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Effect of premature activation in analyzing QT dynamics instability using QT-RR model for ventricular fibrillation and healthy subjects

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***Abstract*— Perturbations in the normal heart rate are generally represented by the presence of premature activation (PA) beats in the surface electrocardiogram (ECG). The presence of PA is one of the main reasons of instability in QT dynamics which could initiate arrhythmia. Analyzing Boundary-Input Boundary-Output (BIBO) stability of the short term linear autoregressive QT-RR model is a way of detecting instability in QT dynamics from the ECG. The aim of this paper is to investigate if PA is the only reason for instability in the ventricular repolarisation process, which is denoted by QT interval of surface ECG. Ten healthy subjects with normal sinus rhythm and seven patients with sustained ventricular tachycardia (VT) were analyzed in this study. 10 min long ECG data were collected from each subject of the healthy group and 10 min ECG before the start of VT were taken for each subject of the VT group. Autoregressive QT-RR model was derived for each non-overlapping 1 min long ECG segment of the 10 min long ECG data. Instability in QT dynamics was quantified by measuring the numbers of unstable segments in ECG data for each subject (N_{us}). Results of this study revealed that like the VT group subjects, QT instability detected by QT-RR model is also found in healthy subjects whose ECG segments are mostly free from PA beats. This finding indicates that BIBO unstable QT characteristics might arise from other inherent factors of cardiovascular system in addition to PA.**

I. Introduction

Mathematical modeling of the interaction between QT and RR intervals form surface ECG is a non-invasive technique to comprehend the relationship between heart rate variability and ventricular repolarisation variability [1]. Ventricular repolarisation (VR) phenomenon can be understood by monitoring the QT interval and any irregularity in this interval like duration change or the distortion in the shape in T wave could be an indication of the initiation of arrhythmia [3]. The linear parametric model developed by Porta et al. [2] explains the effect of Autonomic Nervous System (ANS) control on the VR process. The adaptation of QT interval with the alteration in heart rate was investigated using a transfer function based model derived by Halamek et al. [3] where the effect of QT hysteresis was also considered. Besides the understanding of VR process, the QT-RR model can also be used to determine the QT dynamics stability. Some recent studies used this technique to detect instability in QT dynamics and used it as an indicator of the onset of ventricular tachycardia (VT) and ventricular fibrillation (VF) in patients having structural heart disease [4,5]. The instability in the QT dynamics could be a prognostic marker of the arrhythmia susceptibility for diseased human heart having prolonged QT interval, acute myocardial infarction (AMI) and dilated cardiomyopathy [4]. These studies showed that the presence of premature activations (PA) in the ECG which are directly related with the unstable action potential dynamics (APD), could alter the normal QT variability and this perturbed QT dynamics could start arrhythmias like sustained ventricular tachycardia in AMI patients [5]. Chen et al.[4] developed a method by calculating the BIBO (bounded-input bounded-output) stability index from the linear autoregressive QT-RR model to detect the unstable ventricular repolarisation characteristics and demonstrated how the amount of PA affects the QT dynamics stability by calculating the frequency of PA in the ECG [4]. They hypothesized that the occurrence and the frequency of PAs affect the stability in QT dynamics and before the onset of arrhythmia (i.e. VT) the QT dynamics instability increases. Their study analyzed 10 minute long ECG signal segments of the patients having sustained VT by forming two groups of ECG form the total data. The Two segments were termed as the Control segment (i.e. the 10 minute duration ECG segment extracted long before the beginning of VT) and the VT segment (i.e. the 10 minute long ECG segment collected just before the initiation of VT). They collected these two groups of ECGs from the same subject. The 10 minute ECG data was then divided into ten 1 min long segments for each subject for the purpose of modeling and the calculation of stability index. The number of unstable segments and the frequency of PA were found to increase before the occurrence of VT [4, 5]. An important conclusion of their study was that, ECG segments which have no PA did not show instability in the analysis [5].

The objective of this paper is to explore whether the instability characteristics in QT dynamics determined from the QT-RR model [4, 5] is due only to the presence of PA beats in the ECG. Another target is to examine how model complexity changes for the identification of the dynamic relation between heart rate and ventricular repolarisation in healthy subjects in comparison the subjects having heart disease.

