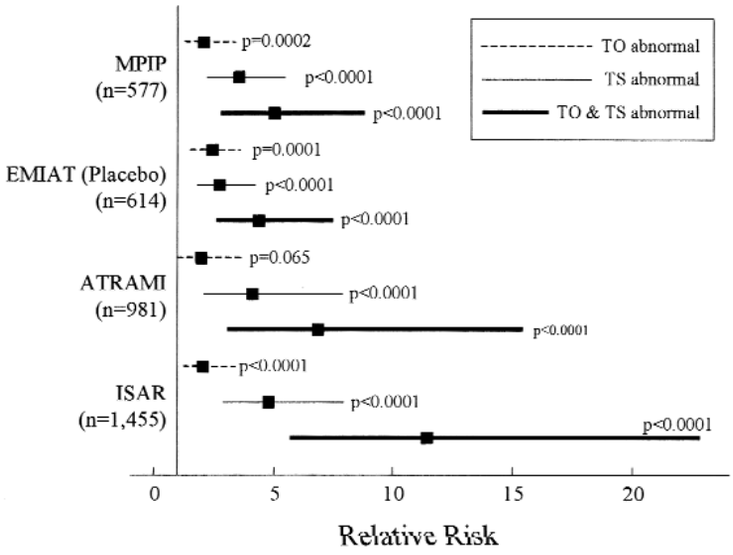

Figure 3. *Hazard ratios for total mortality (MPIP, EMIAT and ISAR) and cardiac mortality (ATRAMI) for turbulence onset (TO), turbulence slope (TS) and heart rate turbulence category 2.*

References

1. Schmidt G, Malik M, Barthel P, et al. Heart-rate turbulence after ventricular premature beats as a predictor of mortality after acute myocardial infarction. Lancet 1999; 353: 1390-6.
2. Watanabe MA. Heart rate turbulence: a review. Indian Pacing and Electrophysiology Journal 2003; 3: 10-22.
3. Marine JE, Watanabe MA, Smith TW, Monahan KM. Effect of atropine on heart rate turbulence. Am J Cardiol 2002; 89: 767-9.
4. Davies LC, Francis DP, Ponikowski P, Piepoli MF, Coats AJ. Relation of heart rate and blood pressure turbulence following premature ventricular complexes to baroreflex sensitivity in chronic congestive heart failure. Am J Cardiol 2001; 87: 737-42.
5. Ghuran A, Reid F, La Rovere MT, et al. Heart rate turbulence-based predictors of fatal and nonfatal cardiac arrest (The Autonomic Tone and Reflexes After Myocardial Infarction substudy). Am J Cardiol 2002; 89: 184-90.
6. Mrowka R, Persson PB, Theres H, Patzak A. Blunted arterial baroreflex causes "pathological" heart rate turbulence. Am J Physiol Regul Integr Comp Physiol 2000; 279: R1171-R1175.
7. Barthel P, Schneider R, Bauer A, et al. Risk stratification after acute myocardial infarction by heart rate turbulence. Circulation 2003; 108: 1221-6.
8. Bonnemeier H, Wiegand UK, Friedlbinder J, et al. Reflex cardiac activity in ischemia and reperfusion: heart rate turbulence in patients undergoing direct percutaneous coronary intervention for acute myocardial infarction. Circulation 2003; 108: 958-64.

ASSESSMENT OF INDIVIDUAL QT/RR RELATIONSHIP AND HYSTERESIS IN POST-INFARCTION PATIENTS

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In this study the QT interval response to RR interval changes was assessed in 24-hour Holter recordings by considering weighted averages of a history of past RR intervals to characterize the influence of heart rate on each QT measurement. An optimum adaptation profile was individually obtained for each patient, from which several descriptors of the QT/RR hysteresis were derived. Two main results were found in this study: first, the process of QT adaptation to heart rate changes is highly individual and, consequently, any generalized approach may lead to inappropriate conclusions; second, it is important to consider RR interval variations in some previous minutes to completely characterize the QT response.

Introduction

It is known that a time lag exists in the adaptation of the QT interval to RR interval changes. This so-called QT/RR hysteresis is, however, usually ignored in automatic QT analysis of 24-hour Holter recordings. Only simple approaches have been implemented in some Holter systems but always assuming that the duration of the QT/RR hysteresis lag is constant 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).

In this study we investigated the QT/RR hysteresis by analyzing the dynamic dependence of the QT interval behind heart rate changes. In order to relate each QT not only to the immediately preceding RR interval but to a history of previous RR intervals, we considered RR averaging windows preceding each QT measurement. A searching was performed for the window that led to the optimum [QTi, $\overline{RRi}$] fit, where $\overline{RRi}$ is the weighted

average of preceding RR measurements. From the individually derived QT/RR adaptation pattern, the hysteresis lag was numerically quantified and a characterization of the time course of the QT response to heart rate changes was obtained in terms of velocity and profile of the adaptation process.

