Detection of Cardiac Autonomic Neuropathy using Linear Parametric Modeling of QT dynamics

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Abstract

In this study a linear parametric modeling technique is applied to model ventricular repolarisation (QT) variability from heart rate variability (RR) and respiration to investigate the change in cardiovascular system complexity in diabetes patients with cardiac autonomic neuropathy (CAN+) and without (CAN-). ECGs were recorded from 32 participants (20 CAN- and 12 CAN+), whilst in a supine resting position for 20 minutes and linear parametric autoregressive models using the first 250 beats were analysed. Models developed from the ECG derived respiration information could explain the QT-RR dynamics better than the models designed without any respiration information and may improve classification of CAN. QT-RR interaction provides useful information about cardiovascular system dynamics and autonomic nervous system modulation and ventricular repolarization on heart rate and heart rate variability.

1. Introduction

Cardiovascular dynamics can be modeled in various ways to improve our understanding of the relationship between the RR intervals and QT signal extracted from ECGs including model-based signal processing. Model-based signal processing is a promising advancement in the description of the regulation of physiological systems (e.g., cardiovascular system) controlled by several factors such as respiration, stress, and more importantly the autonomic nervous system. RR interval variability is related to the modulation of heart rate by the autonomic nervous system, whilst the QT interval provides information on ventricular repolarization. One of the serious clinical complications of diabetes is cardiac autonomic neuropathy (CAN) which gradually causes damage to the autonomic nerve fibers that innervate the heart and blood vessels, resulting in abnormalities in heart rate control and vascular dynamics [1,2].Various tests are currently used for the detection and determination of CAN progression. One requires patient involvement and was proposed by Ewing [3]. The main drawback of Ewing's autonomic reflex tests is the necessity of active participation of the patients that is not possible at all times due to comorbidities such as cardio respiratory pathology, obesity or frailty. Traditional time and frequency domain analysis of the RR interval tachogram derived from an ECG is an alternative method for detecting CAN and CAN progression [1]. Time and frequency domain measures provide an indication of the contribution of the sympathetic and parasympathetic nervous system on heart rate and ventricular repolarization, which identify patients with symptomatic CAN. But the results are not very sensitive in the case of asymptomatic CAN subjects [4]. QTc (Heart rate corrected QT interval) prolongation and either reduced or increased QT dispersion (QTd) are signs of perturbed ventricular repolarisation that may be present in diabetic CAN patients [2]. Therefore, the study of the relationship between heart rate (HR) and ventricular repolarisation (VR) may provide a better understanding of the effect of CAN on cardiovascular dynamics.

The main objective of this study is to investigate whether QT-RR modeling could be used for the detection of cardiac autonomic neuropathy and to gain a better understanding of cardiac function in patients with diabetic CAN. In this study, we used the short term QT-RR model developed by Porta et al. [5] to model the QT-RR interactions in patients with and without CAN to determine the change in complexity of heart dynamics associated with CAN. We also validated the model performance by adding respiration information to assess whether including respiration as a factor to the model improves its prediction capability of ventricular repolarization variability in CAN subjects as repolarisation stability is an important component of cardiac dynamics [10]. We used the ECG derived respiration (EDR) signal as the respiratory information of

the model and checked the validity of using EDR in CAN patients as in a previous study we reported that the addition of respiratory information in the form of EDR improves the QT-RR model fit significantly and that EDR could be used as a surrogate for respiration in normal healthy subjects [8].

2. Method

For this study we randomly selected 20 patients without CAN (CAN-) and 12 subjects who are classified as having CAN (CAN+) from the database used in a study done by Karmakar et al. [4]. All patients in this study were individuals enrolled in the Diabetes Complications Research Initiative (DiScRi) at Charles Sturt University. CAN+ was determined using the suggested reference range for the outcome of five cardiac autonomic nervous system function tests as described by Ewing [3]. The exclusion criteria used for subject selection are the presence of cardiovascular, respiratory, renal disease or use of antihypertensive or antiarrhythmic medication and any other co-morbid conditions that could influence inter-beat variability or T-wave characteristics. These conditions ensured that any changes in T wave morphology and the inter-beat or heart-rate variability (HRV) were due to the presence of CAN.

2.1. ECG analysis

The twenty minute lead II ECG signals were first filtered using the technique described in [4]. The RR and QT interval series were formed by detecting the R wave peak, Q wave onset, T wave peak and T wave end from the ECG signal using the technique described in [7]. The T wave end or offset was found by searching for the point where the gradient of the T wave first changes its sign after the occurrence of T wave peak. This method of detecting the end of the T wave is similar to the maximum slope intercept method, which defines the end of the T wave as the intercept between the isoelectric line with the tangent drawn through the maximum down slope of the T wave [7]. The respiratory information was extracted from the RR interval time series as ECG derived respiration (EDR) using the R wave amplitude method as described in [9].

