will be denoted by QT_n and the RR interval *preceding* this beat by RR_n. Note that this convention may differ from the definition of RR_n in other papers.

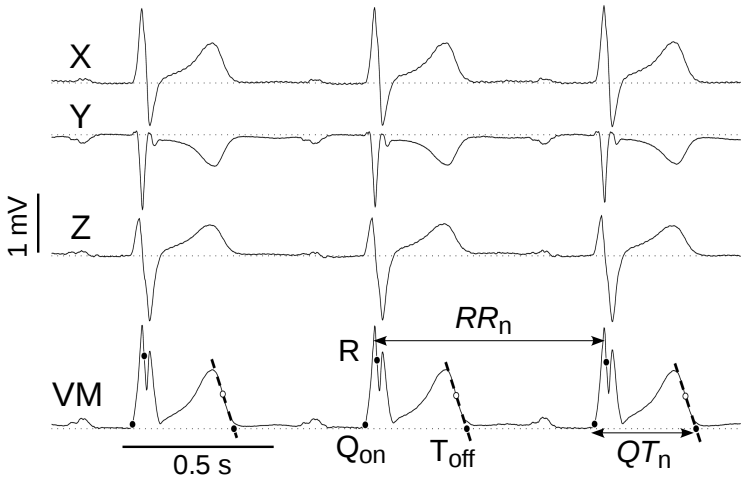

Figure 1. Example of ECG signals (lead X, Y, Z and vector magnitude VM) with identification of the markers R, Q_{on} and T_{off} (black circles) and steepest negative slope of the T wave (white circles). The definition of the intervals QT_n and RR_n is also indicated.

These extracted QT and RR time series were validated semi-automatically using a combination of ECG analysis software VCGMI (Dubé et al. 1988) and Burdick Vision Premier Holter (Cardiac Science, Bothell, WA, USA). In rare instances where R waves could not be reliably detected, RR intervals were interpolated based on local heart rate (median of a 19-beat window). Artifacts, signal saturation, premature ventricular contractions, ventricular arrhythmias and noisy or unreliably detected T waves were identified through a careful and comprehensive manual validation process. A list of beat indices associated with normal sinus beat and reliable QT intervals was created.

3. Data analysis

3.1. Principles of the QT correction method

The objective of the method is to compute an estimate of the QT interval corrected for variations in heart rate (QTc), as well as its confidence interval, based on the time series of QT and RR intervals. The hypotheses underlying this method are:

(i) The time series of QTc is a function of the QT interval and of an effective RR interval ($\overline{RR}$) computed as a weighted sum of past RR intervals (Pueyo et al. 2003, Pueyo et al. 2004, Luo et al. 2004):

$$QTc_n = F(QT_n, \overline{RR}_n)\,, \quad \text{where} \quad \overline{RR}_n = \sum_{k=0}^{\infty} w_k RR_{n-k}\ . \tag{1}$$

(ii) The QTc corresponds to the QT interval at 60 bpm or $RR = 1$ s (Bazett 1920):

$$F(QT, 1) = QT\ . \tag{2}$$

(iii) The QTc is statistically independent from $\overline{RR}$ (Pueyo et al. 2004):

$$\mathrm{cov}(QTc, \overline{RR}) = 0 \ , \tag{3}$$

where 'cov' is the covariance.

(iv) In a time interval where physiological conditions can be assumed to be stable, the parameters are optimized to minimize the variance of QTc.

In the parameter fitting procedure, all RR intervals will be used in order to preserve the time sequence throughout the calculation of the effective RR intervals ($\overline{RR}$). However, when computing statistical quantities involving QT intervals such as covariance, only the beats with reliably-identified QT intervals will be included.

3.2. Model of rate adaptation

An abrupt change in heart rhythm triggers a combination of slow and fast response as observed in the QT interval (Lau et al. 1988) as well as in the action potential duration (Franz et al. 1988). The slow response, with a time scale of 2–3 minutes, demonstrates rate adaptation of repolarization. The fast response, with a time scale of a few beats, includes transient oscillations in QT intervals (alternans) associated with restitution properties (Weiss et al. 2006). When heart rate accelerates and decelerates, the slow, delayed response results in a hysteresis (Halamek et al. 2010). In the model, the choice of the weights w_k in Eq. (1) will reflect the nature of these responses.

Pueyo et al. used linearly and exponentially decreasing weights w_k, as well as individualized weight profiles (Pueyo et al. 2004). A natural generalization of the exponential model is the Auto-Regressive model with eXternal output, ARX(n_z,n_p), with n_z zeros and n_p poles in the transfer function (Box et al. 2008). This model enables the use of a long memory (many k with $w_k \neq 0$) while requiring only a limited number of parameters ($n_z + n_p + 1$) and a simple recursion formula. Previous studies in subjects undergoing tilt-table test (Hamidi et al. 1997) and in patients under normal and paced rhythm (Halamek et al. 2007, Halamek et al. 2010) demonstrated using the Akaike criterion for linear system identification that the optimal model order was $n_z = n_p = 1$ (3 parameters) in order to reduce prediction error while avoiding overfitting.

Cabasson et al. proposed a model to reproduce the fast oscillations of QT intervals induced by irregular ventricular rhythms during stress or atrial fibrillation (Cabasson 2008, Cabasson & Meste 2009). These oscillations, however, are not expected to be relevant to the determination of QTc and will consequently be ignored to reduce the number of parameters to adjust. They may also be eliminated by low-pass filtering of the QT time series.

