Characterization of QT Interval Adaptation to RR Interval Changes and Its Use as a Risk-Stratifier of Arrhythmic Mortality in Amiodarone-Treated Survivors of Acute Myocardial Infarction

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***Abstract*—A new method is proposed to evaluate the dynamics of QT interval adaptation in response to heart rate (HR) changes. The method considers weighted averages of RR intervals ($\overline{\mathrm{RR}}$) preceding each cardiac beat to express RR interval history accounting for the influence on repolarization duration. A global optimization algorithm is used to determine the weight distribution leading to the lowest regression residual when curve fitting the $[\mathrm{QT}, \overline{\mathrm{RR}}]$ data using a patient-specific regression model. From the optimum weight distribution, a memory lag L_{90} is estimated, expressing the delay in the QT adaptation to HR changes. On average, RR intervals of the past 150 beats (approximately 2.5 min) are required to model the QT response accurately. From a clinical point of view, the interval of the initial tens of seconds to one minute seems to be most important in the majority of cases. A measure of the optimum regression residual (r_{opt}) has been calculated, discriminating between post-myocardial infarction patients at high and low risk of arrhythmic death while on treatment with amiodarone. A similar discrimination has been achieved with a variable expressing the character of QT lag behind the RR interval dynamics.**

***Index Terms*—Amiodarone, arrhythmic mortality, global optimization, QT adaptation, [QT, RR] relationship.**

I. Introduction

THE QT interval, i.e., the overall duration of ventricular repolarization, is predominantly influenced by changes in heart rate in addition to other physiological factors, such as autonomic activity and electrolyte disorders [1]–[3]. Both immediate and delayed changes of action potential duration due to cycle length variations have been reported [4], [5]. Consequently, the QT interval response to changes in cardiac cycle is not immediate and time lag exists in the adaptation. These so-called QT/RR hysteresis and restitution have been investigated mostly in studies of QT interval adaptation to abrupt changes in pacing rate [6]. A time lag of 2–3 min was found to cover 90% of the QT interval adaptation. The hysteresis phenomenon has also been studied in exercise protocols. Krahn *et al.* [7] showed that for long-QT syndrome patients, continuous shortening of the QT interval exists during the recovery from exercise. However, in automatic QT interval analysis of continuous 24-h Holter recordings, this QT/RR hysteresis is usually ignored and only the preceding RR interval is considered when relating the QT interval to heart rate [8]–[13]. The QT/RR hysteresis is only considered in some Holter systems that, however, assume that the duration and profile of the hysteresis is the same in all subjects.

To investigate the QT/RR hysteresis, we hypothesized that the QT corresponding to the ith beat is related to a history of several previous RR intervals and that this dependence can be modeled by using a weighted average of preceding RR intervals ($\overline{\mathrm{RR}}_i$). In order to account for the individual differences and subject-specific characteristics, the optimum weighting function is individually estimated, considering independently the following scenarios: 1) the whole electrocardiogram (ECG) recording (also analyzed over separate circadian time windows [14], [15]); 2) exclusively focusing on segments of the recording with sharp RR transitions. The clinical interest of studying unstable heart rate segments has been repeatedly reported, e.g., by Malfatto *et al.* [16] and Toivonen *et al.* [17]. In our study, we characterized each Holter recording in terms of both duration and profile of the QT/RR hysteresis.

Repeated clinical and experimental studies suggested that abnormalities of ventricular repolarization play a role in the genesis of ventricular arrhythmias [18]–[21]. Consequently, we compared the descriptors of QT/RR hysteresis between patients with ischemic heart disease treated and not treated with amiodarone (one of the anti-arrhythmic drugs) ([22], [23]) as well as between patients who subsequently did or did not suffer from arrhythmic death.

II. Methods

A. Population

The study evaluated 24-h 3-lead Holter ECG recordings obtained from 939 patients of the EMIAT trial [24] that investigated survivors of acute myocardial infarction and randomized

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them to treatment with amiodarone or placebo. All recordings were obtained one month after randomization. Meaningful data were available in 866 patients who were followed-up for a mean time of 620 ± 176 days. Of these patients, 404 were treated with placebo (26 suffered from arrhythmic death during follow-up) and 462 with amiodarone (18 arrhythmic deaths).

B. Data Measurement

The Holter recordings contained three ECG channels and in each channel of each recording, individual QT and RR intervals were measured using the software tools of Pathfinder 700 Holter system (Reynolds Medical, Hertford, U.K.). Initial automatic measurement was checked by a trained operator on computer screen and where appropriate, erroneous automatic measurements were corrected manually or deleted. This semi-automatic system had to be used since it was in principle not possible to measure the QT interval of each beat of each recording manually.

C. Data Analysis

For each lead of each recording, only cardiac cycles for which the measurement determined both QT and RR intervals were considered. Subsequently, the lead with most accepted measurements was selected for each recording. Anomalies caused by QRS detector errors and by ectopic beats were identified using a previously proposed strategy [25]. For the main analysis, all beats either classified as anomalous or preceded by a 300-s window with any no valid RR measurement were rejected.

One of the main objectives of the analysis was to determine the optimum subject-specific RR averaging window describing the QT/RR hysteresis both in terms of profile and duration. In this text, we firstly describe the optimization of the QT/RR hysteresis assessment which is followed by the description of possibilities of its practical use. In the description, the total number of cardiac cycles used in the analysis is denoted by N_T (individually determined) and the numerical expression of the history of preceding RR intervals influencing the QT interval of the ith cardiac cycle is denoted by $\overline{\mathrm{RR}}_i$.