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II. DATA AND METHODS

A. Subjects

We have collected 10 Healthy subjects' ECG data from MIT-BIH Normal Sinus Rhythm Database (nsrdb) with no sign of arrhythmia and 7 patients' data with episodes of sustained ventricular tachycardia, ventricular flutter and ventricular fibrillation from the MIT BIH Malignant Ventricular Arrhythmia Database (vfdb) for this analysis [6]. The selection criterion of the subjects was less noisy ECG data so that from their ECG, the QRS complex and T wave could be visibly detected.

B. ECG Analysis

Ten minute long segments of ECG data were taken from the ECG recording for each subject. For the fibrillation patient group, ECGs of 10 min duration were taken just before the beginning of the fibrillation. The instant of starting of the fibrillation in the ECG signal were detected from the annotation file provided in the database. Each 10 min ECG segments were then divided into 1 min long segments having 10 segments for each subject like the method presented by Chen et al. [4]. The healthy subjects' ECG segments are grouped as Healthy and the ventricular arrhythmia patients' ECG segments are collectively termed as VT. The ECG segments were filtered only for the baseline wandering using the median filtering technique described in [7]. The ectopic beats were not removed from the collected ECGs by filtering as they represent the presence of premature activation (PA) beats. The presences of ectopic beats are necessary for the detection of instability in QT dynamics using the method developed by Chen et al. [4]. The RR and QT intervals of the ECG segments were calculated using the method described in [7]. Premature activation beats were counted from the RR time series for each 1 min ECG segment using the approach of Huikuri et al. [9]. PA beat was detected each time when RR interval of a beat was shortened by at least 100 ms with respect to that of the preceding beat.

Healthy group subjects with normal sinus rhythm have almost no or very small number of PA beats in their ECG, whereas VT group with sustained ventricular tachycardia have ECGs which contain a large number of PA beats. Frequency of premature activation f_{PA} was calculated as the number of PA beats present in a segment divided by the total duration of a subject's ECG (i.e. 10 mins).

C. QT-RR model formation

From the extracted RR and QT time series we derived the QT-RR model using System Identification techniques [8]. To model the dependence of QT on the previous QT intervals and RR intervals, an autoregressive model with an exogenous input (ARX) formed from the RR and QT time series for each 1 min ECG segment. The model equation is:

$$QT_n = \sum_{i=1}^{M} a_i \times QT_{n-i} + \sum_{i=1}^{N} b_i \times RR_{n-i}$$

where, n is the beat number in each 1 min ECG segment. QT and RR are the equal length discrete time series extracted from each 1 min ECG segment. M and N represent the number of model parameters i.e., number of poles and zeros, which also represent the extent of memory effect of the QT and RR needed for the representation of dynamic relationship of heart rate and ventricular repolarisation. In this study, we have used $M = N$ which indicates that the same memory effect of heart rate and repolarisation were considered in the model for prediction of following QT interval. Model parameters were determined using least square technique. The prediction capability of the model were measured using the normalized Root Mean Square Error fitness value (NMRSE) which actually calculate the normalized error between the validation data and simulated data from the derived model. These calculations were done in MATLAB R2012a using System Identification Toolbox functions.

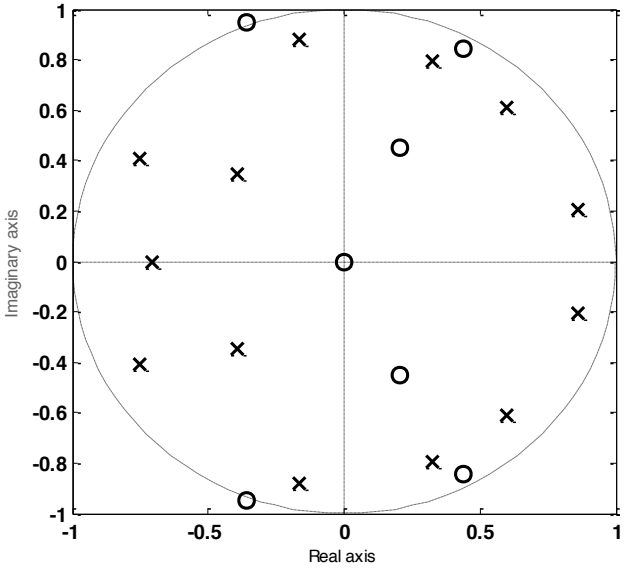

Figure 1. A stable model pole zero diagram showing all the poles inside the unit circle.