The effective RR interval will be written as a linear combination of an instantaneous and a slow response:

$$\overline{RR}_n = \ f\, \overline{RR}_n^{\mathrm{instant}} + (1-f)\, \overline{RR}_n^{\mathrm{slow}} \tag{4}$$

where $0 \leq f \leq 1$. The instantaneous response term is simply the current RR interval

$$\overline{RR}_n^{\mathrm{instant}} = \ RR_n \ , \tag{5}$$

and the slow response is obtained through an autoregressive low-pass filter

$$\overline{RR}_n^{\text{slow}} = c\,RR_n + (1-c)\,\overline{RR}_{n-1}^{\text{slow}} \tag{6}$$

with $0 < c \leq 1$. The z-transform of the previous equations (Oppenheim & Schafer 2009) gives the transfer function $H(z)$ such that $\overline{RR}(z) = H(z)RR(z)$:

$$H(z) = \frac{f + (1-f)c - f(1-c)z^{-1}}{1-(1-c)z^{-1}} \ . \tag{7}$$

The model is therefore an ARX(1,1) model similar to that from (Halamek et al. 2010), stable when $0 < c < 2$, and with a gain of $H(1) = 1$. Its step response (abrupt change in heart rate) is

$$\overline{RR}_n = f + (1-f)(1-(1-c)^{n+1}) \qquad \text{for } n \geq 0 \ . \tag{8}$$

The resulting graph is a vertically-shifted exponential; 90% of the change needed to reach steady-state (Pueyo et al. 2003) is obtained after τ beats, where (provided that $f + (1-f)c < 0.9$):

$$\tau = \frac{\log 0.1 - \log(1-f)}{\log(1-c)} - 1 \ . \tag{9}$$

Two parameters related to memory effects (f, c) have to be identified: f describes the short-term memory (instantaneous response), while c is associated with long-term memory (slow response). The optimization procedure is described in Subsect. 3.4.

3.3. Static QT–RR relationship

The QT interval is assumed to be directly related to the effective RR interval through the following equation:

$$QT_n = \beta + \alpha\, g_\gamma(\overline{RR}_n) + \epsilon_n \tag{10}$$

where $g_\gamma(RR)$ is a possibly nonlinear function depending on a parameter γ (allowing to adjust the curvature of the QT–RR curve), α and β are parameters, ϵ_n represents local modeling error, noise and QT fluctuations uncorrelated with RR variations. The function g_γ is assumed to be one of the functions listed in Table 1. This list covers all the functions used in (Malik et al. 2002) and (Pueyo et al. 2004). In addition, we have added the scaling parameter γ to reproduce non-linearity with more flexibility. The parameter range for γ facilitates the optimization and avoids degeneracy, e.g. $g_\gamma(x) \approx \gamma x$ when $\gamma \to 0$.

The corrected QT is the QT interval at $\overline{RR} = 1$ including rate-unrelated fluctuations:

$$QTc_n = \beta + \alpha\, g_\gamma(1) + \epsilon_n = F(QT_n, \overline{RR}_n) \ , \tag{11}$$

where

$$F(QT, \overline{RR}) = QT + \alpha\Big(g_\gamma(1) - g_\gamma(\overline{RR})\Big) \ . \tag{12}$$

Table 1. The 3-parameter function $\beta + \alpha\, g_\gamma(RR)$ is fitted to the QT–RR data, where $g_\gamma(RR)$ is one of the following functions. The range is the one used for parameter optimization. RR in seconds; the unit of γ is specific to each function (s, s^{-1} or nondimensional).

Name	Function	Parameter range
lin	$g_\gamma(RR) = RR$	–
pow	$g_\gamma(RR) = RR^\gamma$	$\gamma \in [-10, 10]$
exp	$g_\gamma(RR) = \exp(-\gamma RR)$	$\gamma \in [0.001, 10]$
log	$g_\gamma(RR) = \log\lvert\gamma + RR\rvert$	$\gamma \in [-0.3, 5]$
atan	$g_\gamma(RR) = \arctan(\gamma RR)$	$\gamma \in [0.001, 10]$
tanh	$g_\gamma(RR) = \tanh(\gamma RR)$	$\gamma \in [0.001, 10]$
asinh	$g_\gamma(RR) = \operatorname{arcsinh}(\gamma RR)$	$\gamma \in [0.001, 10]$
acosh	$g_\gamma(RR) = \operatorname{arccosh}(1 + \gamma RR)$	$\gamma \in [0.001, 10]$

The condition $\mathrm{cov}(QTc, \overline{RR}) = 0$, which implies that the Pearson correlation coefficient between QTc and $\overline{RR}$ is zero, enables the determination of α. Malik et al. showed that the correlation coefficient is a sigmoid-shaped decreasing function of α (Malik et al. 2002). Pueyo et al. used a golden cut search to optimize the correlation coefficient (Pueyo et al. 2004). Our formulation gives a simple analytical formula for the optimal value of α, denoted by $\hat{\alpha}$:

$$\hat{\alpha}(c, f, g_\gamma) = \frac{\mathrm{cov}(QT, \overline{RR})}{\mathrm{cov}(g_\gamma(\overline{RR}), \overline{RR})} \ . \tag{13}$$

If $g_\gamma(\overline{RR}) = \overline{RR}$, this is equivalent to linear regression. The parameter β is then obtained by imposing that the average QTc is equal to the static QT–RR relationship at $\overline{RR} = 1$ s, i.e. $\hat{\beta} + \hat{\alpha} g_\gamma(1) = \mathrm{mean}(QTc)$, where $\hat{\beta}$ is the optimal value of β, leading to:

$$\hat{\beta}(c, f, g_\gamma) = \mathrm{mean}(QT - \hat{\alpha}\, g_\gamma(\overline{RR})) \ , \tag{14}$$

which implies that $\mathrm{mean}(\epsilon_n) = 0$. Note that the parameter β will not be explicitly needed as part of the determination of the QTc. Confidence intervals on $\hat{\alpha}$ and $\hat{\beta}$ are computed using standard linear regression formulas (Draper & Smith 1998). The parameter γ remains to be identified for each choice of the function g_γ (see next Subsect.).

3.4. Parameter identification

Given the time series RR_n and QT_n, the goal is to identify the parameters c, f, γ and the function g_γ. According to our principle (iv), the error function E to be minimized is the standard deviation (std) of QTc:

$$E(c, f, g_\gamma) = \mathrm{std}\Big(QT - \hat{\alpha}\, g_\gamma(\overline{RR})\Big) \ , \tag{15}$$

where $\hat{\alpha} = \hat{\alpha}(c, f, g_\gamma)$ is computed from (13) and $\overline{RR}$ from the time series RR using the recursion formulas (4)–(6) and the parameters c and f.

