Time for QT Adaptation to RR Changes and Relation to Arrhythmic Mortality Reduction in Amiodarone-treated Patients

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Abstract

A new method is proposed to evaluate, in continuous 24-hour recordings, the influence on QT of changes in heart rate occurred during some previous minutes. The method is based on considering averages of the RR intervals preceding the ith beat ($\overline{RR}_i$) using window lengths of up to 10 minutes. The averages are performed using several forgetting strategies, with the exponential weighted average turning out to be the best in modeling the QT dependence on previous RR intervals. For each patient, the regression model (selected from a defined set) and the window length leading to the optimum fit of the [QT_i,$\overline{RR}_i$] relationship are selected. RR variations in the past 4 minutes, on average, are shown to be required to accurately model the QT response to changes in frequency. A measure of the optimum fit residuum (ORR) is then calculated, showing a remarkable discriminative power to identify post-myocardial infarction patients at high risk of arrhythmic death after treatment with amiodarone.

1. Introduction

The QT interval, expressing the duration of ventricular repolarisation, is largely influenced by changes in heart rate as well as many other factors, such as sympathetic and parasympathetic activity and electrolyte disorders [1]. The QT response to changes in cardiac cycle is not immediate, having a known time lag in the adaptation. There are immediate and delayed changes of action potential duration secondary to cycle length variations [3, 4]. This effect of "cardiac memory" has been investigated in studies of QT adaptation to abrupt changes in pacing rate [5]. A time lag of 2-3 minutes was found to correspond to 90% of the resulting QT change. However, with automatic QT interval analysis from continuous 24-hour Holter recordings, this "lag hysteresis" is usually ignored and only the preceding RR interval is taken for analysis while some Holter systems assume that the lag is constant for all subjects and patients.

To investigate the lag of the hysteresis in the [QT,RR] relationship more comprehensively, this study considered the effect of different window lengths (L) preceding each ith beat to be taken into consideration when measuring the goodness of fit of different formulae expressing the [QT,RR] relationship.

After compensating for the effect of QT lag by obtaining an averaged RR measurement for each ith beat ($\overline{RR}_i$), and using it in the [QT_i,$\overline{RR}_i$] fit, we obtained a parameter measuring the impairment in the [QT_i,$\overline{RR}_i$] relationship. Some studies suggested that abnormalities in the adaptation of ventricular repolarisation to heart rate changes play a role in the genesis of arrhythmia [6]. Therefore, we analysed how the heart rate dynamics of the QT interval is modified by amiodarone in post-myocardial infarction (MI) patients and how does it differ between survivors and victims of arrhythmic death among post-MI patients.

2. Methods

The study evaluated 24-hour 3-lead Holter ECG recordings obtained from 939 patients of the EMIAT database [7]. All these recordings were obtained one month after randomisation in a double-blind placebo-controlled trial to assess the effects of amiodarone in survivors of MI, aged$\leq$75 years, with a left-ventricular ejection fraction (LVEF) $\leq$40%. Meaningful data were available in 866 patients who were followed-up during a mean time of 620 days ($\pm$176). Of these patients, 404 were in the placebo group (26 had arrhythmic death during follow-up) and 462 in the amiodarone group (18 arrhythmic deaths).

In each subject, QT and RR intervals were automatically measured in each lead using a commercial software package.

2.1. Data analysis

For each patient and each lead, only beats with accepted QT_i and RR_i interval measurements were considered. The lead with more accepted measurements was independently selected for each patient. One of the aims of the work was to determine, for each patient, the optimum RR averaging window length, L_{opt}, according to the criterion

later described in section (2.1.3). For that purpose, three averaging methods were considered and 10 regression models were fitted to the $[QT_i,\overline{RR}_i]$ data, with $\overline{RR}_i$ representing in each case the moving-window average of preceding RR intervals.