D. Stability analysis

The BIBO stability criterion was checked for the derived models of each segment of the Healthy and VT groups ECGs in z domain. This method calculates the pole zero pairs from the transfer function of the developed model and checks the values of poles if any pole magnitude is greater than 1 (i.e. $|\text{pole}| > 1$). The model was considered unstable when at least one pole was found to be outside of the unit circle, (i.e.$|z| = 1$) in the pole zero map [10]. The pole-zero map of stable and unstable models are shown in Figure 1 and 2. Redundant poles were removed and the models were validated by residual analysis using System Identification toolbox functions in MATLAB R2012a.

The minimum number of poles required to detect instability is defined as M_{min} and the number of poles needed to achieve the predefined prediction capability is defined as M_{max}. M_{min} was calculated by increasing the value of M from 1 sequentially up to the value when the model became unstable for the first time. M_{max} is the first value of M where the model achieved a predetermined prediction value of the QT. Model prediction capability of 90% was considered for the determination of M_{max}. The number of unstable model segments was counted by detecting how many segments in a

10 Min long ECG became unstable for each subject. The total number of unstable segments of each subject in each group is counted and termed as N_{us}. Wilcoxon rank-sum test to test statistical significant difference between model parameters. A p value less than 0.05 was considered significant.

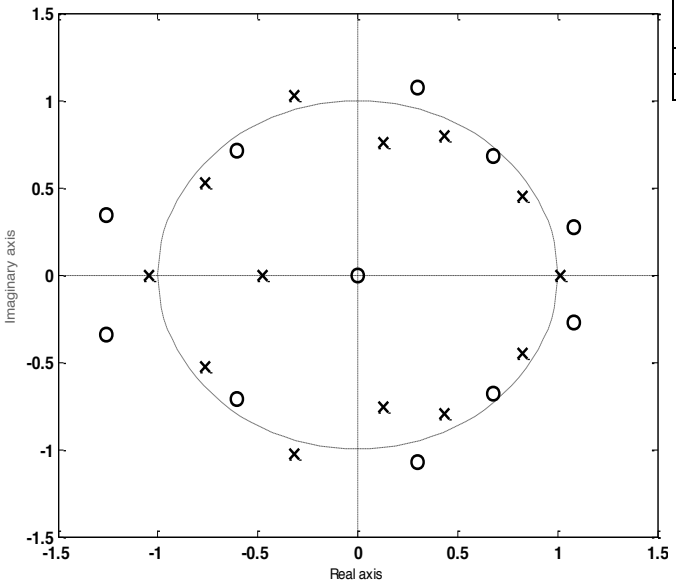

Figure 2. An unstable model pole zero diagram showing at least one the pole outside the unit circle.

III. RESULTS

A total of 100 ECG segments of 10 healthy subjects from Healthy group and a total of 70 ECG segments of 7 patients from VT group patients were analyzed. In table 1, the values of $M_{min,}$ M_{max} and f_{PA} are shown and found to be significantly (p<0.05) different between the VT and Healthy groups. However, difference between number of unstable segments (N_{us}) was found insignificant (p>0.05). The frequency of premature activation is significantly higher in the VT group than the healthy group but the numbers of unstable segments which determine the BIBO stability criteria are not different between the groups. In Healthy group the models were significantly more complex than VT group (Table 1).

TABLE I. MODEL VALUES OF BETWEEN VT AND HEALTHY GROUP

Feature	VT	Healthy	p
M_{min}	16.83 ± 4.75	20.03 ± 3.86	<0.001
M_{max}	19.79 ± 4.92	23.82 ± 3.89	<0.001
$f_{PA,}$ (beats/min)	1.2 ± 1.1	0.04 ± 0.08	<0.001
N_{us}	8 ± 1	8.8 ± 0.92	>0.05

All values are given as Mean ± SD

To investigate whether all the stable segments were free from PA, we analysed all the 1 min segments to check the condition for stability and the presence of PA. The distribution of stable and unstable segments of the VT and Healthy group is shown in Table 2. In Healthy group 64% of 1 min ECG segments without PA found unstable, which is 28% in VT group.

