31st Annual International Conference of the IEEE EMBS
Minneapolis, Minnesota, USA, September 2-6, 2009

Open Loop Linear Parametric Modeling of the QT Variability

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Abstract—**Open loop linear parametric modeling approach was applied to describe the variability of the ventricular depolarization and repolarization duration (i.e. the QT interval from the ECG). Several model structures were compared. The model maximizing the goodness of fit describes the QT interval as a linear combination of its own past values plus two exogenous influences (i.e. heart period interval and respiration) and a colored noise. When this model was applied to a protocol imposing a progressive increase of the sympathetic activity and modulation (i.e. the graded head-up tilt), the goodness of fit gradually decreased, thus suggesting a progressive uncoupling between QT duration and heart period that cannot be the result of influences unrelated to heart period changes.**

I. Introduction

The duration of the ventricular depolarization and repolarization, defined as the time interval between the Q-wave onset and T-wave offset (QT interval) on the ECG, is usually measured automatically as the temporal distance between the R peak and T wave apex (RTapex) or T wave end (RTend). The automatic measure of the QT interval (i.e. RTapex or RTend) exhibits a rhythmical variability when observed on a beat-to-beat basis. Two major oscillations have been detected in the low frequency (LF) band (from 0.04 to 0.15 Hz) and in the high frequency (HF) band (above 0.15 Hz) [1]. Several mechanisms have been proposed to explain the rhythms present in the RTapex and RTend beat-to-beat variabilities: i) RT oscillations are simply the reflection of the LF and HF rhythmicities present in the heart period variability and appearing in the QT variability due to the link between the QT interval and preceding cardiac cycle duration [1-3]; ii) RT fluctuations are expressions of the regulation carried out by the autonomic nervous system independently of the regulation of the heart period [3.4]; iii) rhythmical RT changes have a non-neural origin, especially at HF band, and are caused by artifacts capable of distorting the Q wave (e.g. cardiac axis movements) [1,5].

The aim of this study is to clarify the origin of the rhythmical oscillations present in the RT variability. We exploited an approach based on open loop linear parametric modeling. The RT variability was described according to different types of models and the goodness of fit was assessed. The comparison of the values of the goodness of fit allows to draw some hypotheses about the origin of the rhythmical oscillations present in the RT variability. The approach was applied during an experimental condition in which the sympathetic activity and modulation were progressively increased (i.e. the graded head-up tilt test) [6].

Manuscript received April 7, 2009.

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II. Methods

A. Model Class

The description of the QT variability is based on the beat-to-beat measures of the RT interval (i.e. RTapex={RTapex(i), i=1,…,N} and RTend={RTend(i), i=1,…,N}, where i is the cardiac beat number and N is the series length), on the beat-to-beat series of heart period approximated by the temporal distance between two consecutive R peaks (i.e. RR={RR(i), i=1,…,N}) and on the respiratory signal (R) (i.e. R={R(i), i=1,…,N}). The RT, RR and R series are first normalized by subtracting the mean and, then, by dividing the result by the standard deviation, thus obtaining rt, rr and r series with zero mean and unit variance.

The model utilized to describe the rt variability belongs to the class of the autoregressive (AR), double exogenous (XX) model with AR noise (ARXXAR) [7]. The i-th RT interval depends on past RT values, on the exogenous actions of the current and past RR intervals and of current and past R samples and on an additive colored noise u_{rt} as follows

$$\mathrm{rt(i)} = A_{rt-rt}(z)\cdot \mathrm{rt(i)} + B_{rt-rr}(z)\cdot \mathrm{rr(i)} + B_{rt-r}(z)\cdot \mathrm{r(i)} + u_{rt}(i) \quad (1)$$

where

$$A_{rt-rt}(z) = \sum_{k=1}^{p} a_{rt-rt}(k)\cdot z^{-k} \quad (2)$$

$$B_{rt-rr}(z) = \sum_{k=0}^{p} b_{rt-rr}(k)\cdot z^{-k} \quad (3)$$

$$B_{rt-r}(z) = \sum_{k=0}^{p} b_{rt-r}(k)\cdot z^{-k} \quad (4)$$

and $a_{rt-rt}(k)$’s, $b_{rt-rr}(k)$’s and $b_{rt-r}(k)$’s are p, p+1 and p+1 constant coefficients and z^{-1} is the one-lag delay operator in the z-domain.