Let us first consider that the function g_γ is known. The 2-D nonlinear minimization problem of determining the optimal values $\hat{c} = \hat{c}(g_\gamma)$ and $\hat{f} = \hat{f}(g_\gamma)$ can be solved numerically using the Nelder-Mead optimization method (fminsearch) implemented in Matlab. An example of function $E(c, f)$ is displayed in Fig. 2. Confidence region for optimal parameters $\hat{c}$ and $\hat{f}$ may be estimated (Seber & Wild 2003) as the region where c and f are such that (95% confidence region)

$$E^2(c, f) \leq E^2(\hat{c}, \hat{f}) \left(1 + \frac{p}{n-p} F^*_{p,n-p}\right) \tag{16}$$

where n is the number of samples, $p = 2$ is the number of parameters and $F^*_{\nu_1,\nu_2}$ is the inverse of the cumulative distribution function of the F distribution with ν_1 and ν_2 degrees of freedom evaluated at 0.95. The confidence interval for $\hat{c}$ and $\hat{f}$ is then computed by approximating E^2 by a quadratic function around the minimum (the second derivatives are estimated numerically using a 3-point centered finite difference formula with a step of 10^{-4}).

The optimal choice of the function g_γ remains to be identified. For that purpose, the whole procedure described in the previous paragraphs is performed for each type of function g_γ listed in Table 1 and the parameter γ is optimized to reduce $E(g_\gamma) = E(\hat{c}, \hat{f}, g_\gamma)$ where $\hat{c}$ and $\hat{f}$ are functions of g_γ computed using the nonlinear optimization described above. Since degeneracy may occur (e.g. when $g_\gamma(x) \approx \gamma x$ for small values of γx), single-variable bounded nonlinear function minimization was used (fminbnd in

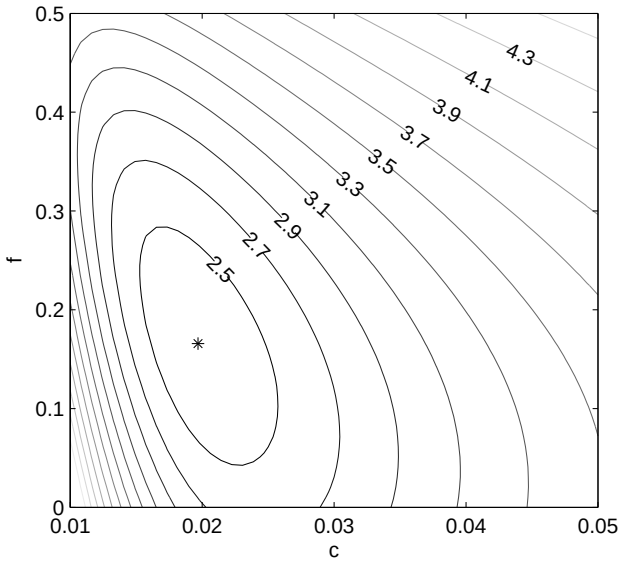

Figure 2. Contour plot of the error function $E(c, f)$ for a linear QT-RR static relationship $g_\gamma(RR) = RR$ in a normal subject during a tilt table test. The star denotes the minimum. E in ms; f and c are nondimensional.

Matlab; bounds are given in Table 1). When the optimum $\hat{\gamma}$ is found at the boundary of the relevant interval for γ, it usually means that the parameters cannot be determined accurately so that this type of function is not appropriate to fit the data (a linear function may be sufficient for instance).

In summary, the optimization procedure is composed of four nested blocks processed step-wise:

$$\min_{g_\gamma,\gamma,c,f,\alpha} E^2 = \min_{g_\gamma} \min_{\gamma} \min_{c,f} \min_{\alpha} E^2 \ , \tag{17}$$

where the last minimum is found analytically, the third numerically by the simplex method, the second by constrained 1-D minimization and the first by exhaustive search.

3.5. Data-dependent weighted regression

Information about the dynamics of QT/RR coupling is found in periods where changes in heart rate occur. When long periods of stable rate are present in the signal (e.g. patient with a pacemaker, in atrial flutter or at rest in supine position), these data points may have too much weight in the parameter optimization procedure. To cope with that limitation, weighted regression can be used (Draper & Smith 1998, Seber & Wild 2003).

If $p(\overline{RR})$ is the distribution of effective RR intervals, the weight of sample n in the time series was set to the inverse of the probability distribution $p(\overline{RR}_n)^{-1}$. The distribution was estimated using a histogram and $p(\overline{RR}_n)$ was computed by interpolation. Histogram bin size was set to $3.49\,\mathrm{std}(\overline{RR})N^{-1/3}$ where N is the number of data points. This choice has been proved to provide the most efficient, unbiased estimation of a probability density function (Scott 1979, Izenman 1991). In formulas (13), (14) and (15), mean, cov and std were replaced by their weighted counterparts. Practically, the evaluation of the modeling error $E(c, f, g_\gamma)$ using weighted regression is performed in three steps: first, $\overline{RR}$ is computed from c, f and the raw data RR_n (Eq. (4)–(6)); second, the weights of all beats are computed by linear interpolation of the inverse $p(\overline{RR}_n)^{-1}$ of the histogram of $\overline{RR}$; third, $\hat{\alpha}$ and then E are determined using weighted covariance.

4. Results

4.1. Validation in a patient with an atrial pacemaker

To validate the estimation of the memory parameters c and f, the algorithm was tested in a simple case in which heart rate can be controlled. QT and RR intervals were measured in a patient with an atrial pacemaker, as proposed by (Halamek et al. 2007). The pacemaker was set up to deliver stimuli at a fixed rate of 60, 80 and 100 bpm, each during a period of 4 to 10 minutes.

QT and RR time series and model predictions (using weighted regression) are displayed in Fig. 3. Optimal parameters describing memory were computed using the