1) Fixed Window Profile of RR Average: Initially, two profiles of moving-window averages were tested to obtain the $\overline{\mathrm{RR}}_i$ values. The considered profiles were: linearly weighted (LW) and exponentially weighted (EW). Specifically, let t_i denote the instant of ith valid cardiac beat, $t_i < t_{i+1}$, and let RR_i denote RR interval duration preceding the ith beat. Then, a given window length L determines a number N_i of beats preceding the ith beat by no more than L

$$\{t_{i+j} | t_i - t_{i+j} \le L\}_i; \quad j = -N_i + 1, \ldots, 0$$

The LW profile performed linear interpolation

$$\overline{\mathrm{RR}}_{\mathrm{LW}_i} = \sum_{j=-N_i+1}^{0} w_j \mathrm{RR}_{i+j} = \sum_{j=-N_i+1}^{0} \frac{2(j+N_i-1)}{N_i(N_i-1)} \mathrm{RR}_{i+j}.$$

The EW profile performed an exponential interpolation

$$\overline{\mathrm{RR}}_{\mathrm{EW}_i} = \sum_{j=-N_i+1}^{0} K\gamma(1-\gamma)^{-j} \mathrm{RR}_{i+j}$$

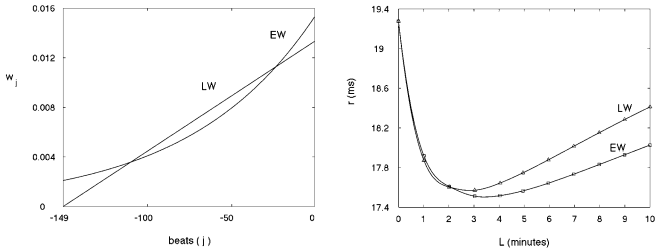

Fig. 1. Left panel: weight assignments by Linearly and Exponentially Weighted averages. In the illustration, a 150-beat window was taken as an example ($N_i = 150$). Right panel: mean of the $[\mathrm{QT}_i, \overline{\mathrm{RR}}_{X_i}]$ fit residual, r, as a function of the window duration L (see the text for details).

where $\gamma = 2/(1+N_i)$ and K is a normalizing constant, $K = 1/[1-(1-\gamma)^{N_i}]$. The distribution of weights for each of the two profiles is shown in Fig. 1. In all cases, the weights w_j are normalized so that

$$\sum_{j=-N_i+1}^{0} w_j = 1.$$

Of the two profiles, the best was selected as the first approximation for QT/RR hysteresis description. This initial selection used the parabolic regression model to fit $[\mathrm{QT}_i, \overline{\mathrm{RR}}_{X_i}]$ data of the 24-h ECG recording

$$\mathrm{QT}_i = \beta\,(\overline{\mathrm{RR}}_{X_i})^{\alpha}$$

where X stands for any of the LW and EW profiles.

For this purpose, the $\overline{\mathrm{RR}}_{X_i}$ series were calculated using window lengths L ranging from 0 to 10 min in 1-min steps, and the corresponding regression residuals

$$r = \sqrt{\sum_{i=1}^{N_T} \frac{1}{N_T} (\mathrm{QT}_i - \hat{\beta}(\overline{\mathrm{RR}}_{X_i})^{\hat{\alpha}})^2}$$

were evaluated, where $\hat{\alpha}$ and $\hat{\beta}$ are the optimum values of coefficients α and β that lead to the minimum residual r in each case. Results of the comparison are shown in Fig. 1.

The minimum value of the mean residual, averaged over the study group, was obtained with the EW profile. Consequently, the EW profile method was taken as starting point for the subsequent procedure.

2) Individualized Profiles of RR Average: The individually optimized QT/RR hysteresis profile, i.e., individually set window duration L and RR interval averaging weights $\{w_j\}$, were assessed by implementing a global optimization algorithm based on the Direct method [26], [27]. This method considers an objective function $f : \mathcal{R}^N \longrightarrow \mathcal{R}$ to be minimized and a design space $D = \{(x_1, \ldots, x_N) \in \mathcal{R}^N | l \le x_j \le u, j = 1, \ldots, N\}$. It normalizes D to become the unit hypercube and evaluates f at its centerpoint. At each of the steps of Direct method, the hypercube is divided into smaller hyperrectangles according to the evaluations of the objective function at their centerpoints. Sampling at the centers instead of at the vertices substantially reduces the computational load, especially for high-dimensional problems. The Direct method is also characterized by fast convergence, due to the combination of global and local search selecting the set of potentially optimal analyzed rectangles at each step.

In the application to our data, an initial window length of $L = 5$ min was considered. This value of L was derived from

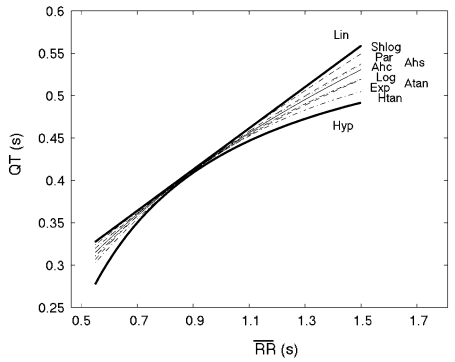

Fig. 2. Regression models considered for representation of the different $[\mathrm{QT}_i, \overline{\mathrm{RR}}_i]$ patterns. To make the plot, the α and β values for each of the regression models were obtained by averaging over patients the parameters from optimally fitting $[\mathrm{QT}_i, \overline{\mathrm{RR}}_i]$, with $\overline{\mathrm{RR}}_i$ calculated using the individual EW distributions.

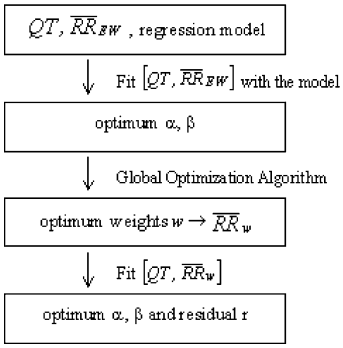

Fig. 3. Flow chart of algorithm for determination of individualized profile of RR average.

the initial results obtained with the EW profile. With that profile, the window durations leading to lowest regression residual r were shorter than 5 min in 80% of the patients. Moreover, even in cases where the optimum EW window length was larger than 5 min, the exponential decay in the initial part of the window was very close to zero. To convert the initial 5-min window length into a number of preceding RR intervals, we considered the average N of all N_i values, that is the average number of RR intervals occurring within the 5-min segments of valid data in the entire 24-h recording. This mean number N of RR intervals was determined separately for each recording. Subsequently, the objective function f at a point $\mathbf{w} = (w_{-N+1}, \ldots, w_0) \in \mathcal{R}^N$ was defined as the global residual r of a regression model (as described later in the text) to the $[\mathrm{QT}_i, \overline{\mathrm{RR}}_i]$ data, where

$$\overline{\mathrm{RR}}_i = \sum_{j=-N+1}^{0} w_j \mathrm{RR}_{i+j}$$

and $\mathbf{w} = (w_{-N+1}, \ldots, w_0)$ are normalized such that $w_{-N+1} + \ldots + w_0 = 1$. Additionally, the lower and upper weight bounds were fixed at $l = 0$ and $u = 1$, respectively, i.e., $0 \le w_j \le 1$ for each $j = -N+1, \ldots, 0$.