2.1.1 Averaging methods

Simple (S), Linear Weighted (LW) and Exponential Weighted (EW) averages were tested. For each fixed window length, L, and each valid beat position t_i, the N-beat set $\{t_j\}_i$ of preceding beats within a window of length L was considered:

$$\{t_j | t_i - t_j < L\}_i$$

with t_j time-ordered. The RR intervals associated with beat positions t_j, denoted $\{RR_j\}_i$, j=i-N+1, ..., i, were weighted according to the averaging method under consideration.

The Simple average, S, assigns the same weight to all the $\{RR_j\}_i$ measurements and then averages:

$$w_j = 1/N, \quad j = i - N + 1, \ldots, i$$

$$\overline{RR}_{S_i} = \sum_{j=i-N+1}^{i} w_j RR_j = \frac{1}{N} \sum_{j=i-N+1}^{i} RR_j.$$

In the Linear Weighted Method, LW:

$$w_j = \frac{2}{N(N-1)}(j - (i - N + 1)).$$

$$\overline{RR}_{LW_i} = \sum_{j=i-N+1}^{i} \frac{2(j - (i - N + 1))}{N(N-1)} RR_j.$$

And finally, in the Exponential Weighted Method, EW:

$$w_j = K\gamma(1-\gamma)^{i-j},$$

where K is a normalising constant, $K = 1/[1-(1-\gamma)^N]$, and $\gamma = 2/(1+N)$ giving:

$$\overline{RR}_{EW_i} = \sum_{j=i-N+1}^{i} K\gamma(1-\gamma)^{i-j} RR_j.$$

In the present study, the initial selection of the best averaging method used the parabolic regression model to fit $[QT_i, \overline{RR}_{X_i}]$ data, where X stands for any of the (S,LW,EW) averaging methods.

$$QT_i = \beta\, \overline{RR}_{X_i}^{\alpha}.$$

For this purpose, the $\overline{RR}_{X_i}$ series were calculated using values of L from 0 to 10 minutes in 1-minute steps, and the corresponding regression residua from these fits were evaluated. The results of the comparisons are shown in Figure 1.

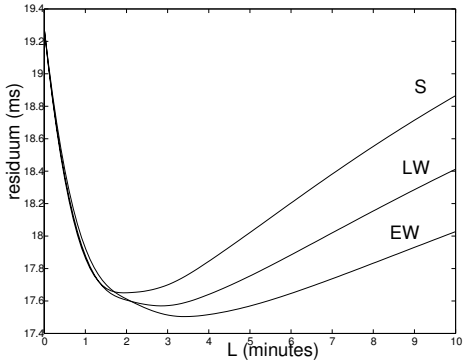

Figure 1. Mean of the $[QT_i,\overline{RR}_{X_i}]$ fit residuum as a function of the value L used to compute the $\overline{RR}_{X_i}$ series for each of the 3 averaging methods ($X = S, LW, EW$). To make the graphic representation continuous, a cubic "splines" interpolation was done.

As it can be observed from the figure, the minimum value of global residuum, averaged over the 939 patients, was achieved using the EW method. From here in advance, we will consider only averaged $\overline{RR}_{EW_i}$ measurments and we will just denote $\overline{RR}_i$ referring to the EW averaging shown to be the optimum.

2.1.2 Regression Models

Ten different regression models were used to fit each $[QT_i,\overline{RR}_i]$ data set. These models were selected to cover a variety of the physiologically possible patterns of $[QT,RR]$ relationship. The ten regression models were the following:

Linear	$QT = \beta + \alpha\overline{RR}$
Hyperbolic	$QT = \beta + \frac{\alpha}{\overline{RR}}$
Parabolic log/log	$QT = \beta\,(\overline{RR})^{\alpha}$
Logarithmic	$QT = \beta + \alpha \ln(\overline{RR})$
Shifted logarithmic	$QT = \ln(\beta + \alpha\overline{RR})$
Exponential	$QT = \beta + \alpha\, e^{-\overline{RR}}$
Arcus tangent	$QT = \beta + \alpha$ arctag$(\overline{RR})$
Hyperbolic tangent	$QT = \beta + \alpha$ tgh$(\overline{RR})$
Arcus hyperbolic sine	$QT = \beta + \alpha$ arcsinh$(\overline{RR})$
Arcus hyperbolic cosine	$QT = \beta + \alpha$ arccosh$(\overline{RR}+1)$

In all formulas, the QT and $\overline{RR}$ intervals were expressed in seconds.