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 ≤ 40%. Recordings available for the study were 24-hour 3-lead Holter ECGs obtained 1 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.). 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 by Mateo and Laguna[2]. Beats for which a preceding 300 s 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, RR_i] data, with RR_i computed for each ith beat as

$$\overline{RR_i} = \sum_{j=i-N+1}^{i} w_{j-i+N}\, RR_j$$

where N is the number of beats contained in preceding 300 s 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 assessment of QT adaptation to RR changes described in the previous paragraph provided an individual profile of the QT/RR hysteresis, from which two parameters characterizing the adaptation process were calculated:

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

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

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 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: $H(j) = e^{Aj+B}$ (Fig. 2). Correlation values > 0.91 confirmed the suitability of the fit. The λ parameter was defined as the time constant of the model: $l = 1/A$.

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 s. 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 $\overline{RR}$.

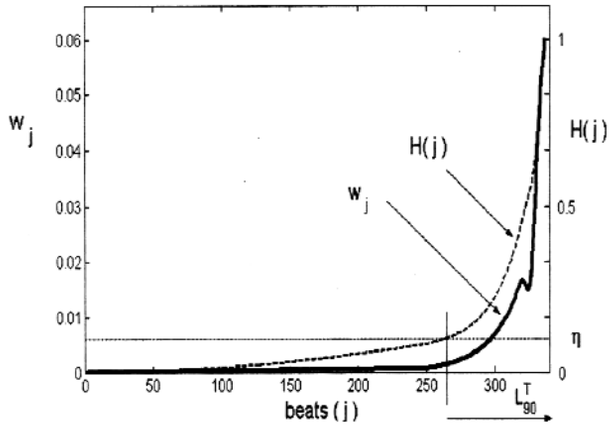

Figure 1. *Determination of the effective window length for RR averaging, considering a threshold* η *covering 90% of the sum of weights. The weight distribution* w_j *is plotted as a* solid line *and its cumulative sum H(j) as a* dashed line.

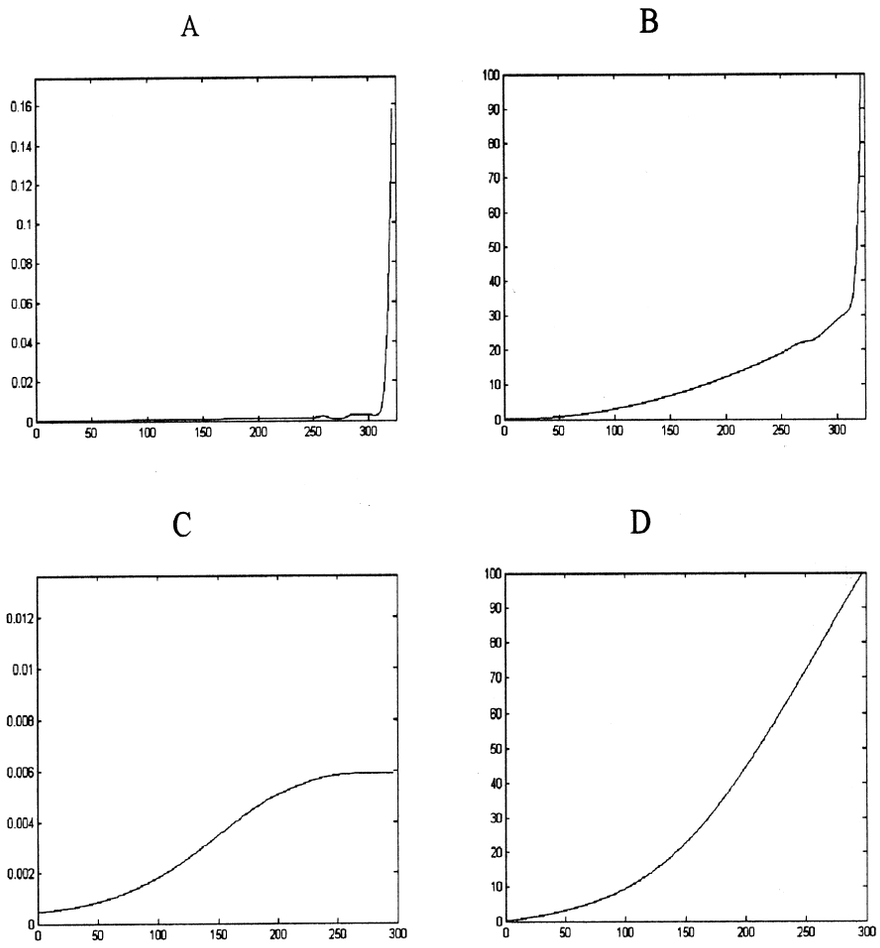

Figure 1. *In* A *and* C, *two different examples of optimum weight distributions corresponding to 2 patients in the study are represented. Their respective cumulative sums of weights are plotted in* B *and* D, *which were fitted with exponential models in order to extract values of the adaptation rate (λ = 46.52 and λ = 54.67 beats, respectively).*

Results

Quantification of the QT hysteresis lag revealed that, on average, 140 s 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 intersubject variability, as confirmed by the high standard deviation of the variable, which was around 35 s. In fact, the lag values ranged from 3 to > 215 s.