As an initialization of the global optimization algorithm, we used the EW distribution of weights previously obtained for each recording. In cases with optimum EW length $L < 5$ min, the distribution was completed by linear padding from zero. In other cases, the EW window length L was truncated to 5 min. A limit on the iteration number defined the stopping criterion of the algorithm. This limit was fixed at 90, since it was found that with this setting, the percent of reduction in the objective function achieved in the last iteration was below 1% of the total reduction for more than 90% of the recordings.

To optimize the regression residuals, ten different regression models were used to fit each $[\mathrm{QT}_i, \overline{\mathrm{RR}}_i]$ data set. These models [28], [29] were chosen to cover a variety of physiologically plausible patterns of $[\mathrm{QT}, \overline{\mathrm{RR}}]$ relationship. The introduction of a spectrum of regression models improved the correlation values between QT and $\overline{\mathrm{RR}}$ leading to more reliable the results of the subsequent analysis. The ten regression models (Fig. 2) considered in the study were as follows:

$$\begin{aligned}
\text{Linear} \quad (\text{Lin}) \quad & \mathrm{QT} = \beta + \alpha \overline{\mathrm{RR}} \\
\text{Hyperbolic} \quad (\text{Hyp}) \quad & \mathrm{QT} = \beta + \frac{\alpha}{\overline{\mathrm{RR}}} \\
\text{Parabolic log/log} \quad (\text{Par}) \quad & \mathrm{QT} = \beta\,(\overline{\mathrm{RR}})^{\alpha} \\
\text{Logarithmic} \quad (\text{Log}) \quad & \mathrm{QT} = \beta + \alpha \ln(\overline{\mathrm{RR}}) \\
\text{Shifted logarithmic} \quad (\text{Shlog}) \quad & \mathrm{QT} = \ln(\beta + \alpha \overline{\mathrm{RR}}) \\
\text{Exponential} \quad (\text{Exp}) \quad & \mathrm{QT} = \beta + \alpha\, e^{-\overline{\mathrm{RR}}} \\
\text{Arcus tangent} \quad (\text{Atan}) \quad & \mathrm{QT} = \beta + \alpha \operatorname{arctag}(\overline{\mathrm{RR}}) \\
\text{Hyperbolic tangent} \quad (\text{Htan}) \quad & \mathrm{QT} = \beta + \alpha \operatorname{tgh}(\overline{\mathrm{RR}}) \\
\text{Arcus hyperbolic sine} \quad (\text{Ahs}) \quad & \mathrm{QT} = \beta + \alpha \operatorname{arcsinh}(\overline{\mathrm{RR}}) \\
\text{Arcus hyperbolic cosine} \quad (\text{Ahc}) \quad & \mathrm{QT} = \beta + \alpha \operatorname{arccosh} \\
& \qquad \times (\overline{\mathrm{RR}} + 1)
\end{aligned}$$

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

Based on the presented methodology, a three-step search scheme (Fig. 3) was designed to determine the optimum weight distribution $\{w_j\}$ for each recording. "Optimum" was defined as leading to the minimum regression residual, r, of fitting the $[\mathrm{QT}, \overline{\mathrm{RR}}]$ data by any of the ten regression models. In the first step, we calculated the parameters α and β of $[\mathrm{QT}, \overline{\mathrm{RR}}]$ regression, with $\overline{\mathrm{RR}}$ corresponding to the initial EW profile, for each recording and each regression model. With such α and β coefficients, the global optimization algorithm was applied to determine the weight sequence $\mathbf{w}$ leading to the lowest residual. Finally, the regression coefficients α and β were recalculated with $\overline{\mathrm{RR}}$ obtained by averaging according to the globally optimized weights $\mathbf{w}$. A new weight distribution associated with the obtained α and β values might have been computed again, repeating this procedure as an iterative process. However, no significant improvement (below 3% in a test group of 100 patients) was observed in the residual reduction when adding more iterative steps.

Eventually, ten different combinations of weights and regression coefficients were determined for each recording, each corresponding to one of the regression models. Finally, a unique pattern of optimum averaging was identified by choosing the regression model that led to the minimum residual.

3) Determination of the Effective RR History: In addition to the optimum profile of RR averaging that best explains the QT adaptation to HR changes, as described in the previous section, we estimated the length L_{90}^T of a window in which preceding cardiac cycles have an effective influence on QT. The L_{90}^T value

was defined by a threshold η applied to the cumulative sum $H(j)$ of individually optimized weights

$$H(j) = \sum_{k=-N+1}^{j} w_k, \quad j = -N+1, \ldots, 0.$$

The threshold η was experimentally set at 10% of the total sum of weights, i.e., $\eta = 0.1$. The minimum beat index j_0 for which $H(j_0) \geq \eta$ was identified and L_{90}^T was calculated as

$$L_{90}^T = \mathrm{RR}_{\mathrm{mean}} \cdot (-j_0)$$

where $\mathrm{RR}_{\mathrm{mean}}$ is the mean RR interval of the 24-h recording measured in seconds. Thus, L_{90}^T represents the time in seconds from j_0 to the end of the window (Fig. 4).