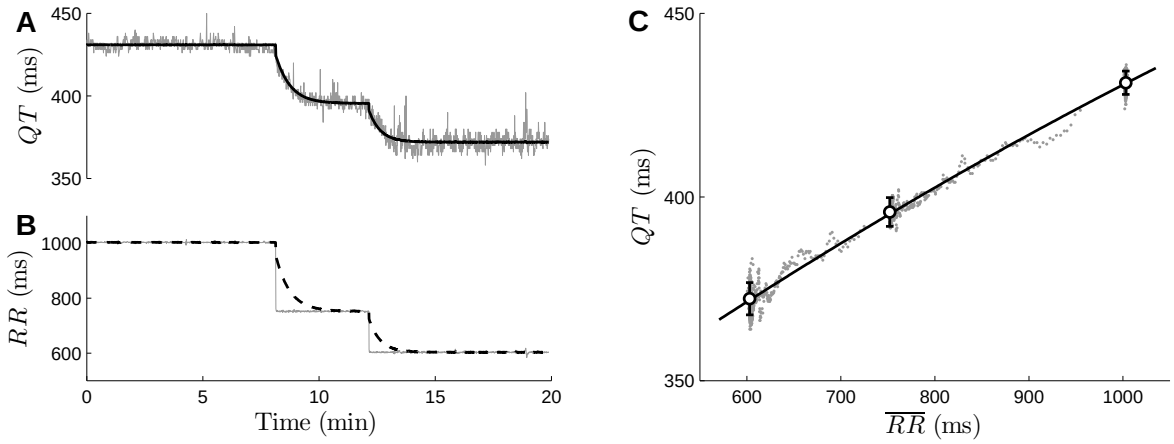

Figure 3. QT–RR relationship in a patient with an atrial pacemaker delivering stimuli at fixed rates (successively 60, 80 and 100 bpm). (A) Measured (gray line) and predicted (thick black line) QT intervals as a function of time. (B) Measured (gray line) and effective (dashed black line) RR intervals. (C) QT interval as a function of effective RR interval: measurements (gray dots; QT filtered with a 5-sample moving average) and model (thick black line). The dots with error bars corresponds to the steady state QT at each of the fixed rate (mean±standard deviation).

parameter identification procedure described in Sect. 3.4, leading to: $\hat{c} = 0.021 \pm 0.004$ (95% confidence interval), $\hat{f} = 0.183 \pm 0.006$; as a result $\tau = 100 \pm 20$ beats. Fluctuations at steady state (standard deviation of QT) were about 4 ms, corresponding to the accuracy of QT intervals or twice the sampling interval (2 ms). The QT–RR relationship was best fitted by the atan model with $\hat{\gamma} = 0.65$ s^{-1}. The atan model was only 1% better than the linear model in terms of QTc standard deviation. Extracted QTc was 430.4 ± 4.0 ms. When uniform weights were used for regression, the memory effect was less accurately reproduced because of the too small weight given to the transition periods, resulting in an overestimation of τ (184 ± 8 beats) although the predicted QTc and its standard deviation were similar.

4.2. Inter-subject variability in the QT–RR relation

Malik et al. demonstrated the high inter-subject variability in the QT–RR relation (Malik et al. 2002). The ability of our subject-specific method to reproduce this variability was analyzed in subjects undergoing tilt-table test. The resulting QT–RR relationship and predicted QTc in 12 subjects are shown in Fig. 4. Model parameters are listed in Table 2. The 'pow' and 'tanh' were selected in all cases, but the difference with the second best function was $< 1\%$, except in subject D (concave up QT–RR relation). In these tilt-test subjects, the parameter $\hat{f}$ was 0.19 ± 0.04. In the linear model from (Halamek et al. 2010), $\hat{f}$ was denoted by $\mathrm{Gain_F}/\mathrm{Gain_L}$ and was found to be 0.18 ± 0.12 in healthy subjects and 0.21 ± 0.16 in hypertensive patients. The memory parameter τ was 91 ± 20 beats. These values obtained during tilt test were smaller

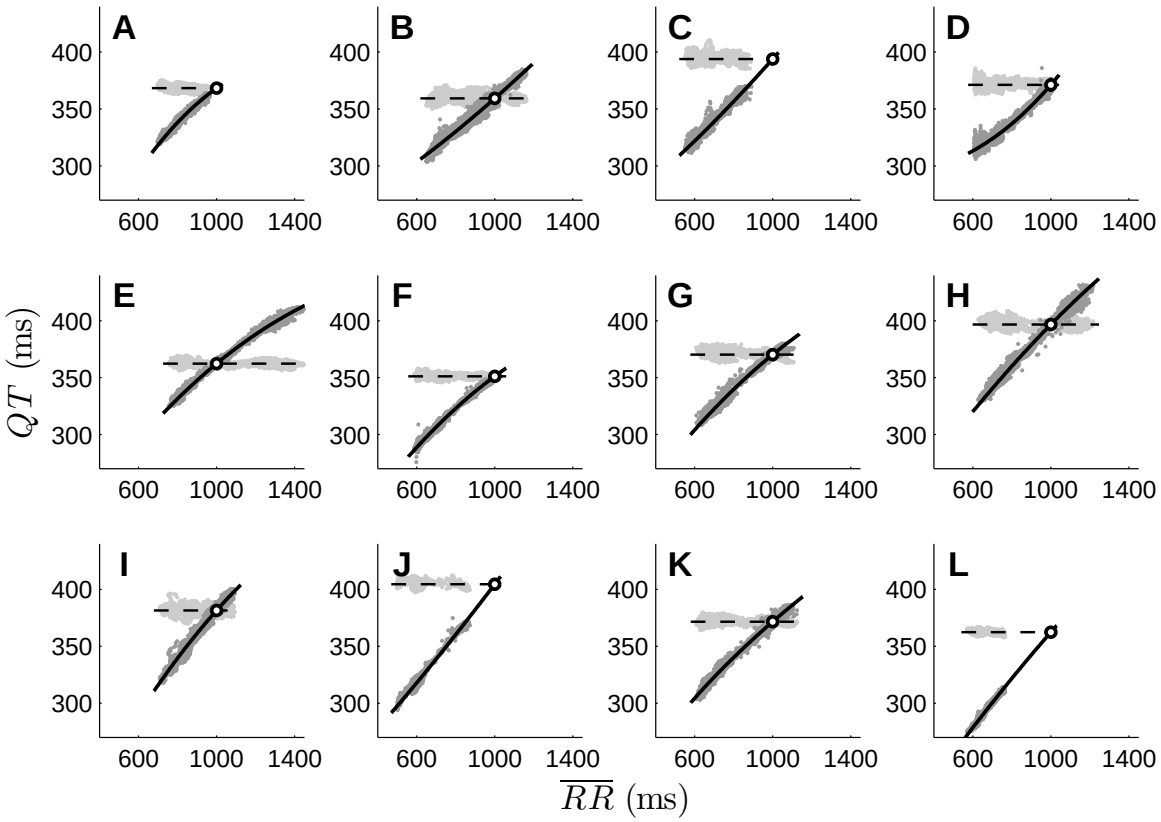

Figure 4. QT–$\overline{RR}$ relationships in 12 subjects (A)–(L) undergoing tilt-table test. In each graph, QT intervals are shown as dark gray dots and QTc as light gray dots (both filtered with a 5-sample moving average); the thick black line is the model QT–RR static relationship and the thick dashed line is the mean QTc, also displayed as a circle.

