Dynamic Repolarization Assessment and Arrhythmic Risk Stratification

E. Pueyo[1], M. Malik[2] and P. Laguna[1]

[1] Aragón Institute for Engineering Research (I3A), University of Zaragoza, Spain
[2] Department of Cardiological Sciences, St. George's Hospital Medical School, London, UK

Abstract— **A dynamic model is proposed to study the relationship between the QT and RR intervals of the surface electrocardiogram. The model accounts for the influence of a history of previous RR intervals on each QT, considering that such an influence may vary along the recording time. For identification of the model parameters, an adaptive methodology that uses the regularized Kalman filter is developed. A set of risk markers are derived from the estimated model parameters and they are tested on ambulatory recordings of post-myocardial infarction patients randomized to treatment with amiodarone or placebo. The results of our study show that amiodarone substantially modifies the QT interval response to heart rate changes. Furthermore, the way amiodarone acts on QT adaptation allows to identify patients in which treatment is being effective and separate them from those in which it is not and, consequently, are at higher risk of suffering from arrhythmic death.**

Keywords— **Electrocardiogram, repolarization, QT/RR, arrhythmic death.**

I. Introduction

Numerous studies have pointed out the tight relationship that exists between the QT interval, which expresses the entire duration of ventricular depolarization plus repolarization, and the RR interval, which is the inverse of heart rate. It has been suggested that characteristics derived from such a relationship can be used to detect or predict states associated with high arrhythmic risk [1]. The use of long-term electrocardiographic (ECG) recordings is recommended for risk stratification studies based on repolarization analysis [2]. Those types of recordings contain sharp changes in heart rate and, consequently, QT hysteresis needs to be considered when exploring the QT/RR relationship. Hysteresis refers to the fact that the QT interval is not able to follow the RR interval changes instantaneously but there is a time lag in the adaptation.

In [3] a method was developed to investigate QT changes after RR in ambulatory recordings of post-myocardial infarction (MI) patients of the EMIAT database that were followed-up during a mean time of two years. Using the proposed method, several indices characterizing QT/RR adaptation, including the time that QT needs to follow RR changes, were evaluated. Those indices showed strong capacity to discriminate between patients at low and high risk of arrhythmic death while on therapy with amiodarone.

Although in [3] the time and profile of QT adaptation were considered to be specific of each patient, it was assumed that those characteristics did not vary along the recording time. In order to account for the dynamic properties of the QT/RR relationship, a time-variant methodology is used in the present paper that extends the one described in [3]. Based on that method we have investigated QT dependence on RR over the same recordings of the EMIAT database and we have derived new markers characterizing QT dynamicity. The potential of those markers for arrhythmic risk stratification is presented.

II. Methods

A. Population and data measurements

The study population comprises 939 patients of the EMIAT database. Patients were survivors of acute MI randomized to treatment with amiodarone or placebo. All of them were aged less than 75 years and had a left ventricular ejection fraction (LVEF) inferior to 40%. Meaningful clinical data were available in 866 patients who were followed-up during a mean time of 620 days (±176). Of these patients, 404 received placebo and 462 were treated with amiodarone. There were 26 arrhythmic deaths in the placebo group and 18 in the amiodarone group.

The electrocardiographic recordings were obtained one month after randomization. All of them were 24-hour Holter ECGs with 3 recorded leads. In each lead, individual QT and RR intervals were measured using the commercial software of Pathfinder 700 Holter system (Reynolds Medical, Hetford, UK). These measurements where checked by an expert and, where necessary, they were corrected manually or deleted. For each patient and lead, the number of cardiac cycles where it was possible to determine both the RR measurement and the QT measurement were counted. The lead that presented the largest number of accepted beats was selected for further analysis. Potential outliers in the RR and QT series were removed by applying a procedure based on a Median Absolute Deviation (MAD) filter. The clean series were interpolated linearly at a sampling fre-

T. Jarm, P. Kramar, A. Županič (Eds.): Medicon 2007, IFMBE Proceedings 16, pp. 74–77, 2007
www.springerlink.com

quency of 1 Hz and low-pass filtered (0.05 Hz) to avoid the sympathetic and parasympathetic influences of the Autonomic Nervous System. The final series are denoted by $x_{RR}(n)$ and $y_{QT}(n)$, respectively.