4) Heart Rate Correction: Each of the ten regression models was converted into a heart rate correction formula projecting the QT interval onto the standard level of $\overline{\mathrm{RR}} = 1$ s. The corrected QTc_i interval of ith beat was defined dependent on the type of the optimum regression model selected for the recording. Simple formula conversions were used to derive the following heart rate correction formulas:

$$\begin{aligned}
\text{Lin:} \quad & \mathrm{QTc} = \mathrm{QT} + \xi\,(1 - \overline{\mathrm{RR}}) \\
\text{Hyp:} \quad & \mathrm{QTc} = \mathrm{QT} + \xi\,\left(\frac{1}{\overline{\mathrm{RR}}} - 1\right) \\
\text{Par:} \quad & \mathrm{QTc} = \frac{\mathrm{QT}}{\overline{\mathrm{RR}}^{\xi}} \\
\text{Log:} \quad & \mathrm{QTc} = \mathrm{QT} - \xi\,\ln(\overline{\mathrm{RR}}) \\
\text{Shlog:} \quad & \mathrm{QTc} = \ln(e^{\mathrm{QT}} + \xi\,(1 - \overline{\mathrm{RR}})) \\
\text{Exp:} \quad & \mathrm{QTc} = \mathrm{QT} + \xi\,\left(e^{-\overline{\mathrm{RR}}} - \frac{1}{e}\right) \\
\text{Atan:} \quad & \mathrm{QTc} = \mathrm{QT} + \xi\,(\mathrm{arctag}(1) - \mathrm{arctag}(\overline{\mathrm{RR}})) \\
\text{Htan:} \quad & \mathrm{QTc} = \mathrm{QT} + \xi\,(\mathrm{tgh}(1) - \mathrm{tgh}(\overline{\mathrm{RR}})) \\
\text{Ahs:} \quad & \mathrm{QTc} = \mathrm{QT} + \xi\,(\mathrm{arcsinh}(1) - \mathrm{arcsinh}(\overline{\mathrm{RR}})) \\
\text{Ahc:} \quad & \mathrm{QTc} = \mathrm{QT} + \xi\,(\mathrm{arccosh}(2) - \mathrm{arccosh}(\overline{\mathrm{RR}} + 1)).
\end{aligned}$$

As the purpose of any heart rate correction formula is to obtain QTc values independent of heart rate, the individually selected formula was optimized by the golden cut search [30] for the value of parameter ξ that satisfies the equation $r_p(\xi) = 0$, where $r_p(\xi)$ is the Pearson correlation coefficient between QTc and $\overline{\mathrm{RR}}$.

5) QT/RR Hysteresis of Abrupt Rate Changes: Results obtained from the described analysis have the drawback of being estimated across the complete recording. In many cases, the weights $\{w_j\}$ are mainly estimated from rhythm episodes containing no important RR changes and from fewer episodes of abrupt heart rate changes, which predominantly contribute to the QT/RR hysteresis. Consequently, the estimation of the RR interval weight profile may be biased by noise and inaccuracies in QT and RR interval measurement. For that reason, we also investigated the QT adaptation during substantial transitions of cardiac rhythm. The main purpose was to compare these two assessments of QT/RR hysteresis in each recording.

Firstly, ECG episodes of sustained heart rate changes had to be individually determined. A signal containing RR values $(\mathrm{RR}(n))$, interpolating RR_i with cubic splines at sampling frequency of 1 Hz, was generated. This $\mathrm{RR}(n)$ signal was low-pass filtered, $\mathrm{RR}_f(n)$, with a Butterworth second-order

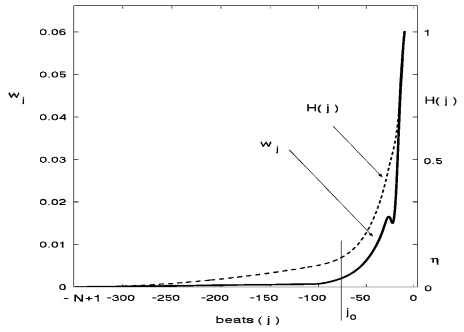

Fig. 4. Determination of the effective window length for RR averaging, considering a threshold η defined to cover 90% of the sum of weights. The solid line shows the weight distribution w_j, the corresponding cumulative sum $H(j)$ is shown in the dashed line.

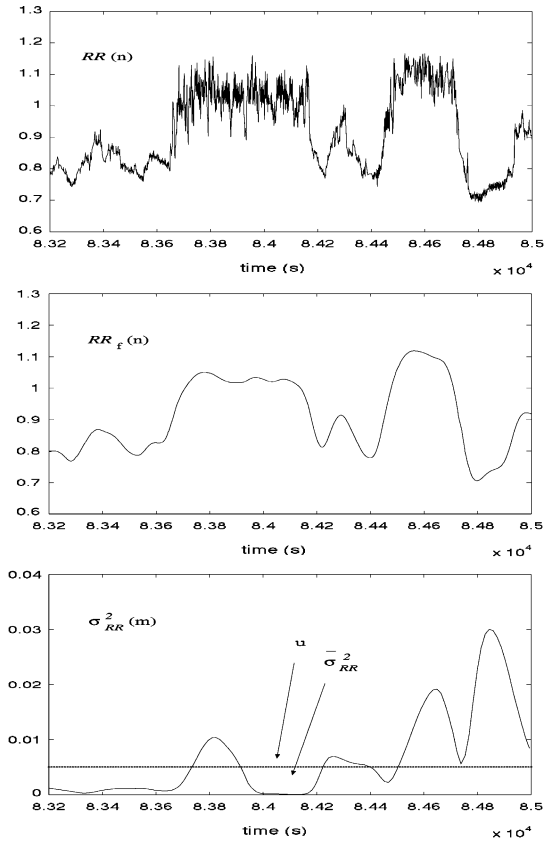

Fig. 5. For identification of ECG segments presenting abrupt HR changes, the RR signal was interpolated and sampled at 1 Hz (top). The obtained signal was low-pass filtered with a cutoff frequency of 0.03 Hz (middle). The variance of the new signal was measured in 300-s segments in 15-s steps (bottom). A threshold $u = 1.5\overline{\sigma}^2_{\mathrm{RR}}$, i.e., 1.5 times the rms of variance, was applied and beats marking final extremes of segments with variance above u were selected.

filter (cutoff frequency 0.03 Hz) to prevent the detection of only transient RR interval variations. On the $\mathrm{RR}_f(n)$ signal, the variance was measured in 300-s segments shifted in 15-s steps. A series $\sigma^2_{\mathrm{RR}}(m)$ was obtained in this way, where m is the consecutive number of a 300-s segment. Subsequently, a threshold u was applied to the $\sigma^2_{\mathrm{RR}}(m)$ series considering the complete 24-h recording (Fig. 5). The threshold u was selected individually for each recording, since the range of RR variations differed substantially among subjects. Experimentally we chose u equal to 1.5 times the root mean square (rms) of $\sigma^2_{\mathrm{RR}}(m), \overline{\sigma}^2_{\mathrm{RR}}$, and positions of cardiac cycles were

identified corresponding to preceding 300-s segments in which $\sigma^2_{\mathrm{RR}}(m) \geq 1.5\overline{\sigma}^2_{\mathrm{RR}}$.