High intersubject variability was observed not only in the delays of the heart rate adaptation of ventricular repolarization but also in the characteristic adaptation profiles, that is the way in which QT reacts to RR changes. Mean value of λ was 47.6 ± 8.1 beats. Figure 2 shows in panels A and C two 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, as it can be corroborated by observation of their respective cumulative sums of weights shown in panels B and D.

Results obtained from the present study 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

The evaluation of the QT/RR hysteresis lag developed in this work 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 mode in which previous RR intervals influence each QT measurement and the time 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 results of this study clearly disagree with the assumption of the lag in the QT adaptation being constant for all subjects.

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. Lancet 1997; 349: 667-73.
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 2003; 50: 334-43.
3. Jones DR, Perttunen CD, Stuckman BE. Lipschitzian optimization without the Lipschitz constant. Journal of Optimization Theory and Applications 1993; 79: 157-81.
4. Lewis RM, Torczon V, Trosset MW. Direct search methods: then and now. Journal of Computational and Applied Mathematics 2000; 124: 191-207.
5. Pueyo E, Smetana P, Hnatkova K, Laguna P, Malik M. Time for QT adaptation to RR changes and relation to arrhythmic mortality reduction in amiodarone-treated patients. In: Murray A, Arzbaecher R, eds. Computers in cardiology. Memphis, TN: IEEE Computer Society Press, 2002: 565-8.

INDIVIDUALIZED CORRECTION OF QT/RR INTERVAL FOR HEART RATE

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While in clinical practice, the standard imprecision of heart rate correction of the QT interval (QTc) by Bazett formula seems to be acceptable, investigations that require accurate assessment of QTc values are frequently substantially affected by this imprecision. In particular, studies of drug-induced QT interval prolongation may lead to completely erroneous conclusions if utilizing imprecise *ad hoc* selected heart rate corrections of QT interval. For this reason, the so-called individual heart rate correction approaches have been developed and shown to be superior to the application of any of the previously published correction formulae.

The article reviews the background of the problem and discusses the scientific evidence that was used as the background of the development of individualized heart rate corrections. Clinical utilities of the technology are discussed.

Introduction

Prolongation of the heart rate-corrected QT interval (QTc) is an established risk factor for cardiac and arrhythmic death in the general population and various patient groups[1-5]. In recent years, the interest in the QTc interval has been additionally fueled by the increased awareness that many cardiac as well as non-cardiac drugs have the potential to affect ventricular repolarization and induce a potentially lethal torsades de pointes (TdP) ventricular arrhythmia[6]. With most drugs administered at standard clinical doses, TdP is rather rare and occurs exclusively in the presence of predisposing conditions, such as heart failure, bradycardia or electrolyte disbalance and/or in susceptible individuals (i.e. asymptomatic carriers of "silent" mutations of long QT syndrome genes[7,8]). Therefore the absence of cases of TdP in clinical program of drug development is not reassuring. The initial post-marketing surveillance of some drugs that were later withdrawn from the market because of clear proarrhythmic toxicity, was both substantial and signal-free[9]. Therefore the assessment of drug-induced changes of cardiac repolarization needs to be based on surrogate markers of which the most important is the prolongation of the QTc interval. If in addition to the QT interval the investigated drug changes also heart rate, either directly or indirectly through therapeutic actions, the appropriate QT heart rate correction becomes very important.

The precision requirements of the QTc interval measurement are different in clinical practice and in risk stratification and/or drug studies. In clinical practice, an imprecision of 10 to 20 ms, or perhaps even more is less likely to lead to incorrect management decisions since all borderline findings are always interpreted within the context of other clinical findings. On the contrary, errors of 10 ms or even lower may be misleading in drug studies and risk stratification trials (e.g. when selecting patients for a prospective intervention), especially when introduced in a biased way due to systematic differences in heart rate.

The fact that the relative duration of cardiac systole changes with heart rate has been recognized even before the invention of electrocardiography[10]. For example, Thurston[11] used sphygmographical tracings of the radial pulse to measure the length of the cardiac systole at different heart rates. He confirmed that "the length of the systole of the heart, as indicated in the radial artery, is constant for any given pulse rate, and varies as the cube root of the rapidity". Earlier, Garrod[12] analyzed sphygmographic recordings of the apex beat in healthy subjects and came to the conclusion that "in health, the length of the first part of the heart beat varies ... inversely as the square root of the rapidity". In other publications the same author observed that "the length of the interval between the commencement of the primary and dicrotic rises (of the sphygmogram) is constant for any given pulse rate, and varies as the cube root of the pulse rate ..."[13].

Following the discovery of electrocardiography, the relationship between mechanical systole and the QT interval was studied extensively and the relationship between the QT and RR intervals has been researched ever since.

Unfortunately, despite all the research work spanning over more than one century, the problem of the appropriate heart rate correction of the QT interval has not been