Estimation of the QT/RR Hysteresis Lag

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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 [$QT,\overline{RR}$] fit, where $\overline{RR}$ 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.

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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 $[QT,\overline{RR}]$ data, where $\overline{RR}$ 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 $[QT_i,\overline{RR}_i]$ data, with $\overline{RR}_i$ computed for each *i*th beat as

$$\overline{\mathrm{RR}}_{\mathrm{i}} = \sum_{\mathrm{j=i-N+1}}^{\mathrm{i}} \mathrm{w_{j-i+N}RR_j}$$

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 $\overline{RR}$ 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:

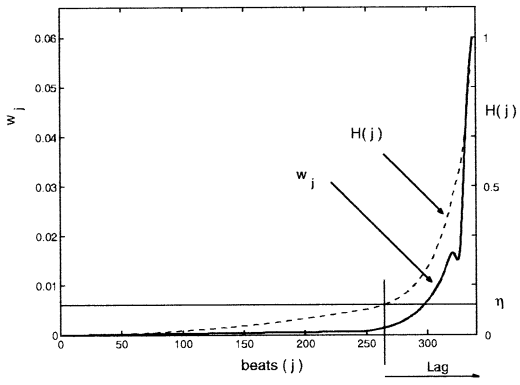

Fig. 1. Determination of the effective window length for *RR* averaging, considering a threshold η covering 90% of the sum of weights. The weight distribution w_j is plotted as a solid line and its cumulative sum *H(j)* as a dashed line.

- *Lag,* describing the effective length of *RR* influence. It was computed from the optimum weight distribution w_j by considering a cumulative sum

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

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 η were counted and *Lag* was defined as the corresponding time in seconds, using the mean *RR* for conversion from beats to seconds.

- λ, inverse beat-velocity of the *QT* adaptation. It was determined from fitting the cumulative sum of weights $H(j)$ with an exponential model: $H(j) = e^{A_j+B}$ (Fig. 2). Correlation values above 0.91 confirmed the suitability of the fit. The λ 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 $\overline{RR} = 1$ 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 $\overline{RR}$.

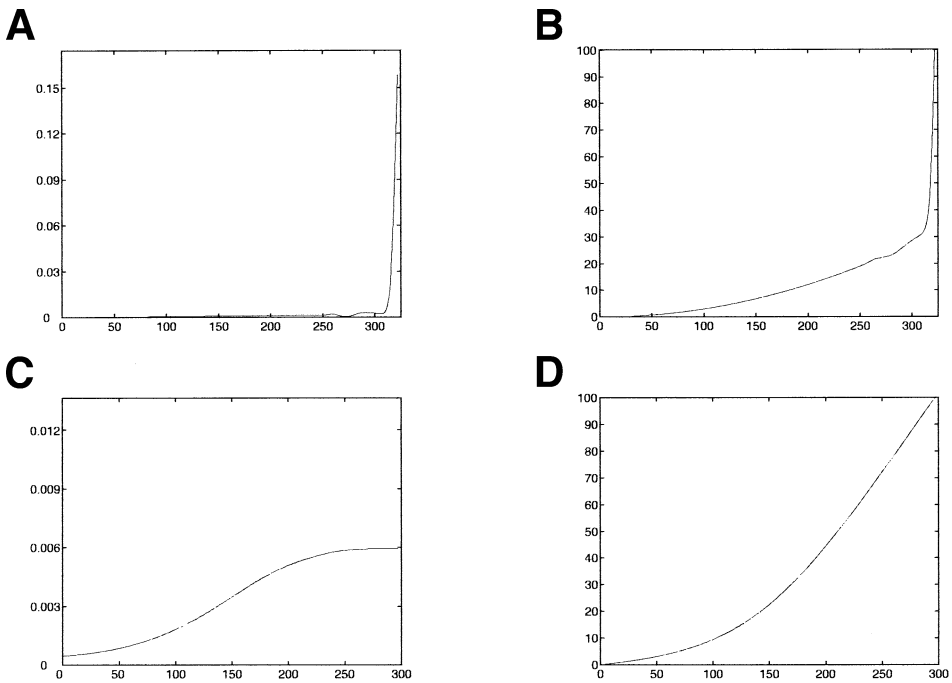

Fig. 2. In (A) and (C), two different examples of optimum weight distributions corresponding to two patients in the study are represented. Their respective cumulative sums of weights are plotted in (B) and (D), which were fitted with exponential models in order to extract values of the adaptation rate (λ = 46.52 and λ = 54.67 beats, respectively).

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 $\pm$ 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

1. Julian DG, Camm AJ, Frangin G, et al: Randomised trial of effect of amiodarone on mortality in patients with left-ventricular dysfunction after recent myocardial infarction. EMIAT. The Lancet 349:667, 1997
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
3. Jones DR, Perttunen CD, Stuckman BE: Lipschitzian optimization without the Lipschitz constant. J Optimiz Theory App 79:157, 1993
4. Lewis RM, Torczon V, Trosset MW: Direct search methods: then and now. Journal of Computational and Applied Mathematics 124:191–207, 2000
5. Pueyo E, Smetana P, Hnatkova K, et al: Time for QT adaptation to RR changes and relation to arrhythmic mortality reduction in amiodarone-treated patients. Comput Cardiol 29:565, 2002