B. Model Composition

The QT/RR relationship is modeled by considering a nonlinear system with memory that has $x_{RR}(n)$ as its input signal and $y_{QT}(n)$ as its output. The system is assumed to be composed of two blocks (see Fig. 1). The first block is a linear time-variant FIR filter of order N:

$$\mathbf{h}(n) = \left[h_0(n) \ \ldots \ h_{N-1}(n)\right]^T \in \Re^{N\times 1} \quad (1)$$

whose output is $z_{\overline{RR}}(n) = \mathbf{h}^T(n) \cdot \mathbf{x}_{RR}(n)$, where

$$\mathbf{x}_{RR}(n) = \left[x_{RR}(n) \ \ x_{RR}(n-1) \ \ldots \ x_{RR}(n-N+1)\right]^T . \quad (2)$$

The second block is a time-varying nonlinearity represented by a first-order polynomial:

$$g\left(z_{\overline{RR}}(n), \mathbf{a}(n)\right) = \mathbf{a}^T(n)\, \mathbf{z}_{\overline{RR}}(n) \quad (3)$$

with $\mathbf{a}(n) = \left[a_0(n) \ \ a_1(n)\right]^T \in \Re^{2\times 1}$ and $\mathbf{z}_{\overline{RR}}(n) = \left[1 \ \ z_{\overline{RR}}(n)\right]^T \in \Re^{2\times 1}$. The order of the linear filter is defined as N=50 based on the results reported in [3] where it is shown that the initial 40 - 50 RR intervals previous to each QT are the most clinically relevant.

The objective of our study is to identify the described system only from the knowledge of the input and output signals. In order to guarantee uniqueness in the determination of the filter weights and the polynomial coefficients, a normalization constraint on the weights is imposed: $\mathbf{h}^T(n) \cdot \mathbf{1} = 1, \ \forall\, n$, with $\mathbf{1}$ denoting the $N \times 1$ vector of ones. Also, constraints referred to weights being positive are introduced so as to be able to derive physiologically plausible interpretations. With all the above mentioned constraints, the output of the first block can be interpreted as a weighted-averaged RR measurement (which is optimally defined at each time n), while the output of the second block expresses the evolution of the QT interval as a function of such an averaged RR measurement. Finally, the output of the global system is considered to be contaminated with some additive white noise v(n) that can include delineation errors and/or inaccuracies due to modeling assumptions:

$$y_{QT}(n) = \mathbf{a}^T(n)\, \mathbf{z}_{\overline{RR}}(n) + v(n) . \quad (4)$$

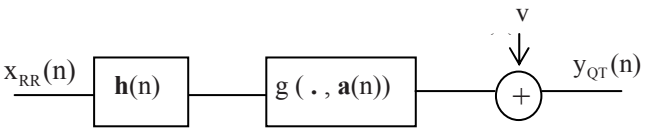

Fig. 1 Block diagram of the dynamic model proposed in this study.

C. System identification

State-space formulation

Denoting

$$\boldsymbol{\theta}(n) = \left[a_0(n) \ \ a_1(n)h_0(n) \ \ldots \ a_1(n)h_{N-1}(n)\right]^T \quad (5)$$

$$\mathbf{s}(n) = \left[1 \ \ x_{RR}(n) \ \ldots \ x_{RR}(n-N+1)\right]^T , \quad (6)$$

the output $y_{QT}(n)$ can be expressed as

$$y_{QT}(n) = \mathbf{s}^T(n)\boldsymbol{\theta}(n) + v(n) \quad (7)$$

where $\mathbf{s}(n)$ is the known observation vector and $\boldsymbol{\theta}(n)$ is the parameter vector to be estimated, both of dimension $(N+1)\times 1$. In addition to the observation equation (7), a second equation describing the time-varying nature of the system state is incorporated:

$$\boldsymbol{\theta}(n+1) = \boldsymbol{\theta}(n) + \mathbf{w}(n) . \quad (8)$$