The noise u_{rt} is an AR process described by

$$u_{rt}(i) = D_{rt}(z)\cdot u_{rt}(i) + w_{rt}(i) \quad (5)$$

where

$$D_{rt}(z)=\sum_{k=1}^{p} d_{rt}(k)\cdot z^{-k} \quad (6)$$

and w_{rt} is a white noise with zero mean and variance λ^2_{wrt}.

B. Prediction Error of the ARXXAR Model

The one-step ahead prediction error of the ARXXAR model is defined as the difference between rt(i) and the best one step ahead prediction of rt(i), $\hat{rt}(i/i-1)$, as

$$e_{rt}(i/i-1)=rt(i)-\hat{rt}(i/i-1) \quad (7)$$

According to [8] the one step ahead prediction error of rt(i) in the case of an ARXXAR model is

$$\begin{aligned} e_{rt}(i/i-1)=&(1-\hat{D}_{rt}(z))\cdot(1-\hat{A}_{rt-rt}(z))\cdot rt(i)-\\ &(1-\hat{D}_{rt}(z))\cdot\hat{B}_{rt-rr}(z)\cdot rr(i)- \quad (8)\\ &(1-\hat{D}_{rt}(z))\cdot\hat{B}_{rt-r}(z)\cdot r(i)\end{aligned}$$

where $\hat{A}_{rt-rt}(z),\hat{B}_{rt-rr}(z),\hat{B}_{rt-r}(z),\hat{D}_{rt}(z)$ are estimated from real data via identification procedures. The ability of the model in fitting data is measured according to the mean squared prediction error (MSPE)

$$MSPE=\frac{1}{N}\sum_{i=1}^{N} e^2_{rt}(i/i-1) \quad (9).$$

The MSPE is bounded between 0 (i.e. the model fits perfectly the rt series) and the variance of the rt series (i.e. the model fails completely to describe the rt variability) that is equal to 1 due to the normalization procedure.

The goodness of fit is defined as

$$\rho_{rt}=1-MSPE \quad (10),$$

thus having an index still bounded between 0 and 1 and positively correlated with the ability of the model to describe the rt dynamics (the larger ρ_{rt}, the better the performance of the model).

C. Different Types of Models

The ARXXAR class can be easily customized by setting to 0 all the coefficients relevant to some polynomials, while identifying those relevant to the remaining ones. The considered model structures are

i) X model: $A_{rt-rt}(z)=0$, $B_{rt-r}(z)=0$, $D_{rt}(z)=0$ while $B_{rt-rr}(z)$ is estimated as $\hat{B}_{rt-rr}(z)$;

ii) ARX model: $B_{rt-r}(z)=0$, $D_{rt}(z)=0$ while $A_{rt-rt}(z)$, $B_{rt-rr}(z)$ are estimated as $\hat{A}_{rt-rt}(z),\hat{B}_{rt-rr}(z)$;

iii) XAR model: $A_{rt-rt}(z)=0$, $B_{rt-r}(z)=0$ while $B_{rt-rr}(z)$, $D_{rt}(z)$ are estimated as $\hat{B}_{rt-rr}(z),\hat{D}_{rt}(z)$;

iv) ARXAR model: $B_{rt-r}(z)=0$ while $A_{rt-rt}(z)$, $B_{rt-rr}(z)$, $D_{rt}(z)=0$ are estimated as $\hat{A}_{rt-rt}(z),\hat{B}_{rt-rr}(z),\hat{D}_{rt}(z)$;

v) XXAR model: $A_{rt-rt}(z)=0$ while $B_{rt-rr}(z)$, $B_{rt-r}(z)$, $D_{rt}(z)$ are estimated as $\hat{B}_{rt-rr}(z),\hat{B}_{rt-r}(z),\hat{D}_{rt}(z)$;

vi) ARXXAR model: $A_{rt-rt}(z)$, $B_{rt-rr}(z)$, $B_{rt-r}(z)$, $D_{rt}(z)$ are estimated as $\hat{A}_{rt-rt}(z),\hat{B}_{rt-rr}(z),\hat{B}_{rt-r}(z),\hat{D}_{rt}(z)$.