The same procedure as previously described for the entire 24-h recording was carried out using only these identified cardiac cycles. For each patient, a new weight distribution characterizing the QT interval response to abrupt RR interval changes was determined and compared with that obtained from the complete recording. For the purposes of such a comparison, the characteristics L_{90} were compared, denoted L^T_{90} when calculated over the complete 24-h recording and L^A_{90} when calculated in abrupt rate change segments. Additionally, characteristics $L^T_{25}, L^A_{25}, L^T_{40}, L^A_{40}, L^T_{50}$, and L^A_{50}, representing 25%, 40%, and 50% of the complete QT/RR adaptation were evaluated using the same principles.

In order to investigate situations of substantial rate transitions, we focused the comparison 24 h and abrupt rate changes on the group of the 100 patients presenting sharpest rhythm alterations (denoted G_{high}), as assessed by highest $\overline{\sigma}^2_{\mathrm{RR}}$ values, and contrasted the obtained results with the ones found when analyzing the same number of patients presenting smoothest RR changes (G_{low}). Only 100 subjects were considered in each group because the distribution of $\overline{\sigma}^2_{\mathrm{RR}}$ was concentrated around the mean and, consequently, considering larger groups would lead to a similar analysis in the two groups.

6) QT/RR Hysteresis at Day and Night-Times: When investigating the QT interval dependence on heart rate changes and the time lag present in the adaptation, it is necessary to consider the long-term autonomic balance influencing both QT and RR measurements.

In order to assess the autonomic nervous system influences, the QT-RR analysis developed for the 24-h recording was carried out as well over different circadian periods. More precisely, the QT/RR hysteresis profile and duration were estimated separately at day-time (between 9 and 18 h) and at night-time (0–6 h).

D. Clinical Study

1) Risk Markers: The following variables were considered as potential risk stratifiers:

- L^T_{90}, as described in Section II-C3.
- r_{opt}, defined as the global regression residual of the complete 24-h $[\mathrm{QT}_i, \overline{\mathrm{RR}}_i]$ fit, using the optimum individually determined regression model and the optimum weight distribution.
- Inverse beat-velocity λ, defined based on the individually specific cumulative sum of weights $H(j)$, as defined in Section II-C3. An exponential model was fitted: $H(j) = e^{Aj+B}$ (correlation values above 0.91 confirmed the suitability of the fit) and λ was defined as the time constant of the model, $\lambda = 1/A$.
- $\overline{\mathrm{QTc}}$, corrected QTc interval as described in Section II-C4 averaged over the 24-h recording.
- *Slope*, coefficient α of the parabolic $[\mathrm{QT}_i, \overline{\mathrm{RR}}_i]$ fit, with $\overline{\mathrm{RR}}_i$ computed using the optimum weight distribution of the parabolic regression model.
- Lag L^A_{90} expressed in seconds and its equivalent M^A_{90} expressed in beat counts.
- SD, standard deviation of the RR interval series computed over the 24 h, providing a measure of heart rate variability (see [31]). (Note that only normal to normal intervals were accepted when initially constructing the RR interval series).

2) Statistics: Continuous variables derived from individual recordings were compared for recordings of patients on amiodarone and on placebo, and for recordings of patients with and without arrhythmic death during follow-up. Student's two-tail two-sample t-test assuming unequal variances was used. Kaplan-Meier probability curves of arrhythmic death-free survival were evaluated in patient groups stratified by the median value of each risk stratifier. The cumulative probabilities of arrhythmic death were compared by the log-rank test. A p-value < 0.05 was considered as statistically significant.

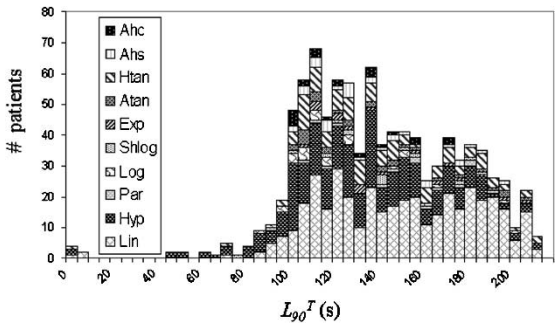

Fig. 6. Histogram of L^T_{90} values for patients in the study population. In each column, patients are grouped by their optimum regression model.

TABLE I
RELATION BETWEEN REGRESSION MODEL AND L^T_{90} (SECONDS), $\overline{\sigma}^2_{\mathrm{RR}}$ (SECONDS^2), MEAN RR INTERVAL (MS), SD (MS), AND r_{opt} (MS) AVERAGED OVER RELATED PATIENTS

Model	L^T_{90}	$\overline{\sigma}^2_{RR}$	mean RR	SD	r_{opt}	# patients
Lin	150.06	1.123	885.74	101.96	18.03	405
Hyp	131.94	1.021	889.55	90.16	17.37	264
Par	148.09	0.975	880.77	96.14	19.69	15
Log	124.42	0.957	793.62	98.09	11.44	28
Shlog	141.17	1.241	895.33	112.32	12.18	13
Exp	142.92	1.838	1133.22	135.87	16.56	18
Atan	139.39	1.081	880.63	107.53	12.11	30
Htan	141.51	1.142	946.39	99.97	17.02	110
Ahs	136.69	1.364	923.20	103.76	13.81	33
Ahc	127.32	1.149	852.42	110.14	12.21	23

III. RESULTS

A. QT Adaptation to RR Changes

The mean of L^T_{90} over the whole study group was 2.36 min. This confirms that QT interval duration is influenced by heart rate changes occurring during previous min, although the degree of influence of previous RR intervals decreases rapidly with increasing time-lag. Very significant differences were found in the individual optimum window durations. While in 21% of the patients, more than 175 s were required to accurately explain the QT dependence on the previous cardiac cycles, in 25% of patients the "QT lag" was shorter than 115 s. The proportions of the L^T_{90} distribution are shown in Fig. 6. The intersubject variability in the adaptation times was studied together with the range of RR interval values registered in each recording. Results, grouped by the optimum regression model, are presented in Table I. A noticeable number of patients exhibited the linear model as the optimum, while the parabolic

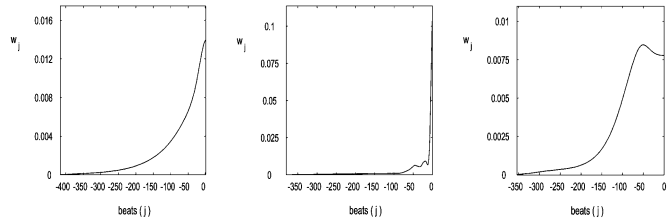

Fig. 7. Optimum window trend shapes for three different patients of the study group. The corresponding L_{90}^{T} values were: 2.02 min (168 beats), 1.97 min (150 beats), and 2.06 min (146 beats), respectively. Substantial intersubject variability in QT/RR adaptation is obvious.