The two equations (7) and (8) constitute a state-space representation of the system to be identified. In such a representation, the noises v(n) and $\mathbf{w}(n)$ are assumed to be uncorrelated zero-mean white processes with the variance of v(n) denoted by $\sigma_v^2(n)$ and the covariance of $\mathbf{w}(n)$ denoted by $\mathbf{Q}_w(n)$. The initial state of the system, $\boldsymbol{\theta}(0)$, is assumed to be uncorrelated with v(n) and $\mathbf{w}(n)$. The mean $\boldsymbol{\mu}_{0,\theta}$ of $\boldsymbol{\theta}(0)$ is defined using equation (5) and vectors $\boldsymbol{\mu}_{0,h}$ and $\boldsymbol{\mu}_{0,a}$ initially defined employing simple fitting procedures applied to the initial samples of the data series. The covariance matrix $\boldsymbol{\Pi}_{0,\theta}$ of $\boldsymbol{\theta}(0)$ is taken as the identity matrix.

Kalman filter with regularization

Estimation of the system vector $\boldsymbol{\theta}(n)$ is performed utilizing the Kalman filter (KF). The Kalman Filter is a linear adaptive MMSE filter that is able to deal with nonstationary environments, which are the type of environments we encounter when analyzing the QT/RR relationship over ambulatory recordings.

Direct application of KF to our formulated problem implies that, at each time n, N+1 parameters need to be estimated from a unique observation, as it can be observed from equation (7). In order to make the solution more robust

against noise or imprecision that can be present at the output $y_{QT}(n)$, regularization is incorporated into the problem. This means that additional a priori information on the solution is added. This is performed in our study by augmenting the observation equation (7) as described next:

$$\tilde{\mathbf{y}}_{QT}(n) = \tilde{\mathbf{S}}^{T}(n)\,\boldsymbol{\theta}(n) + \tilde{\mathbf{v}}(n) \tag{9}$$

where

$$\tilde{\mathbf{y}}_{QT}(n) = \begin{bmatrix} y_{QT}(n) \\ \mathbf{0} \end{bmatrix}, \tilde{\mathbf{S}}(n) = \begin{bmatrix} \mathbf{s}^{T}(n) \\ \beta(n)\,\mathbf{D}(n) \end{bmatrix}, \tilde{\mathbf{v}}(n) = \begin{bmatrix} v(n) \\ \mathbf{v}'(n) \end{bmatrix} \tag{10}$$

In equation (10), $\mathbf{0}$ denotes the $N \times 1$ vector of zeros and $\beta(n)$ is a scalar called regularization parameter, which is selected using the so-called L-curve criterion [4]. The matrix $\mathbf{D}(n)$ is defined so as to force the filter weights follow a relation close to an exponential one. That selection is based on our experience about QT dependence on RR [3] and, in any case, the strength put on that type of smoothing is determined along with the state estimation. The noise $\mathbf{v}'(n)$ is a fictitious zero-mean noise uncorrelated with $\boldsymbol{\theta}(n)$ and $v(n)$ and with covariance matrix taken as the identity.

In the application of the KF, the variance $\sigma_v^2(n)$ of the measurement noise $v(n)$ and the covariance $\mathbf{Q}_w(n)$ of the process noise $\mathbf{w}(n)$ are estimated following the approach proposed in [5].