2.2. Liner parametric model formation

Ventricular repolarisation process is completely described by QT interval rather than RT interval. Furthermore, QT_{end} interval (Q wave onset and T wave end) should be used for proper description of the mechanism of ventricular repolarisation process [11]. We used both QT_{peak} (time interval between Q wave onset and T wave peak) and QT_{end} (time interval between Q wave onset and T wave peak) intervals to design and validate the model performance. As T wave end detection is a challenging task we choose the 5 min ECG segments so that they contain detectable T wave and no drastic fluctuations in RR and QT interval variations. This makes the segments exhibit some stationarity which is a condition for this type of linear autoregressive modeling.

The initial 250 beats of the derived RR, QT (both QT_{peak} and QT_{end}), and EDR time series were used for the formation of the autoregressive models with single and double exogenous inputs with an autoregressive noise term. We analyzed a bivariate ($ARX_{RR}AR$) and a trivarite ($ARX_{RR}X_{EDR}AR$) linear parametric model with RR and EDR as exogenous inputs and used the methodology developed by Porta et *al.* [5] for model estimation and validation.

The equation of the bivariate QT-RR model is:

$$QT(i) = A_{QT-QT}(i) * QT(i) + B_{QT-RR}(i) * RR(i) + n(i) \quad (1)$$

The equations of the trivariate QT-RR model including respiratory information are:

$$QT(i) = A_{QT-QT}(i) * QT(i) + B_{QT-RR}(i) * RR(i) + B_{QT-EDR}(i) * EDR(i) + n(i) \quad (2)$$

Where, $QT = \{QT(i), i = 1,2, \dots \dots N\}$, $RR = \{RR(i), i = 1,2, \dots \dots N\}$, $and\ \{EDR(i), i = 1,2, \dots \dots N\}$. are the beat to beat time series of model output and input variables and N is total number of beats counted for building the model, in this study N =250. $EDR(i)$ is the respiratory information derived from ECG RR time series. The *i*th QT_{peak} or QT_{end} intervals are followed by the *i*th RR interval which ensures a direct link of the present QT interval with preceding RR interval.

The model equations indicate that it takes account of the QT variability due to RR, respiration information independent of RR and other unknown inherent factors independent of RR and respiration, which is modeled by the noise term $n(i)$. *A* and *B* represent the model transfer function polynomials whose order actually indicate the memory effect of QT, RR, and EDR that shows how QT interval is affected by the previous QT and RR intervals and other factors (i.e. respiration). The equations of *A* and *B* polynomials are described in details in [5].

2.3. Model parameter estimation and validation

Prediction error estimation (PEM) method for linear models was used for estimating model parameter coefficients [12]. Residual analysis was performed to check if the model passed the whiteness test and independence test to clarify that model residuals were not correlated with past input values. Model stability was also checked using a pole zero analysis technique. The prediction capability of the stable model was determined by the value of the goodness of fit of the derived model

and it was calculated by measuring the Normalized Root Mean Square Error (NRMSE) fit value. NRMSE computes the normalized error between the measured QT and one step ahead predicted QT form the model. All these analysis were done using system identification toolbox in MATLAB R2012a.

Statistical difference between the two groups was calculated by the Mann-Whitney U-test after checking the normality of the distribution using Lilliefors test. $p<0.05$ was considered significant.

3. Results and discussion

To determine the model complexity variation between the CAN- and CAN+ group we first modelled the RR and QT time series using the $ARX_{RR}AR$ model. The model performance was validated using both QT_{peak} and QT_{end} as model output. The results are given in Table 1. Smaller model fit values found form this modeling are an indication that the model could not describe the internal dynamics properly with this model structure and a more complex model structure is required that is able to explore the system dynamics [12].

To improve the model performance we have added the EDR in the trivariate model and estimated the model performance. Recent studies have established that the ventricular repolarisation process is modulated cyclically by respiration [6]. Therefore, respiration should be included in the QT-RR interaction model when investigating cardiovascular system dynamics.

Table 1: Model goodness of fit values for the CAN- and CAN+ group subjects with different QT dynamics.

QT dynamics	**$ARX_{RR}AR$ model**	
	CAN-	CAN+
QT_{peak}	0.49(0.42-0.62)	0.41(0.33-0.55)
QT_{end}	0.45 (0.40-0.50)	0.39 (0.36-0.45)

All values are expressed in median (first-third quartile).

Addition of EDR as another exogenous input with RR increases the prediction capability of the model significantly. This proves the direct effect of respiration on the ventricular repolarization process. Also including EDR increased the model fit significantly for both QT_{peak} and QT_{end} dynamics models (Figure 1). The fitting value of the model describing QT_{end} dynamics is lower than that of the model describing QT_{peak} dynamics, which is aligned with the findings reported by Porta et.al [5]. This difference in fitting value of QT_{peak} and QT_{end} may be due to missing variability of T_{peak}-T_{end} in QT_{peak} modeling [11]. This is also supported by the system identification theory of generating a better fit for less complex system parameter interaction [12]. Results are shown in Figure 1.