than those reported by (Halamek et al. 2010) during sinus rhythm: 166±43 (healthy) and 136±45 (hypertensive). The slope of the QT-$\overline{RR}$ relation at $\overline{RR} = 1$ averaged over the subjects was 0.167 ± 0.033 (range: 0.124 to 0.225), which is close to the fixed value 0.154 used in the Framingham's method (Sagie et al. 1992). Bazett's correction formula (Bazett 1920) would give a slope of 0.187±0.008 and Fridericia's formula 0.125±0.006 (Fridericia 1920). The standard deviation of the QTc time series [Eq. (15)] ranged from 1.8 to 4.8 ms. These values were of the order of the natural QT fluctuations observed at fixed heart rate in the patient with pacemaker (see previous Subsect.). This suggests that the modeling error was small in tilt-test cases. Moreover, the modeling error tended to be larger right after a change in tilt-table angle, when the activity of the autonomic nervous system is expected to vary the most. The reduction in QTc standard deviation in a nonlinear static QT–RR model as compared to a linear model ranged from 1% to 9%, except in the case of Fig. 4E where the difference was 27%.

Table 2. Optimal parameters for subjects undergoing tilt-table test. Subject label corresponds to the panels of Fig. 4. The function name relates to Table 1. The slope is that of the static QT–RR relationship at $RR = 1000$ ms, that is, $\hat{\alpha} g'_{\hat{\gamma}}(1)$.

Subject	function	QTc (ms)	τ (beats)	$\hat{f}$ (-)	slope (-)
A	tanh	368.4 ± 2.4	82.0 ± 2.1	0.20 ± 0.01	0.124
B	pow	359.3 ± 3.8	75.9 ± 2.0	0.19 ± 0.01	0.151
C	pow	393.9 ± 3.6	113.6 ± 2.8	0.14 ± 0.01	0.192
D	pow	371.3 ± 4.8	87.4 ± 2.6	0.11 ± 0.02	0.199
E	tanh	362.3 ± 2.3	92.6 ± 1.0	0.20 ± 0.01	0.141
F	tanh	351.2 ± 2.3	104.5 ± 1.6	0.17 ± 0.01	0.126
G	tanh	370.2 ± 3.2	80.9 ± 1.7	0.19 ± 0.01	0.140
H	tanh	396.7 ± 3.4	102.0 ± 1.3	0.16 ± 0.01	0.175
I	tanh	381.4 ± 3.8	42.9 ± 1.4	0.20 ± 0.02	0.192
J	pow	404.5 ± 4.0	83.6 ± 3.1	0.23 ± 0.02	0.225
K	pow	371.6 ± 2.8	117.1 ± 1.5	0.20 ± 0.01	0.148
L	tanh	362.3 ± 1.8	109.6 ± 2.0	0.29 ± 0.01	0.196

4.3. Nonlinearity in the QT–RR relation

When a wide range of RR intervals is observed in the ECG, the QT–RR relation usually exhibits strong nonlinearity. Stress and orthostatic heart rate test were performed in 4 normal subjects to extend the range of RR intervals present in the signals. Figure 5 displays the QT-RR relation in these subjects. These relations showed significant nonlinear behavior. As compared to a linear model, the improvement in terms of modeling error [Eq. (15)] was 50% in case A, 19% in case B, 3% in case C and 17% in case D. The minimal modeling error (E) was respectively 6.5 ms, 5.6 ms, 7.7 ms and 5.1 ms.

Figure 6 shows an example of $\overline{RR}$, QT and QTc time series during stress/orthostatic test. Despite large variations in RR and QT, the QTc remains within a small interval. During stress test, QTc appears to fluctuate randomly, irrespective of the RR intervals. During recovery and orthostatic test, the average QTc seems to shift. This may indicate changes in physiological conditions affecting the QT interval not only through the RR interval, but also directly. In particular, there are evidences that the autonomic nervous system may be involved (Fossa 2008). Variations in QTc might indicate such changes.

4.4. QT–RR relation revealed by the effective RR intervals

The static QT–RR relation can sometimes be estimated without taking into account memory effects (parameters c and f), notably when there is no marked hysteresis, as suggested by the results in (Pueyo et al. 2004) for sinus rhythm. The use of the effective

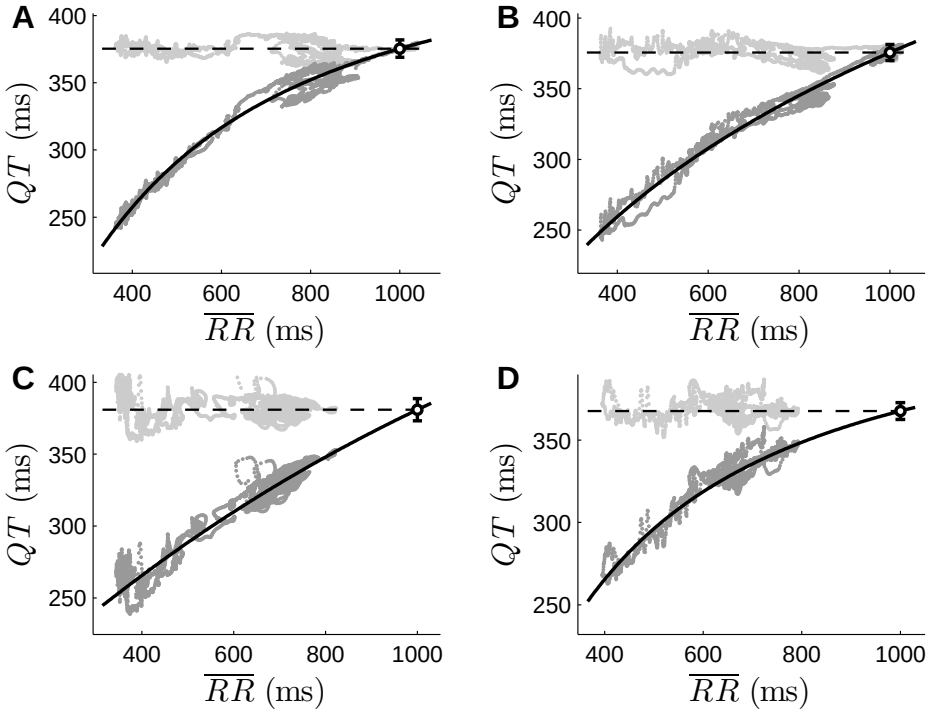

Figure 5. QT–RR relationships in 4 subjects undergoing stress test and orthostatic test. In each graph, QT intervals are shown as dark gray dots and QTc as light gray dots (both filtered with a 5-sample moving average); the thick black line is the model QT–RR static relationship and the thick dashed line is the mean QTc, also displayed as a circle.