Constraints

With the objective of having an estimate of $\boldsymbol{\theta}(n)$ satisfying the constraints described in section II.B, the constraint space Ω is built and the unconstrained solution $\hat{\boldsymbol{\theta}}(n)$ is projected onto it. Ω is defined by the condition that all of the elements of the estimated state vector, except the first one, have the same sign. This guarantees that the estimated weights are positive. Once the projection

$$\hat{\hat{\boldsymbol{\theta}}}(n) = \arg \min_{\boldsymbol{\theta}(n) \in \Omega} \left\{ \left(\breve{\boldsymbol{\theta}}(n) - \hat{\boldsymbol{\theta}}(n) \right)^{T} \left(\breve{\boldsymbol{\theta}}(n) - \hat{\boldsymbol{\theta}}(n) \right) \right\} \tag{12}$$

is obtained, the constrained solution is renamed as $\hat{\boldsymbol{\theta}}(n)$. Estimates $\hat{\mathbf{h}}(n)$ and $\hat{\mathbf{a}}(n)$ are readily derived from $\hat{\boldsymbol{\theta}}(n)$.

D. Clinical markers

A number of indices are proposed for clinical comparisons. Some of those indices are defined from the variable $L_{90}(n)$ that measures the time required by the QT interval to complete 90% of its adaptation in response to RR changes. The variable $L_{90}(n)$ is calculated at each instant n using the weight profile $\hat{\mathbf{h}}(n)$ estimated in II.C [5]. The proposed indices are $L_{90,acc}$, $L_{90,dec}$ and $L_{90,sta}$, which are defined as the mean of $L_{90}(n)$ in response to heart rate accelerations, decelerations and stable rate periods, respectively. In each recording, those types of periods are identified following the approach proposed in [5].

Other indices are defined from the slope of the line that fits the $\left[y_{QT}(n), z_{\overline{RR}}(n) \right]$ data in small neighborhoods around each value of $z_{\overline{RR}}(n_0)$. The proposed markers are s_{acc}, s_{dec} and s_{sta}, which are calculated as the mean of the estimated $\hat{a}_1(n)$ in periods of accelerating, decelerating and stable rate, respectively.

III. Results and Discussion

A. Dynamic QT adaptation

Evaluation of QT lag behind RR changes revealed substantial differences along the 24-hour recording. In mean over recordings, the time required by the QT interval to complete 90% of the adaptation was $L_{90,dec}$ = 2.1 min when measured after a heart rate deceleration, $L_{90,ace}$ = 1.6 min after a rate acceleration, and $L_{90,sta}$ = 1.9 min under stable rate conditions.

The slope s described in section II.D was as well evaluated in episodes of decelerating, accelerating and stable heart rate. The mean slope values were s_{dec} = 0.152, s_{acc} = 0.135 and s_{sta} = 0.127, respectively.

The results obtained in our study corroborate the hypothesis that QT dependence on RR is not constant along the recording time but such a dependence changes in response to heart rate variations. Specifically, we found that QT adaptation after a sudden rate acceleration is more rapid than after a stable or a decelerating rate period. This can be explained by the fact that readjustment of cell mechanisms needs to be completed faster after a heart rate acceleration so as to avoid beat overlapping.

B. Clinical risk stratification

The risk markers described in section II.D were separately assessed in the placebo and amiodarone arms. In each of the two arms, independent analysis was performed for the group of patients who suffered arrhythmic death while on therapy and the group of those who survived. Results are presented in Table I. It can be observed that survivors treated with amiodarone have prolonged QT adaptation times as compared to those treated with placebo, either when the adaptation time is measured in accelerating ($L_{90,acc}$), decelerating ($L_{90,dec}$) or stable ($L_{90,sta}$) rate periods.

Table 1 Mean and standard error of the mean for the markers described in II.D. Units are: min for $L_{90,acc}$, $L_{90,dec}$ and $L_{90,sta}$; n.u. for s_{acc} , s_{dec} and s_{sta}