2.1.3 Optimum model and window length

A three-step 1-second-precision search was designed to determine, for each patient, the optimum L: L_{opt}. "Optimum" was defined as leading to the minimum regression residuum from fitting $[QT_i,\overline{RR}_i]$ data using any of the 10 regression models.

In the first step of the search method, the residual variance from the $[QT_i,\overline{RR}_i]$ fit was independently evaluated for each of the regression models considering L ranging from 0 to 10 minutes in 1-minute steps. The value of L providing the smallest global residuum was identified for each of the models. The search was repeated in 1-minute window around the optimum with a 5-second step and again with a 1-second step to achieve a 1 second resolution of the results.

With this procedure, ten L values were determined corresponding to the optimum length for the different regression models. Finally, L_{opt} was defined by choosing the model associated with minimum residual variance.

2.1.4 Heart rate correction

Each of the ten regression models described in section (2.1.2) was converted into a heart rate correction formula, projecting the QT interval onto a standard level of $\overline{RR} = 1$ second. As an example, the correction formula derived from the linear model can be estimated from the model equation

$$\begin{aligned} QT &= \beta + \alpha\overline{RR} \\ &= QT(\overline{RR} = 1) + \alpha(\overline{RR} - 1) \end{aligned}$$

We can then say that

$$QT(\overline{RR} = 1) = \beta + \alpha = QT + \alpha(1 - \overline{RR}).$$

Then we can define the corrected QT interval, QTc as

$$QTc_i = QT_i + \alpha(1 - \overline{RR}_i).$$

Similar procedures were considered for the other models.

For each patient, the individualised QT correction formula was selected corresponding to the optimum regression model as determined by the procedure described in (2.1.3). To optimise such a formula, the parameter α was computed by golden search solving the equation $r(\alpha) = 0$, where $r(\alpha)$ is the Pearson correlation coefficient between QTc_i and $\overline{RR}_i$.

2.2. Statistical analysis

2.2.1 Risk markers

The following variables obtained from the present analysis were considered as potential risk stratifiers:

- Optimum window, L_{opt}
- ORR, which is defined as the global regression residuum from the $[QT_i, \overline{RR}_i]$ fit, evaluated using the optimum model and the optimum window duration.
- Mean of QTc, $\overline{QTc}$, that is the heart rate corrected QTc interval calculated according to the correction method proposed in section (2.1.4) and averaged over the 24-hour recording.
- $Slope$, determined as the parameter α of the parabolic $[QT_i,\overline{RR}_i]$ fit, with $\overline{RR}_i$ computed using the optimum window length associated with the parabolic model.

3. Results and discussion

Two aspects of the QT interval have been considered in this study: the QT adaptation lag behind RR changes and the risk stratification value of QT related measures in amiodarone-treated post-MI patients.

3.1. QT adaptation to RR changes

For each patient in the study, the optimum RR averaging window length L_{opt} and the corresponding minimum residuum ORR were evaluated according to the iterative search method described in (2.1.3). Averaged results were: $L_{opt} = 4.13$ minutes and $ORR = 17.24$ ms.

Our findings confirm that each QT measurement is influenced by heart rate changes in some previous minutes, although the influence of the most distant RR intervals is small as compared to that of the most recent ones.

Furthermore, very substantial differences in the individual optimum windows were found. While in 15% of the patients more than 7 minutes were required to completely explain the QT dependence on previous cardiac cycles, in some others (6%) the 'QT lag' was inferior to 90 seconds.