RR interval becomes necessary, however, when sudden changes in heart rhythm are frequent. A particularly illustrative example is the case of patients in atrial flutter with varying atrioventricular block ratio.

Figure 7 shows the difference between QT–RR and QT–$\overline{RR}$ relationships in patients with atrial flutter. Note that flutter waves were removed before QT detection. The RR intervals are clustered in point clouds representing different atrial-to-ventricular rate ratios, from 2:1 to 6:1. In panel A, 63.1% of the beats ($N = 67,461$) are in 4:1 ratio, 35.8% in 2:1, 0.5% and 0.6% in 3:1 and 5:1. In panel C, 66.7% of the beats ($N = 14,714$) are in 4:1 ratio, 15.7% in 2:1, 10.6% in 3:1, 5.6% in 5:1 and 1.4% in 6:1. After application of the subject-optimized low pass filter (Eq. (7)) to construct the $\overline{RR}$ time series, the QT–RR relationship is linearized, as illustrated in Figs. 7B and D. As a result, the histograms of $\overline{RR}$ intervals are qualitatively more uniform (QT histogram is unchanged). Since the 4:1 ratio still carries more weight than other ratios in the transformed data, weighted regression reduced modeling error.

The standard deviation of the QTc time series represents the modeling error (Eq. 15) as well as the uncertainty on the determination of the QTc. In the 9 patients in atrial flutter, this modeling error (E) was 7.0±2.1 ms (range: 3.6 to 10.6 ms). The reduction in modeling error obtained by using a nonlinear QT-RR static relationship

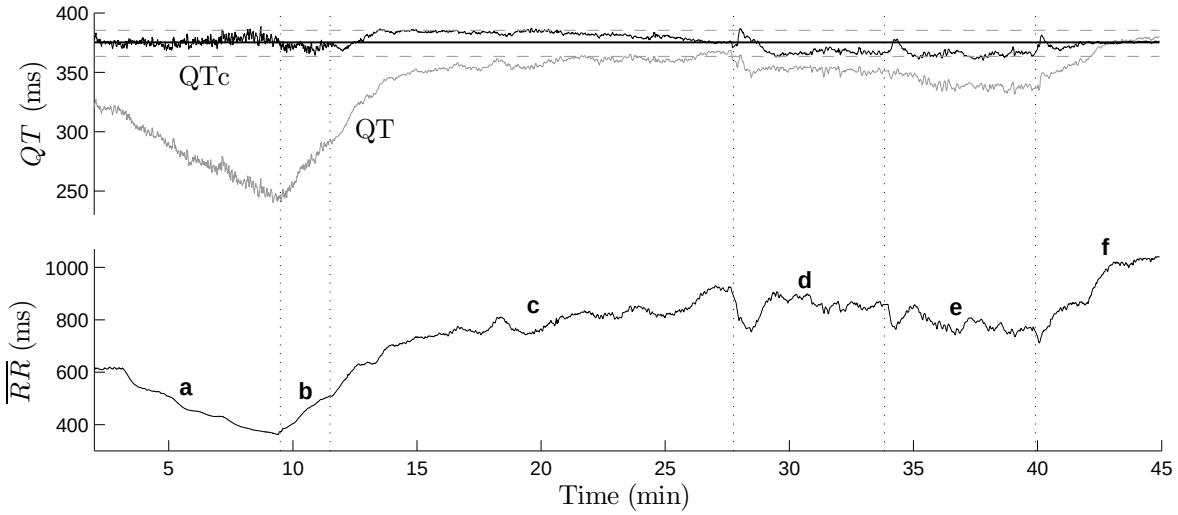

Figure 6. RR and QT evolution during stress test and orthostatic test for the subject A of Fig. 5. *Bottom panel*: effective RR interval as a function of time (parameters of the transfer function: $c = 0.027$, $f = 0.069$, $\tau = 82$ beats). *Top panel*: QT (gray curve) and QTc (black curve) as a function of time. The mean QTc is shown as a thick black line and the 95% confidence interval of QTc (2.5% and 97.5% percentiles) as dashed lines. The different steps of the protocol are: (a) running, (b) walking, (c) recovery lying in a bed, (d) sitting, (e) standing, (f) lying in a bed.

was moderate ($< 10\%$), except in two cases (15% and 37% improvement). Among these 9 patients, 4 patients underwent catheter ablation. In these cases, the QTc computed during atrial flutter was compared to the QTc computed during sinus rhythm post-ablation. Parameter optimization was performed separately in flutter and sinus rhythm. Results are reported in Table 3. QTc values before and after catheter ablation were found to be similar. Larger differences in QTc were observed when the average RR interval was further from 1000 ms (patients 1 and 2), that is, when the QTc is an extrapolation rather than an interpolation. Note, however, that changes in physiological conditions due to the procedure or to the autonomic nervous system may temporarily affect ventricular repolarization and the QTc independently from changes in heart rate.

4.5. Comparison with other methods

Different QT correction methods were compared:

(i) Bazett's formula: $QTc_n = QT_n \cdot \widetilde{RR}_n^{-1/2}$ (Bazett 1920). To mimick the beat selection process done manually by clinicians typically over a short window, the effective RR interval $\widetilde{RR}$ (in sec.) is defined as a moving average of RR intervals over 10 beats.

(ii) Fridericia's formula: $QTc_n = QT_n \cdot \widetilde{RR}_n^{-1/3}$ with the same effective RR interval as for the Bazett's formula (Fridericia 1920).

(iii) Hodges' formula: $QTc_n = QT_n + 105\,(\widetilde{RR}_n^{-1} - 1)$ with QT in ms and $\widetilde{RR}$ in sec. This formula is linear with respect to heart rate (Hodges et al. 1983).