TABLE II. NUMBER OF STABLE AND UNSTABLE 1 MIN ECG SEGMENTS IN TWO GROUPS

Group	Segments having PA		Segments not having PA	
	Stable segment	*Unstable Segment*	*Stable Segment*	*Unstable segment*
VT	10	36	5	19
Healthy	3	23	10	64

IV. DISCUSSIONS

The simple autoregressive model used by Chen et al. [4] for the stability analysis of ventricular repolarisation process only considers the effect of any disturbance added by the heart rate represented by PA beats. RR was used as the exogenous input in the model and no additional noise term was considered that can induce instability in QT dynamics. Their findings conclude that the presence of PA is the main reason for unstable QT characteristics [4, 5].

In our study we used exactly the same methodology for exploring the effect of alteration of heart rate on the QT dynamics in healthy and arrhythmia patients. From the results of this study it is obvious that, the absence of PA might not be the only reason for stability in repolarisation process, since 64% and 28% of 1 min ECG segments became unstable for Healthy and VT group respectively which were free from PA beats (Table 2). Several modeling studies have established that QT variability is not only affected by heart rate variability and other factors like effect of respiration, temperature, gender ,age , genetic profile and autonomic nervous system [1,2,3]. Almeida et al. [1] and Porta et al. [3] quantified the QT variability through spectral analysis and showed that, factors other than RR variability affect ventricular repolarisation process which might also introduce QT instability.

The correlation found between N_{us} and f_{PA} in the VT group was similar to the findings of Chen *et al* [4, 5] but it did not hold for the Healthy group. One possible reason might be the use of separate healthy subject to form the Healthy group ECG segments in our study in contrast to the Control group in [4] where same subject's ECG data were divided into two groups for comparison.

Furthermore, healthy heart shows high heart rate variability (HRV) and more asymmetry in comparison to diseased heart [11]. Higher HRV corresponds to complex dynamics of heart which is difficult to identify and modelled by simple autoregressive model. Healthy heart model developed for the understanding of QT-RR dynamics might become unstable due to the presence of other intrinsic factors that can affect QT, as we found in our analysis. These findings showed that though a segment has no PA it become unstable when we tried to model that. Also the model became stable and unstable for variation of the value of M which was also reported by Chen et al. [5]. Our finding also demonstrated that more complex model was necessary for healthy subjects to understand the effect of only RR on QT variability without considering any external noise in the model. In the analysis for only stable model segments, it was found that the value of M_{max} for Healthy group (24.5 ± 4.6)

was significantly higher than VT group (19.6 ± 5.3). However, this result contradicts the findings reported by Chen *et al.* [4, 5], where authors have showed that the value of M_{max} is smaller in the Control group than the VT group. This is may be due to the selection of both the Control and VT ECG segments from the same subject whose cardiovascular system was already damaged [4, 5]. Since the diseased heart has less complex heart rate dynamics, Control ECG segments were less complex to model as the ECG considered was collected from the unhealthy heart. The model complexity was increased in the VT group before the start of VT could be due to increased heart rate variability.

Finally, the results of this study suggest that the presence of PA might not be the only factor for instability in QT dynamics as concluded in [5] (Table 1 and 2). The derived QT-RR model for understanding the interaction of QT and RR may have good prediction capability but it may not be BIBO stable or the stable model could not predict properly the QT dynamics. Further studies should be carried out to investigate whether this type of short term linear models could be used to comprehend the effect of RR perturbations on QT stability with healthy subjects. This could be done by analyzing nonlinear stability analysis techniques since heart rate time series shows some nonstationarity. These investigations could enable better explanation of healthy heart dynamics.

V. Conclusion

In conclusion, using the ARX modeling of QT-RR interaction to determine instability as described in [4], it was found that similar to arrhythmia patients the healthy subjects' ECG segments also become unstable with the change in model parameters. However, the model becomes relatively complex to identify and characterize the healthy heart dynamics. The QT-RR dynamics of the healthy heart might be more clearly understood by using more complex model structure which account other factors that can affect the ventricular repolarisation process [1,3].These investigations also specify that the presence of premature activation (PA) due to perturbed heart rate dynamics might not be the only reason for the instability of ventricular repolarisation.

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