The high inter-subject variability in the time of QT adaptation to RR changes should be taken into account when correcting the QT interval for the effects of heart rate. Any generalised approach will tend to over or underestimate the true $[QT,RR]$ relationship and will lead to wrong QTc values.

3.2. Clinical risk stratification

In Table 1, results from the comparison between placebo and amiodarone using the variables derived in our study are presented. As expected, a significantly prolonged QTc interval was observed in patients on amiodarone compared with those on placebo. Substantial differences could also be found by measuring the variables ORR and $slope$, both of them taking greater values among amiodarone-treated patients. The optimum window duration was also different between both groups, although not as strongly as the other descriptors.

	Mean±SD		p-value	Placebo			Amiodarone		
				Mean±SD		p-value	Mean±SD		p-value
	Placebo	Amiodarone	t-test	Non-arrhy	Arrhy	t-test	Non-arrhy	Arrhy	t-test
L_{opt}	3.86 ± 2.35	4.33 ± 2.65	$5.7 \cdot 10^{-3}$	3.85 ± 2.34	3.92 ± 2.51	0.893	4.34 ± 2.65	4.04 ± 2.51	0.635
ORR	14.06 ± 6.59	19.96 ± 9.30	$< 10^{-17}$	14.03 ± 6.62	14.49 ± 6.17	0.735	20.18 ± 9.31	14.37 ± 7.02	0.009
$\overline{QTc}$	419.2 ± 35.9	442.9 ± 36.1	$< 10^{-17}$	418.2 ± 34.7	435.9 ± 48.5	0.021	443.8 ± 36.0	420.3 ± 31.3	0.007
$Slope$	0.48 ± 0.19	0.54 ± 0.24	$7.8 \cdot 10^{-6}$	0.47 ± 0.19	0.49 ± 0.19	0.635	0.55 ± 0.25	0.44 ± 0.20	0.055

Table 1. Mean values and standard deviations of the parameters described in the work and t-test results for separation of placebo and amiodarone and of the patients with and without arrhythmic death during follow-up. Units are: minutes for L_{opt}, and ms for ORR and $\overline{QTc}$

Table 1 also shows the comparison of patients who suffered arrhythmic death and those who did not, in placebo and amiodarone groups separately. ORR differentiated arrhythmic and non-arrhythmic death in the amiodarone group, showing considerably larger values for those who did not have arrhythmic death. Similar results were found using the variable $slope$, although differences were less significant. $\overline{QTc}$ also showed significantly different values between arrhythmic death victims and survivors. However, while arrhythmic death victims had longer QTc on placebo, they had shorter QTc on amiodarone.

When the variables considered in the univariate analysis were tested for arrhythmic risk stratification using Kaplan-Meier event probabilities, ORR proved to be a meaningful risk stratifier among patients on amiodarone, but not among those on placebo. In the amiodarone group, the ORR median value allowed significant risk stratification ($p < 0.005$ in the log-rank test), with values less than 14.86 indicating much worse survival. The $slope$ also showed the ability to risk stratify patients on amiodarone, but less significantly ($p = 0.013$ in the log-rank test).

Results obtained in the present work evidence that amiodarone modifies the [QT,RR] relationship increasing its complexity and, at the same time, making the frequency dependence of the QT interval stronger. We related this modification of the ventricular adaptation to the reduction in arrhythmic mortality among amiodarone-treated patients.

4. Discussion and conclusions

The method introduced in the study for evaluation of the QT lag behind heart rate changes verifies that QT is not only influenced by the preceding cardiac cycle but also by RR measurements contained in a window of several minutes. The QT adaptation to RR changes is modified by the effects of amiodarone. There is a close link between this action and the reduction in arrhythmic mortality among amiodarone-treated post-MI patients.

The window length duration resulted in about 4 minutes on average, but this value should be taken with the view of a exponential decay close to zero at the window onset. Estimating the length as the exponential decay to $1/e$ we will have values close to 2 minutes that agrees with those already presented in [5].

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