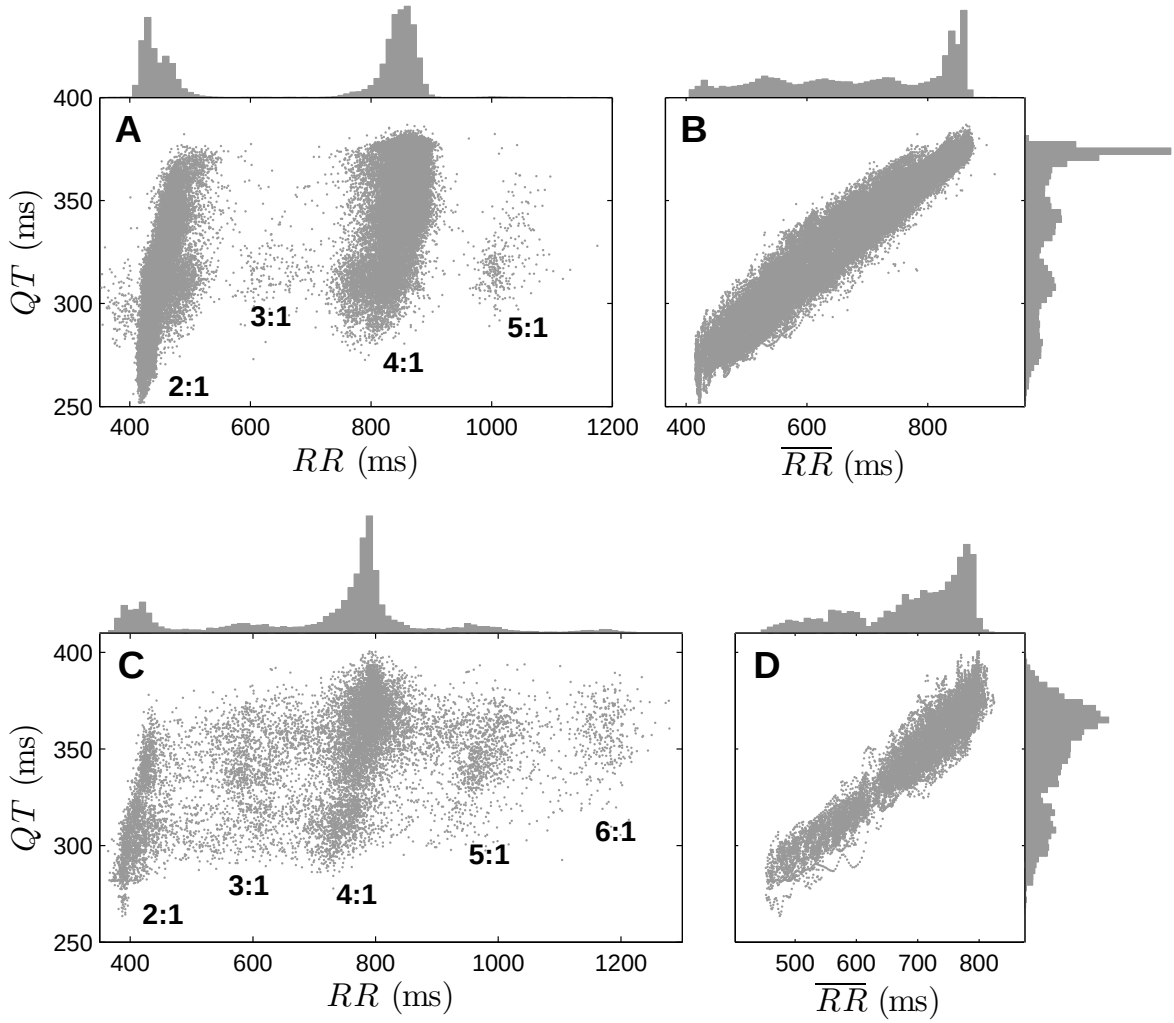

Figure 7. QT–RR relationships in patients during atrial flutter. (A) and (C) QT as a function of the original RR. Each point represents a beat. The ratio of atrioventricular block is indicated near each point cloud. Histogram of RR intervals is shown on the top of the graph to illustrate point density. (B) and (D) QT as a function of the effective RR. Histogram of QT intervals is shown at the right of the graph.

(iv) Sagie's formula: $QTc_n = QT_n + 154(1 - \widetilde{RR}_n)$ with QT in ms and $\widetilde{RR}$ in sec. (Sagie et al. 1992).

(v) Method adapted from Karjalainen et al.: $QTc_n = QT_n + \alpha\,(1 - \widetilde{RR}_n)$ where α is adapted to each subject to minimize prediction error (Karjalainen et al. 1994).

(vi) Method based on Halamek et al.: the ARX(1,1) transfer function is used in combination with a linear QT–RR relation (Halamek et al. 2010). No weighted regression is used.

(vii) Method based on Pueyo et al.: the ARX(1,1) transfer function is used in combination with different nonlinear formulas as QT–RR relation, but the parameter γ is not optimized (Pueyo et al. 2004). No weighted regression is used.

Table 3. Corrected QT interval (QTc) measured using the patient-specific approach in patients undergoing catheter ablation. QTc and effective RR intervals (mean ± standard deviation) are reported before ablation during atrial flutter and after ablation in sinus rhythm.

	Atrial flutter		Sinus rhythm	
Patient	QTc (ms)	$\overline{RR}$ (ms)	QTc (ms)	$\overline{RR}$ (ms)
1	408.8 ± 7.5	635.6 ± 64.4	420.5 ± 6.2	686.5 ± 70.0
2	349.8 ± 11.	732.7 ± 192.	358.1 ± 5.7	886.3 ± 87.0
3	401.7 ± 7.5	694.6 ± 141.	400.8 ± 2.8	1011.3 ± 76.2
4	395.8 ± 4.9	875.9 ± 48.9	395.3 ± 3.5	998.6 ± 31.9

(viii) Our method without weighted regression.

(ix) Our method with weighted regression.