TABLE II
TIME LAGS (A FOR ABRUPT RATE CHANGES, T FOR 24-h ANALYSIS) ESTIMATED IN THE TWO EXTREME GROUPS DESCRIBED IN THE TEXT: G_{low} AND G_{high}, AND p-VALUES FROM T-TESTS FOR PAIRED SAMPLES

	G_{low}			G_{high}		
	A	T	p-value	A	T	p-value
L_{25}	15.35	13.26	0.076	23.06	15.88	10^{-6}
L_{40}	26.19	25.40	0.584	43.92	37.53	10^{-4}
L_{50}	35.67	35.74	0.968	61.25	57.67	0.027
L_{90}	119.49	123.13	0.164	158.87	160.21	0.301

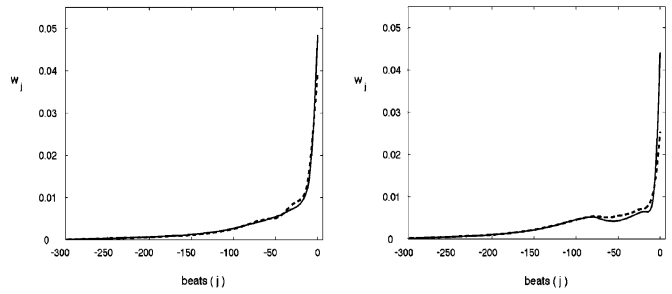

Fig. 8. (left) Mean optimum weight distributions averaged over G_{low} patients. The solid and dashed lines show the characteristics derived from 24-h and abrupt rate changes, respectively. (right) Corresponding weight distributions for the G_{high} group are shown. Note that normalization on the number of beats was carried out by interpolation in order to obtain averaged results.

model, traditionally used for correcting the QT interval, was much less frequent. However, a considerable number of patients had RR interval values only around 1 s where the behavior of linear and parabolic models is fairly similar.

A high intersubject variability was found not only in the QT interval adaptation time but also in the profile of QT interval adjustment, as observed in substantially different weight distributions obtained even for patients with similar adaptation times. Examples of optimum weight distributions are shown in Fig. 7.

Table II shows the comparison of the results obtained from the 24-h analysis with the ones obtained from episodes of sudden rate changes. In the G_{low} group, composed of patients with the smoothest RR transitions, the way QT adapts to sustained RR changes is similar to the one derived from the complete 24-h recording. However, in G_{high} L_{25}^{A} and L_{40}^{A} were significantly longer than L_{25}^{T} and L_{40}^{T}, with the differences between L_{50}^{A} and L_{50}^{T} being only marginal and the differences between L_{90}^{A} and L_{90}^{T} being negligible. Thus, in situations of substantial heart rate changes, where the repolarization adaptation can be estimated more reliably, the onset of the QT adaptation is significantly slower. These differences are shown in Fig. 8.

TABLE III
MEAN AND STANDARD DEVIATION VALUES FOR THE PARAMETERS DERIVED IN THE STUDY AND T-TEST RESULTS FOR SEPARATION OF PLACEBO AND AMIODARONE GROUPS. UNITS ARE: SECONDS FOR L_{90}^{T} AND L_{90}^{A}; MS FOR r_{opt}, $\overline{\mathrm{QTc}}$, AND SD; AND BEATS FOR λ AND M_{90}^{A}

	Placebo	Amiodarone	p-value
L_{90}^{T}	135.61 ± 31.57	145.94 ± 36.52	$1.1 \cdot 10^{-5}$
r_{opt}	13.816 ± 6.613	19.656 ± 9.280	$< 10^{-17}$
λ	49.44 ± 7.80	45.92 ± 8.02	$1.2 \cdot 10^{-10}$
$\overline{QTc}$	425.74 ± 38.45	444.15 ± 37.02	$1.6 \cdot 10^{-12}$
$Slope$	0.480 ± 0.187	0.543 ± 0.247	$2.8 \cdot 10^{-5}$
L_{90}^{A}	134.43 ± 32.16	143.70 ± 38.85	$1.6 \cdot 10^{-4}$
M_{90}^{A}	157.93 ± 37.44	149.57 ± 38.91	0.001
SD	100.61 ± 35.24	98.06 ± 33.22	0.273

The QT adaptation times studied separately during day and night hours revealed that a slightly faster adaptation occurs during the nocturnal period. This was confirmed by the different mean times required to achieve 90% adaptation, which were: 142.56 ± 33.00 s at day and 139.64 ± 36.65 s at night, $p = 0.106$. Despite the limited significance, these results agree with those derived from the analysis of abrupt rate changes: at night time, the cardiac rhythm is more stable than during the day and, thus, shorter time lags in the QT adaptation would be expected, what was confirmed by the above given results.

B. Clinical Comparisons

1) Univariate Analysis: Table III shows the comparison of the descriptors of QT/RR hysteresis in placebo and amiodarone treated subjects. As expected, a significantly prolonged QTc interval was observed in patients on amiodarone. Substantial differences were also found between the values of L_{90}^{T} and *Slope*, both being numerically greater in amiodarone-treated patients. The strongest separation between amiodarone and placebo treated groups was obtained with r_{opt}. The variable λ reflecting the inverse of the adaptation velocity also distinguished strongly the two groups. The variables measuring the adaptation lag in the QT response to abrupt heart rate changes were statistically significantly different in amiodarone and placebo, both when expressed in seconds, L_{90}^{A}, and when expressed in beat counts, M_{90}^{A}. This separation power shown by variables expressing QT adaptation times can not be exclusively attributed to mean heart rates found in placebo and amiodarone (72.36 bpm versus 62.78 bpm, $p < 10^{-17}$), since correlation values between mean HR and L_{90}^{T}, L_{90}^{A}, and M_{90}^{A} are 0.239, 0.301, and 0.296, respectively; however, the parameter λ showed stronger correlation with heart rate (0.664). HRV expressed by the SD index was not significantly different between placebo and amiodarone groups. When the separation placebo/amiodarone was assessed by the corresponding variables evaluated separately during day and night periods, the results in terms of significance did not differ considerably from the ones obtained for the 24-h evaluation.

