Estimation of the QT/RR Hysteresis Lag

Esther Pueyo, BSc,*† Peter Smetana, MD,* Pablo Laguna, PhD,† and Marek Malik, PhD, MD*

Abstract: The process of QT interval adaptation to heart rate (HR) changes was evaluated by considering weighted averages of RR intervals to characterize the influence of previous cardiac cycles. An optimum adaptation pattern was individually derived for each patient and several descriptors of the QT/RR hysteresis were subsequently calculated. The values of these parameters showed that the QT adaptation to HR changes is highly individual and, consequently, any generalized approach may lead to inappropriate conclusions. Key words: QT/RR Hysteresis, QT lag, [QT/RR] relationship, repolarization.

It is known that the changes in the QT interval lag behind the changes in RR interval (QT/RR hysteresis). However, at present, only simple approaches have been implemented in some Holter systems assuming a constant duration of the QT/RR hysteresis lag in all patients. In addition, not only the duration but also the way in which QT adapts may substantially differ between subjects. Among others, the omission of the individual adaptation characteristics might result in significant errors in the estimation of heart rate corrected QT interval (QTc).

We therefore investigated the QT/RR hysteresis by analyzing the dynamics in which the QT intervals adapt to the changes in the RR intervals. For this purpose, we considered RR averaging windows preceding each measured QT interval, that is to relate each QT interval not only to the immediately preceding RR interval but to a history of previous RR interval values. A searching was performed for the window that led to the optimum [QT,RR] fit, where RR is the weighted average of preceding RR measurements. From such an individually obtained QT/RR adaptation pattern, a numerical quantification of the hysteresis lag was obtained together with a descriptor of the QT/RR hysteresis dynamicity that quantifies the velocity and profile of the QT interval adjustment.

Materials and Methods

Study Population

The study investigated a population of 866 patients taken from the EMIAT trial database (1). All subjects were survivors of acute myocardial infarction, aged ≤75 years, with left-ventricular ejection fraction (LVEF) ≤40%. Recordings available for the study were 24-hour 3-lead Holter ECGs obtained one month after treatment randomization; 462 were obtained on amiodarone and 404 on placebo.
Data Analysis

RR and QT intervals were automatically measured on a beat-to-beat basis using a commercial Holter system (Pathfinder, Reynolds Medical Inc., Hertford, UK). In each lead, only beats with accepted QT and RR intervals were considered and, in each recording, the lead with more accepted measurements was selected. Detection of incidences in the RR signal (false positives, false negatives and ectopic beats) was carried out according to the methodology described in (2). Beats for which a preceding 300-second window included no valid measurements were rejected.

QT Adaptation Pattern

QT interval dependence on preceding RR intervals was characterized by an RR interval averaging window that was optimized to lead to the lowest regression residual of the \([QT,RR]\) data, where \(\bar{RR}\) is the corresponding weighted average of RR interval measurements in the window. In order to determine such an optimum weight distribution individually, a global optimization algorithm based on the Direct method (3,4) was implemented, in which the objective function to be minimized was defined at each weight vector \(w = (w_1, \ldots, w_N)\) as the global residual from fitting any of 10 a-priori selected regression models (5) to the \([QT,\bar{RR}]\) data, with \(\bar{RR}_i\) computed for each \(i\)th beat as

\[
\bar{RR}_i = \frac{1}{N} \sum_{j=i-N+1}^{i} w_{j-i+N} RR_j
\]

where \(N\) is the number of beats contained in preceding 300-second window within the 24-hour recording, and \(w = (w_1, \ldots, w_N)\) are all positive and normalized such that \(w_1 + \ldots + w_N = 1\).

As a result, 10 different combinations of weights \(w_i\) and regression parameters were determined for each recording, each combination characterizing the optimum RR influence associated with one regression model. A unique pattern of averaging window was identified by selecting the model leading to the minimum residual when the \(\bar{RR}\) intervals were computed from the original RR interval measurements with the regression model-specific optimum weights.

QT/RR Descriptors

The developed analysis of QT adaptation to RR changes provided an individual profile of the QT/RR hysteresis, from which two parameters characterizing the adaptation process were calculated:

- \(\text{Lag}\), describing the effective length of RR influence. It was computed from the optimum weight distribution \(w_j\) by considering a cumulative sum

\[
H(j) = \sum_{k=1}^{j} w_k, \quad j = 1, \ldots, N
\]

reaching a threshold \(\eta = 0.1\) defined to cover 90% of the adaptation (Fig. 1). The number of beats required to achieve the limit imposed by \(\eta\) were counted and \(\text{Lag}\) was defined as the corresponding time in seconds, using the mean RR for conversion from beats to seconds.

- \(\lambda\), inverse beat-velocity of the QT adaptation. It was determined from fitting the cumulative sum of weights \(H(j)\) with an exponential model: \(H(j) = e^{\lambda_j + \beta}\) (Fig. 2). Correlation values above 0.91 confirmed the suitability of the fit. The \(\lambda\) parameter was defined as the time constant of the model: \(\lambda = 1/A\).

Heart Rate Correction

Each of the 10 regression models was converted into a heart rate correction formula by projecting the QT interval onto a standard level of \(\bar{RR} = 1\) second. For each patient, the individualized QT correction formula was selected corresponding to the optimally determined regression model. Such a formula was optimized according to the criterion of null Pearson correlation coefficient between QTc and \(\bar{RR}\).
Results

Evaluation of the QT adaptation lag revealed that, on average, 140 seconds of the preceding RR intervals have influence on the QT interval duration. Nevertheless, observation of weight distributions characterizing the adaptation profiles showed that the influence of the most distant RR intervals is small compared to the most recent ones. This proportion was differently expressed in different patients.

Examining the individual values of the parameter Lag, we observed high inter-subject variability, as confirmed by the high standard deviation of the variable, which was around 35 seconds. In fact, the Lag values ranged from 3 to over 215 seconds.

Furthermore, not only the delays in the heart rate adaptation of ventricular repolarization but also the characteristic adaptation profiles, that is the way in which QT reacts to RR changes, showed very high inter-subject variability. Mean value of λ was 47.6 ± 8.1 beats. Figures 2A and 2C shows 2 examples representative of very different adaptation profiles, with λ = 46.52 beats characterizing a fast adaptation, and λ = 54.67 beats characterizing much slower adaptation.

These results demonstrate the necessity of considering the individual QT/RR hysteresis patterns and the use of an individualized correction formula to correct the QT interval for the effects of heart rate.

Discussion and Conclusions

In this study, the evaluation of the QT/RR hysteresis lag showed that, despite the strong dependence of QT on the preceding cardiac cycle, an individually variable history of heart rate also contributes to QT variations. The way QT is influenced by previous RR intervals and the interval necessary to describe the complete adaptation process varies significantly among patients. This fact enhances the importance of having obtained individual adaptation profiles representative of optimum weights assigned to past RR measurements, which should be taken into account within Holter systems. The assumption of the lag in the QT adaptation being constant for all subjects is clearly contradicted by the results of this study.

References

2. Mateo J, Laguna P: Analysis of heart rate variability in
the presence of ectopic beats using the heart timing signal. IEEE Trans Biomed Eng 50:1099, 2002