III. EXPERIMENTAL PROTOCOL AND DATA ANALYSIS

A. Experimental Protocol

We studied 16 healthy nonsmoking humans (aged from 21 to 54, median=28; 6 females and 10 males). After 7 minutes at rest (R), the subjects underwent a session (lasting 10 minutes) of head-up tilt (T) with table angles randomly chosen within the set {15,30,45,60,75,90} (T15, T30, T45, T60, T75, T90). Each tilt session was always preceded by an R session and followed by 3 minutes of recovery. ECG (lead II) and respiration via thoracic belt were recorded. The signals were sampled at 1000 Hz. The QRS complex was detected using a derivative threshold algorithm. The T-wave peak was searched in a predefined temporal window the duration of which depended on the preceding RR interval. Both R-wave and T-wave apexes were located using parabolic interpolation and their temporal distance was taken as RTapex. The T-wave offset was located according to a threshold on the first derivative set as a fraction (i.e. 30%) of the absolute maximal first derivative value computed on the T-wave downslope. The temporal distance between the R peak and T-wave offset was taken as RTend. The i-th RTapex or RTend were inside the (i+1)-th RR interval. The i-th respiratory sample (R(i)) was taken in correspondence of the R peak ending the i-th RR interval. Before identifying

TABLE I
GOODNESS OF FIT OF THE MODELS OF THE RTAPEX DYNAMICS DURING GRADED HEAD-UP TILT

	R	T15	T30	T45	T60	T75	T90
ρ_{AR}	0.446 (0.199-0.553)	0.399 (0.229-0.592)	0.462 (0.287-0.617)	0.397 (0.210-0.588)	0.402 (0.273-0.625)	0.346 (0.234-0.494)	0.335 (0.271-0.641)
ρ_{X}	0.586 (0.406-0.716)	0.634 (0.378-0.745)	0.579 (0.391-0.696)	0.497 (0.263-0.670)	0.456 (0.348-0.561)	0.396 (0.220-0.537)	0.405 (0.298-0.700)
ρ_{ARX}	0.683 (0.549-0.872)	0.720 (0.466-0.900)	0.694 (0.490-0.844)	0.580 (0.407-0.798)	0.547 (0.445-0.810)	0.516 (0.373-0.669)	0.489 (0.379-0.764)
ρ_{XAR}	0.685 (0.523-0.871)	0.755 (0.476-0.883)	0.725 (0.482-0.833)	0.582 (0.473-0.793)	0.574 (0.432-0.817)	0.546 (0.439-0.658)	0.472 (0.412-0.745)
ρ_{ARXAR}	0.713 (0.527-0.887)	0.785 (0.515-0.899)	0.769 (0.518-0.850)	0.632 (0.493-0.801)	0.601 (0.451-0.836)	0.557 (0.496-0.696)	0.520 (0.422-0.778)
ρ_{XXAR}	0.648 (0.531-0.797)	0.742 (0.457-0.861)	0.647 (0.508-0.807)	0.574 (0.440-0.781)	0.545 (0.452-0.827)	0.542 (0.443-0.663)	0.497 (0.395-0.752)
ρ_{ARXXAR}	0.771 (0.650-0.896)	0.798 (0.590-0.904)	0.802 (0.603-0.856)	0.669 (0.506-0.839)	0.673 (0.524-0.849)	0.657 (0.502-0.759)	0.609 (0.478-0.798)

Values are expressed as median (first quartile – third quartile).
ρ = goodness of fit; R = rest in supine position; T15, T30, T45, T60, T75, T90 = 15°, 30°, 45°, 60°, 75°, 90° head-up tilt.