Table IV shows the comparison of patients who did and did not suffer from arrhythmic death during follow-up. The r_{opt} variable differenciated arrhythmic death victims from others in the amiodarone group. While r_{opt} values were considerably larger in survivors on amiodarone, the values found in

TABLE IV
MEAN AND STANDARD DEVIATION VALUES FOR THE PARAMETERS DERIVED IN THE STUDY AND T-TEST RESULTS FOR SEPARATION OF PATIENTS WITH AND WITHOUT ARRHYTHMIC DEATH DURING FOLLOW-UP. UNITS ARE: SECONDS FOR L_{90}^{T} AND L_{90}^{A}; MS FOR $r_{\rm opt}$, $\overline{\rm QTc}$, AND SD; AND BEATS FOR λ AND M_{90}^{A}

	Placebo			Amiodarone		
	Survivors	Victims	p-value	Survivors	Victims	p-value
L_{90}^{T}	135.61 ± 31.67	135.72 ± 30.68	0.985	146.36 ± 35.84	135.67 ± 50.81	0.224
r_{opt}	13.787 ± 6.636	14.242 ± 6.375	0.735	19.879 ± 9.298	14.141 ± 7.006	0.009
λ	49.102 ± 7.592	54.341 ± 9.246	0.001	45.795 ± 7.806	49.085 ± 12.125	0.088
$\overline{QTc}$	424.45 ± 36.96	444.53 ± 53.24	0.010	444.87 ± 37.01	426.60 ± 33.63	0.040
$Slope$	0.478 ± 0.187	0.504 ± 0.199	0.498	0.548 ± 0.248	0.437 ± 0.199	0.063
L_{90}^{A}	134.46 ± 32.09	133.91 ± 33.78	0.933	143.79 ± 38.37	141.38 ± 50.49	0.797
M_{90}^{A}	156.98 ± 36.72	171.65 ± 45.38	0.053	148.84 ± 37.57	167.67 ± 62.55	0.044
SD	101.49 ± 35.46	87.82 ± 29.45	0.056	98.39 ± 33.38	89.95 ± 28.82	0.291

arrhythmic death victims on amiodarone were similar to those obtained in all patients on placebo, suggesting that the evaluation might be potentially used to test amiodarone efficacy. Similar results were found with the variable *slope*, although differences were less significant. Victims of arrhythmic death on amiodarone had even lower *slope* values than those on placebo. The parameter λ showed a very strong separation of victims and survivors of arrhythmic death, both on placebo and amiodarone, indicating that the lag hysteresis phenomenon was more accentuated among patients who suffered arrhythmic death. $\overline{\rm QTc}$ also was significantly different in arrhythmic death victims and survivors. However, while victims had longer QTc on placebo, they had shorter QTc on amiodarone. In respect of the QT interval adaptation to abrupt RR interval changes, the variable measuring the adaptation time in beats, M_{90}^{A}, could identify patients at high risk of arrhythmic death. This suggests that the way in which QT interval reacts during major changes in heart rate might be important in arrhythmo-genesis. Finally, results obtained with SD index confirmed that heart rate variability is reduced in high-risk survivors of acute myocardial infarction, although the significance was only moderate in the placebo group and even lower on amiodarone.

2) Survival Analysis: Evaluating Kaplan-Meier event probabilities, $r_{\rm opt}$ proved to be a meaningful risk stratifier among patients on amiodarone, but not among those on placebo. In the amiodarone group, the $r_{\rm opt}$ median value of 14.52 ms led to highly significantly different event probabilities in both stratas of the population ($p = 0.0065$, Fig. 9). *slope* values also risk stratified patients on amiodarone, although less significantly ($p = 0.0152$). In the amiodarone group, but not among patients on placebo, the parameter M_{90}^{A}, expressing beat delay, led to statistically different probabilities of arrhythmic death-free survival during follow-up ($p = 0.0063$). Survival analysis using the λ parameter led only to borderline significance ($p = 0.0722$ on placebo and $p = 0.0749$ on amiodarone).

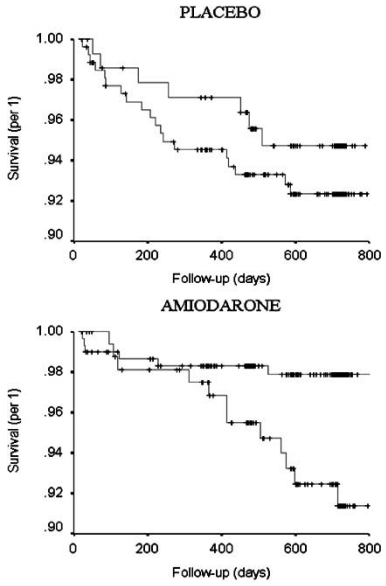

Fig. 9. Kaplan-Meier event probability curves (arrhythmic end point) for patient groups with $r_{\rm opt}$ above and below the median value.

IV. DISCUSSION

A. Result Interpretation and Relation to Previous Studies

Different adaptation patterns of the QT/RR hysteresis were found for different patients in the study together with very distinct QT/RR adaptation times. When investigating the QT/RR adaptation in rhythm episodes of considerable RR interval changes, the hysteresis phenomenon was even more evident. In the case of less marked RR interval changes, the QT/RR hysteresis could be potentially biased by measurement precision. This would suggest to investigate the hysteresis during RR interval variations provoked in a controlled way.