These methods were assessed in terms of modeling error $E = \mathrm{std}(QTc)$. All cases were included for statistical analysis ($n = 29$: 12 tilt tests, 4 stress tests, 9 in atrial flutter, 4 in sinus rhythm after ablation). Performance statistics are presented in Fig. 8. The Bazett method yielded the largest QTc variability, in agreement with previous studies in sinus rhythm (Luo et al. 2004, Chiladakis et al. 2010). Hodges' formula performed similarly to Fridericia's and Sagie's formulas with subjects in sinus rhythm and tilt test, but resulted in higher modeling errors during stress test and atrial flutter. When subject-specific slope was used (Karjalainen), significant improvement was obtained as compared to Sagie's fixed-slope linear formula. The elimination (or at least reduction) of QT–RR hysteresis achieved by the transfer function of the Halamek approach translated

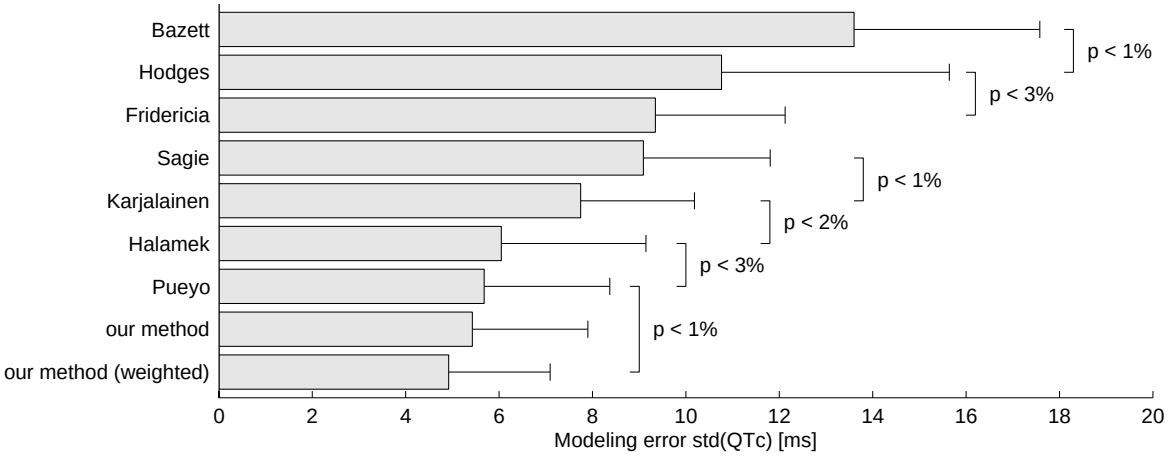

Figure 8. Modeling error E, which is equal to std(QTc), for different QT–RR modeling methods (see text for details). The bar represents the mean and the error bar the standard deviation. Methods are compared using paired t-test ($n = 29$).

into a decrease in modeling error. The nonlinear QT–RR relations introduced by (Malik et al. 2002) and implemented in (Pueyo et al. 2004) helped in cases where a broader range of RR intervals were available. Our method provides even more flexibility and lower modeling error with the additional parameter γ and a variational formulation that facilitates the incorporation of weighted regression (especially useful during atrial flutter or when different regimes of heart rate variability coexist in the recording). An average modeling error of 4.9 ms was achieved, despite the sampling interval of 2 ms that limits the accuracy of QT calculations during Holter recording.

5. Discussion and conclusion

We have developed a subject-specific nonlinear QT correction formula for the analysis of Holter ECG data. The proposed method outperformed the ones currently used in the clinic in terms of robustness (standard deviation of QTc) and ability to handle different forms of heart rate variations (stress test, orthostatic positions, atrial arrhythmia). The optimization framework for parameter identification is sufficiently flexible to facilitate future generalizations or adjustments. The duration of ECG recording remains however a major constraint for selecting the QT correction formula. When only 10-s ECGs are available (as is often the case), a standard rate-correction formula such as Sagie's is the only applicable approach. With a few minutes of ECG recording, a subject-specific QT-RR relationship can be determined. Longer signals (at least 10 min Holter recording) are necessary to identify subject-specific memory effect. If only a 5-min ECG is available, it is still possible to use a transfer function with predefined values for the coefficients c and f (fixed memory of 2 min for example). The present method, although designed for pseudo-orthogonal 3-lead Holter ECGs, could be applied to any lead system provided that reliable QT and RR time series can be extracted. However, depending on T wave morphology (e.g. biphasic shape), a slightly different definition of T_{off} may have to be used. Because of spatial dispersion in measured QT intervals, electrode position may also influence computed QTc values.

Another issue is natural or induced variations in heart rate. Variations in RR intervals within a sufficiently wide range are needed to correctly estimate QT-RR relationships. Weighted regression proved to be useful to adjust for skewed or unbalanced RR distributions. Ideally, the measured RR intervals should cover the range between the normal heart rate of the subject and 60 bpm to guarantee the validity of the extracted QTc. Exercise or changes in position may be needed to extend the range of RR intervals provided the patient is able to do so. During atrial flutter, heart rate variability is largely affected by antiarrhythmic drugs used for rate control. In case of a constant atrio-ventricular block ratio (e.g. 2:1 or 3:1 block), no subject-specific correction can be applied since RR is constant. In contrast, when transitions occur (e.g. intermittent 2:1 and 4:1 blocks), the transfer function that linearizes the QT-RR relationship can be estimated and the QTc can be more reliably estimated.

Observed temporal variations in QTc can originate from different sources. First,

QT measurement is affected by uncertainty/error due to noise or simply to the 2-ms sampling interval. This effect is estimated to contribute from 2 to 4 ms in QTc standard deviation based on the pacemaker patient (fixed rate) and tilt-test data (very low modeling error). Second, our QT-RR model cannot predict exactly all rate-related QT variations. Memory (and thus the transfer function) could be rate-dependent for instance. Third, non-stationarity can be present in the signal, in particular related to the influence of the autonomic nervous system or to circadian rhythm. Note, however, that our method might be used to detect these changes by analyzing the fluctuations of QTc, as suggested by Fig. 6. Finally, the fraction of QT intervals manually rejected as part of the validation process might affect the determination of the QTc. This issue may be relevant for the comparison of ECGs with different signal-to-noise ratios.

In summary, this study advocates the use of subject-specific rate correction for a more accurate clinical interpretation of QT intervals. Nonlinearity becomes important when a wide range of RR interval is observed. In the presence of abrupt variations in ventricular rate (for instance due to a change in orthostatic position or induced by an atrial arrhythmia), cardiac memory is a critical factor accounted for through the effective RR interval. Longer ECG recordings (>10 min) and a sufficiently broad range in measured RR intervals are needed to obtain a significantly more accurate and robust value of QTc as compared to standard rate correction formulas.

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