TABLE II
GOODNESS OF FIT OF THE MODELS OF THE RTEND DYNAMICS DURING GRADED HEAD-UP TILT

	R	T15	T30	T45	T60	T75	T90
ρ_{AR}	0.296 (0.155-0.448)	0.317 (0.258-0.436)	0.288 (0.129-0.451)	0.280 (0.155-0.431)	0.198 (0.124-0.359)	0.243 (0.069-0.384)	0.190 (0.105-0.448)
ρ_{X}	0.491 (0.359-0.600)	0.495 (0.356-0.575)	0.417 (0.262-0.667)	0.320 (0.221-0.518)	0.310 (0.197-0.441)	0.252 (0.129-0.457)	0.220 (0.122-0.461)
ρ_{ARX}	0.510 (0.407-0.702)	0.575 (0.380-0.730)	0.528 (0.283-0.742)	0.408 (0.247-0.621)	0.356 (0.252-0.565)	0.318 (0.141-0.566)	0.263 (0.177-0.599)
ρ_{XAR}	0.530 (0.430-0.691)	0.569 (0.431-0.699)	0.525 (0.288-0.729)	0.433 (0.266-0.660)	0.374 (0.256-0.624)	0.326 (0.165-0.552)	0.278 (0.213-0.605)
ρ_{ARXAR}	0.562 (0.448-0.709)	0.612 (0.519-0.746)	0.584 (0.336-0.737)	0.453 (0.343-0.739)	0.436 (0.289-0.566)	0.344 (0.236-0.592)	0.357 (0.223-0.611)
ρ_{XXAR}	0.612 (0.453-0.724)	0.586 (0.494-0.723)	0.600 (0.348-0.730)	0.456 (0.317-0.689)	0.443 (0.346-0.658)	0.385 (0.247-0.606)	0.339 (0.243-0.604)
ρ_{ARXXAR}	0.696 (0.464-0.780)	0.651 (0.560-0.771)	0.674 (0.547-0.751)	0.549 (0.438-0.793)	0.527 (0.379-0.701)	0.494 (0.332-0.643)	0.435 (0.268-0.614)

Values are expressed as median (first quartile – third quartile).
ρ = goodness of fit; R = rest in supine position; T15, T30, T45, T60, T75, T90 = 15°, 30°, 45°, 60°, 75°, 90° head-up tilt.

the parameters of the models, the series were linearly detrended. The series length was kept constant in any subject in any experimental condition (N=256).

B. Identification Procedure

The coefficients of the X and ARX models were identified using traditional least-squares approach, while those relevant to XAR, ARXAR, XXAR and ARXXAR ones using generalized least-squares approach [7]. The latter procedure was stopped when the current iterate did not produce a significant percent decrease of the MSPE with respect to the previous iterate (the threshold was 0.001). The solution of both the traditional and generalized least-squares problems was found using the Cholesky decomposition method [8]. The best model order was selected according to the Akaike figure of merit for multivariate processes. The best model order was searched in the range from 6 and 16.

C. Statistical Analysis

Wilcoxon signed rank test was applied to the pooled values of the goodness of fit derived from all the models to check whether the RTapex variability was more predictable than the RTend one (i.e. the goodness of fit was larger). Friedman repeated measures ANOVA on ranks (Dunn's test) was applied to the pooled values of the goodness of fit to compare the ability of the different models to describe the RTapex and RTend variabilities regardless the experimental condition. Assigned the type of model, Spearman rank order correlation analysis was carried out to assess the degree of association between the goodness of fit and tilt angles. A $p<0.05$ was considered significant.

IV. RESULTS

The goodness of fit derived from the RTapex variability (median=0.575) was found significantly larger than that derived from the RTend variability (median=0.45) independently of the experimental condition and models. This finding indicates that the RTapex dynamics were more predictable than the RTend one (Tabs.I,II).

Independently of the experimental condition, the goodness of fit of the X model was found similar to that of the AR one. All the remaining models (i.e. ARX, XAR, ARXAR, XXAR, ARXXAR) exhibited goodness of fit significantly larger than the X model. The ARXAR model was better than ARX and XAR ones in fitting the RT variability. These results held in the case of both RTapex and RTend variabilites. The goodness of fit of the XXAR model was not increased with respect to XAR, ARX, ARXAR in the case of RTapex variability and to ARXAR model in the case of RTend variability. The performance of the ARXXAR model was significantly better than that of any other model in the case of both RTapex and RTend variabilities.

Assigned the type of open loop linear parametric model, Spearman rank order correlation analysis was carried out to assess the degree of association between the goodness of fit and tilt angles (Tabs.III,IV). The correlation coefficient between the AR model and the inclination of the tilt table was insignificant regardless the type of RT variability (i.e. RTapex or RTend). On the contrary, the goodness of fit derived from bivariate (i.e. X, ARX, XAR, ARXAR) and trivariate (i.e. XXAR, and ARXXAR) models identified from both RTapex and RTend variabilities was significantly associated with the tilt table inclination with the notable exceptions of the XAR and XXAR models in the case of the RTapex variability. The correlation coefficient was negative, thus suggesting that predictability of the RT dynamics decreased as a function of the angle of the tilt table. It is worth noting that correlation coefficient was more negative when the RTend variability was considered.