Another interesting finding is that in contrast to the $ARX_{RR}AR$ model the $ARX_{RR}X_{EDR}AR$ model fit values for both QT_{peak} and QT_{end} can significantly ($p<0.05$) differentiate between the CAN- and CAN+ group (Table 2). This indicates that the effect of respiration on QT dynamics is different in CAN- and CAN+ group. Since, the model fit values of CAN- group is higher than CAN+ group, it can be concluded that models having respiration information better estimate the QT dynamics of subjects in CAN- group than CAN+ group.

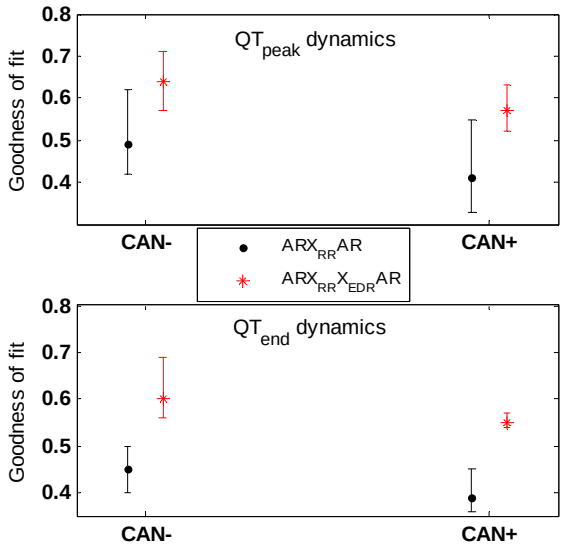

Figure 1. Significant increases in model fit with the addition of EDR information in the QT-RR model. The increase in fit values is statistically significant in both CAN- and CAN+ groups for the two model types in both QT_{peak} and QT_{end} dynamics.

Table 2: Improvement in model fitting with the addition of respiration information for different QT dynamics

QT dynamics	**$ARX_{RR}X_{EDR}AR$ model**	
	CAN-	CAN+
QT_{peak}	0.64(0.57-0.71)	0.57 *(0.52-0.63)
QT_{end}	0.60(0.56-0.69)	0.55*(0.54-0.57)

All values are expressed in median (first-third quartile). * indicates significant difference ($p<0.05$) between CAN- and CAN+ group in model fit.

To check the classification efficiency between the two groups (CAN+ and CAN-), we performed ROC analysis for both QT_{peak} and QT_{end} models [13]. ROC area of 0.74 and 0.73 were found for the QT_{end} and QT_{peak} model respectively. These values indicate that the model designed with EDR ($ARX_{RR}X_{EDR}AR$) and any of QT the dynamics (QT_{peak} or QT_{end}) can be used as a potential classifier for differentiating CAN+ from CAN- in diabetes.

Recent studies have shown that ECG based analysis of diabetes patients with asymptomatic CAN assists greatly in the clinical prognosis of fatal cardiac diseases [2]. The findings of this study have shown that presence of CAN alters the QT-RR-respiration relation, which affects the ventricular repolarisation process. The study of such a relationship is important as a small perturbation of ventricular repolarisation can lead to fatal ventricular arrhythmia [10]. Moreover, QT-RR dynamics modeling quantified the increase in complexity of the cardiovascular system dynamics of QT interval variability and RR variability interactions by decreasing the fit values. To consolidate these findings more subjects are required to test this modeling approach.

An advantage of the parametric autoregressive model used here is that through applying a multivariate spectral decomposition technique, the spectral analysis could be done on the best fitted model and it can provide a better understanding of how the output of the model is affected by different inputs and other external factors [5]. As CAN gradually progresses and damage to the autonomic nervous system (ANS) control on the cardiovascular system, the modeling approach described here may provide useful information on the effect of the ANS on the ventricular repolarisation process in CAN patients.

Finally, the effect of other factors such as age and duration of diabetes need to be assessed in the model. As cardiovascular dynamics is not completely linear, a nonlinear modeling approach with long duration ECG data such as 24 hour recordings should be evaluated to validate the use of the short term modeling in clinical prognosis applied in this research.

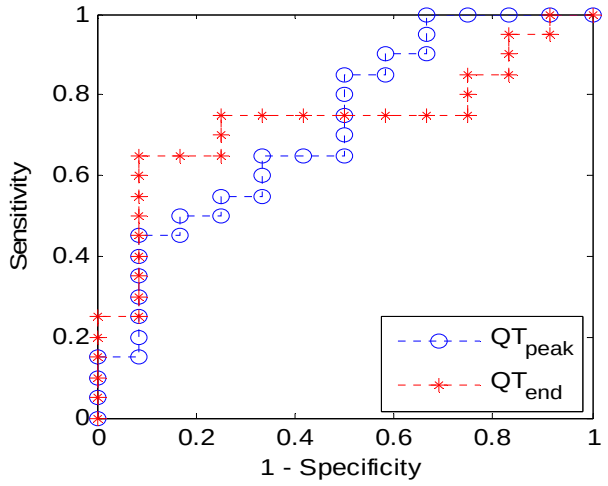

Figure 2. ROC curves for the CAN- and CAN+ group in **ARX$_{RR}$X$_{EDR}$AR** model with QTpeak (ROC curve area: 0.73) and QTend dynamics (ROC curve area: 0.74).

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