	Placebo			Amiodarone		
	Survivors	Victims		Survivors	Victims	
	Mean ± SEM	Mean ± SEM	p-value	Mean ± SEM	Mean ± SEM	p-value
$L_{90,acc}$	67,89 ± 2,77	110,55 ± 27,04	0,133	112,31 ± 6,43	75,68 ± 7,21	$4 \cdot 10^{-4}$
$L_{90,dec}$	99,25 ± 4,18	153,50 ± 28,61	0,075	146,35 ± 7,98	111,93 ± 14,34	0,047
$L_{90,sta}$	88,76 ± 6,08	190,59 ± 73,91	0,186	134,36 ± 9,08	115,42 ± 32,35	0,581
s_{acc}	0,059 ± 0,003	0,091 ± 0,024	0,200	0,084 ± 0,005	0,045 ± 0,011	0,006
s_{dec}	0,085 ± 0,003	0,122 ± 0,025	0,159	0,113 ± 0,005	0,064 ± 0,011	0,001
s_{sta}	0,066 ± 0,004	0,114 ± 0,029	0,120	0,095 ± 0,006	0,063 ± 0,014	0,049

On the other hand, victims on amiodarone show reduced adaptation times with respect to values found in the placebo arm. Similar observations can be made using the variables that measure the slope of the QT/$\overline{RR}$ relationship: in amiodarone, survivors exhibit increased slope values, while victims have reduced values.

These results confirm our previous observations that amiodarone modifies QT adaptation and such a modification is different for victims and survivors of arrhythmic death [3]. The advantage of the dynamic method presented in this study is that local repolarization heterogeneities can be effectively detected even if they occur only at isolated episodes of the recording where heart rate experiments sudden changes. On the contrary, with the assumption that QT adaptation preserves constant characteristics in one and the same patient, local heterogeneities can be masked if, on average, the adaptation process is not severely altered. Arrhythmic death has been usually associated with rate exertion [6]. Our results suggest that amiodarone improves repolarization adaptation by delaying the response of the QT interval to rate accelerations. Those patients, in which amiodarone is not able to provoke such a delay are at higher risk of suffering from arrhythmic death. In a similar manner, when a heart rate deceleration occurs, amiodarone increases the QT adaptation time so as to prevent excessive increased QT lengthening in the early phase of rate decelerations, which could trigger ventricular arrhythmias [7]. Patients, in which amiodarone is not being effective show shorter adaptation times, indicating higher vulnerability to arrhythmic death.

Acknowledgment

This study was supported by Ministerio de Ciencia y Tecnología and FEDER under Project TEC2004-05263-C02-02, in part by the Diputación General de Aragón (DGA), Spain, through Grupos Consolidados GTC ref:T30, and by CIBER through ISCIII CB06/01/0062.

References

1. Chevalier P, Burri H, Adeleine, Kirkorian G, Lopez M, Leizorovicz A, Andre-Fouet X, Chapon P, Rubel P, Touboul P (2003) QT dynamicity and sudden death after myocardial infarction: results of a long-term follow-up study. J Cardiovasc Electrophysiol, 14(3):227–233
2. Lux R, Kirchhof P, Cygankiewcz I, Brockmeier K (2007) Electrocardiographic markers of sudden cardiac death. J Electrocardiol 40(1 Suppl):S9–S10
3. Pueyo E, Smetana P, Caminal P, Bayés de Luna A, Malik M, Laguna P (2004) 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. IEEE Trans Biomed Eng 51(9):1511–1520
4. Golub GH, Hansen PC, O´Leary DP (1999) Tikhonov regularization and total least squares. SIAM J Matrix Annal Appl 21(1):185-194
5. Pueyo E (2006) Detección de heterogeneidades en la depolarización y repolarización cardiacas a partir del electrocardiograma como mejora en la predicción del riesgo frente a arritmias. PhD dissertation. University of Zaragoza, Spain, 2006
6. Cobb LA, Weaver WD (1986) Exercise: a risk for sudden death in patients with coronary heart disease. J Am Coll Cardiol 7(1):215–219, Review
7. Singh JP, Johnston J, Sleight P, Bird R, Ryder K, Hart G (1997) Left ventricular hypertrophy in hypertensive patients is associated with abnormal rate adaptation of QT interval. J Am Coll Cardiol 29(4):778–784

Esther Pueyo
Aragon Institute for Engineering Research (I3A),
University of Zaragoza
C/ Maria de Luna, 1
Zaragoza
Spain
Email: epueyo@unizar.es