V. DISCUSSION

The RTend variability is significantly less predictable than the RTapex one as a likely effect of the greater difficulty in automatically locating the T wave offset with respect to the T wave apex, especially in presence of broad band noise [5]. Even though the goodness of fit calculated over the RTapex and RTend variabilities is different, the interpretation of the rhythms present in the QT variability provided by the models does not depend of the type of the QT measure.

Although the QT interval depends on past RR intervals [2], the goodness of fit of the X model is not significantly higher than that of the AR model. This finding suggests that

TABLE III
CORRELATION ANALYSIS OF THE GOODNESS OF FIT OF THE MODELS OF THE RTAPEX DYNAMICS VERSUS TILT ANGLES

	r_S	p	
ρ_{AR}	0.0109	0.909	no
ρ_{X}	-0.258	0.0062	yes
ρ_{ARX}	-0.209	0.0274	yes
ρ_{XAR}	-0.184	0.0523	no
ρ_{ARXAR}	-0.188	0.0466	yes
ρ_{XXAR}	-0.168	0.0768	no
ρ_{ARXXAR}	-0.211	0.0254	yes

r_S: Spearman rank correlation coefficient
p: probability of the type-I error
yes: ρ was significantly related to tilt angles with $p<0.05$.

TABLE IV
CORRELATION ANALYSIS OF THE GOODNESS OF FIT OF THE MODELS OF THE RTEND DYNAMICS VERSUS TILT ANGLES

	r_S	p	
ρ_{AR}	-0.146	0.126	no
ρ_{X}	-0.279	0.00295	yes
ρ_{ARX}	-0.233	0.0134	yes
ρ_{XAR}	-0.233	0.0136	yes
ρ_{ARXAR}	-0.233	0.0137	yes
ρ_{XXAR}	-0.247	0.00877	yes
ρ_{ARXXAR}	-0.264	0.00497	yes

r_S: Spearman rank correlation coefficient
p: probability of the type-I error
yes: ρ was significantly related to tilt angles with $p<0.05$.

the bivariate model that explains the QT variability as a linear combination of past RR intervals plus a white noise (i.e. the X model) is too simple and is not capable of giving any additional advantage with respect to the univariate AR model. On the contrary, bivariate models more complex than the X one, especially the ARXAR model [3], are more effective in explaining the QT variability. This finding indicates that past QT durations, current and past RR intervals and colored noises modifying the QT interval independently of the RR changes are all important in producing the QT variability. The good performance of the trivariate ARXXAR model with respect to simpler bivariate models suggests that the introduction of respiration as an exogenous input can be helpful to improve the prediction of the QT variability. It is worth observing that all models that impose a regression of the RT interval over its own past values (e.g.. ARXAR and ARXXAR) perform better than models with similar structures but that do not account for the influences of past QT values (i.e. XAR and XXAR). This result suggests the presence of memory effects on the RT dynamics.

The correlation analysis indicates that the predictability of the QT dynamics decreases as a function of the relevance of the gravitational stimulus. This finding is in agreement with the observation that the amount of information carried by the QT variability given past RR intervals increases as a function of the importance of the sympathetic drive [9], thus suggesting a progressive uncoupling between the QT and RR variabilities. As a new finding of the present study, it seems that respiratory influences unrelated to RR changes do not play any role in explaining the gradual QT-RR uncoupling: indeed, accounting for respiration as an exogenous input is helpful to improve the predictability of the QT dynamics but it does not prevent the gradual decrease of the goodness of fit. We conclude that the gradual QT-RR uncoupling is actually related to the weakening of the QT-RR relationship instead of the action of exogenous influences.

It is worth noting that, although the goodness of fit of the RTend variability is smaller than that of the RTapex one, its degree of association with the tilt angles is more important (i.e. it is more negative), thus suggesting that the link between the sympathetic modulation and RTend variability is stronger.

VI. CONCLUSION

The comparison between different open loop linear parametric model structures confirms the dependence of the QT variability on RR interval changes and rhythmical unmeasurable noises. In addition, the approach suggests the important role of respiratory inputs unrelated to fast RR interval changes in producing the QT variability and the negligible role of respiratory influences unrelated to RR dynamics in generating the loss of coupling between the QT and RR variabilities in presence of a high sympathetic drive.

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