The principal results of this study agree well with previous observations [6] based on recordings made during abrupt changes in pacing rate. Lau *et al.* found that the QT interval adapted to a sudden sustained change in heart rate in two phases. An initial adaptation covering 50% of the QT change was completed in <1 min (in our assessment, the mean value of L_{50}^{A} was around 50 s) and it was followed by a secondary adaptation phase that took several minutes to complete (mean value of $L_{90}^{A} > 2$ min in our analysis). From a clinical point of view, the interval of the initial tens of seconds to one minute seems to be most important in the majority of cases. The observation that both the duration and profile of QT/RR hysteresis is highly individual has not been previously reported. It is, however, consistent with the observation [28] that stabilized, i.e., hysteresis-free, QT/RR patterns show high intersubject variability together with high intraindividual stability.

The analysis of the QT/RR relationship regarding the influence of several past RR intervals has been reported in different works. Porta *et al.* [32] proposed a model to quantify the dependence of ventricular repolarization duration on heart rate and other immeasurable factors. It is, however, restricted to steady-state conditions, when there are no large changes in cardiac rhythm. The purpose of our study was to investigate QT dependence on past cardiac cycles over 24-h ambulatory recordings and also focusing on segments of such recordings where abrupt rate changes occur. A different approach for studying the rate dependency of QT interval was proposed by Badilini *et al.* [33]. They provided a method for selection of cardiac beats preceded by stable heart rate and, over those hysteresis-free segments, a selective beat averaging is developed to analyze the QT/RR relationship, separately over different circadian periods. Rather than considering only stable episodes, our study shows that analysis of QT lag in unstable episodes is of considerable importance. Other contributions to the QT/RR analysis include the work by Lande *et al.* [34], who showed that the QT/RR relationship is different when only hysteresis-free segments are selected and when no beat selection is made. Kligfield *et al.* [35] studied QT interval-heart rate relation during exercise, considering measurements obtained at the end of different exercise stages to avoid hysteresis, and, similar to many other studies, Karjalainen *et al.* [36] investigated the relation between QT intervals and distinct levels of heart rate in resting electrocardiograms.

The analysis presented in our study also provided novel descriptors of QT/RR hysteresis and relationship that suggested that amiodarone not only prolongs the QT interval, but also modifies the entire dynamic QT/RR relationship in cardiac patients. The series of the introduced QT/RR descriptors, as well as the individually corrected $\overline{\mathrm{QTc}}$ interval, suggest that amiodarone has different effects on ventricular repolarization in survivors of myocardial infarction who do and do not suffer from arrhythmic death while on therapy. Hence, the observations seem potentially suitable for a prospective assessment of the prophylactic efficacy of class III antiarrhythmic drugs.

The discriminative power of the characteristics derived from the QT/RR analysis was improved when concentrating on the assessment within ECG segments with more clearly visible RR interval changes. As already discussed, it seems that the extent of QT/RR hysteresis during marked variations in heart rate improves signal to noise ratio that is driven by measurement accuracy. We have also observed an improved assessment in risk stratification when expressing the QT/RR adaptation lag in cardiac cycles instead of in seconds. However, it is not obvious whether this observation is independent of heart rate, which tends to be slower in low risk subjects.

Finally, the study has confirmed previously observed [28] individual-specific QT/RR relationship, which should be taken into account when correcting the QT interval for heart rate. Calculation of QTc values should be done considering the individual QT dependence on past RR intervals, unless evaluation is made over selected segments with stable heart rate. Also, the correction formula needs to be derived from an adequate $[\mathrm{QT}, \overline{\mathrm{RR}}]$ pattern. Any generalized approach will clearly over- or under-estimate the true and individual QT/RR relationship and will lead to imprecise QTc values.

B. Study Limitations and Future Extensions

Automatic measurement of the QT and RR intervals using a commercial electrocardiograph may well lead to inaccuracies in the data. However, careful visual verification for gross delineation errors and subsequent manual correction, where needed, was applied. Moreover, we investigated changes in QT interval that are not affected by a uniform bias.

In the initial approach (fixed window RR averages), only the parabolic model was considered. This arbitrary choice might have biased the following steps of the method. However, we repeated the first part of the analysis considering all the ten regression models (described in Section II-C2) and measured the maximum difference between the optimum window length associated to the parabolic model and any of the other nine optimum values. These differences were below 4 s for more than 90% of the recordings (5.8 s on average).

Ten different biparametric regression models were used to fit $[\mathrm{QT}_i, \overline{\mathrm{RR}}_i]$ data pairs. These models were chosen to cover a physiologically plausible spectrum of QT/RR patterns. Other regression models with more parameters might have also been considered. In such a case, however, other additional considerations would have been required since multiparametric models may easily be influenced by data outliers.

The analysis of the QT interval dynamics that has been developed in our study accounts for the influences of a history of previous RR intervals on each QT measurement. However, there are other factors apart from heart rate that also affect the dynamics of the QT interval [32]. The study could be improved by generalizing the proposed regression models so that each QT measurement is related to a history of both previous RR intervals and other sources independent of heart rate.

Our study investigated the hysteresis phenomenon considering both 24-h recordings and selected segments with abrupt heart rate changes. In other studies, different approaches to assess the QT/RR relationship have been proposed, which provide methods for the determination of hysteresis-free segments [33].

A truly comprehensive assessment of the effects of drug therapy needs to be based on at least two recordings per patient, including one before the start of treatment, and another while on therapy. Unfortunately, the prerandomization recordings of the EMIAT trial were not available for the purposes of this study.

Finally, the study was performed using recordings of a large population. However, the number of arrhythmic death victims (endpoint used in the study) was relatively small. This imposes some limitations on the statistical comparisons.

V. Conclusion

The study introduced a new method to evaluate the duration and profile of the so-called QT/RR hysteresis. On average, RR measurements contained in a window of more than 2 min were found to effectively contribute to QT variations, although the time and profile describing the QT/RR adaptation are highly individual. In ambulatory recordings, a focused analysis on areas with sharp RR changes clearly improves the estimation of QT/RR hysteresis. The whole adaptation of ventricular repolarization is modified by amiodarone and the study suggests a link between this drug action and its antiarrhythmic efficacy.

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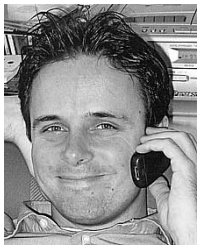

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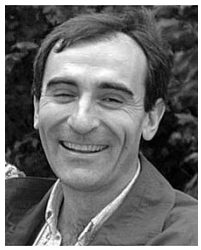

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