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A Method for Characterizing Circadian Changes in QT Intervals of Diabetic Patients

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Abstract— **This paper proposes a method to characterize circadian changes in QT intervals for diabetic studies. Although properties of QT intervals for diabetic patients are extensively studied, their circadian changes are not fully understood. Recently, the traditional cosinor method has been utilized for a study examining the relationship between QT circadian changes and the insulin resistance of the diabetic patients. For better characterization of the circadian change in QT intervals of this kind, spline smoothing technique applied to a decimated data set of QT intervals is proposed. New indices named QT circadian transition time (QTCT) and QT circadian transition amplitude (QTCA) associated with the subjects' awakening process are defined to characterize diabetic patients' condition. The method is applied to ten normal and fifteen type 2 diabetic patients. The proposed indices showed significantly lower values for type 2 diabetic patients compared to the control subjects indicating their effectiveness for the characterization.**

Keywords—**diabetes, circadian rhythm, cosinor method, QT intervals, biosignal classification.**

INTRODUCTION

The number of patients suffering from diabetes, especially life-style related Type 2 diabetes (T2DM, ICD-10:E11) has been rapidly increasing and is a serious social problem in many countries[1]. For diabetic patients, QT abnormalities are extensively studied to probe the risk of cardiac death[2]. Although there are many studies examining the QT intervals and QT dispersions of diabetic patients[3], research on their circadian variation is limited. Tanaka *et al.* recently reported the positive correlation between the amount of circadian variation of QT intervals and the insulin resistance of the diabetic patients[4]. The simple cosinor method has been utilized for the study. This paper proposes an extended cosinor method to characterize changes in QT intervals for more precise characterization of their circadian change. For efficient data analysis based on a huge number of beats obtained from Holter ECG recording, decimated sets of data were utilized for the analysis. Then the spline smoothing technique has been applied to estimate the underlying process to determine mean QT intervals. Then new parameters to characterize the change are introduced, namely QT circadian transition time (QTCT) and QT circadian transition amplitude (QTCA) associated with the subjects' awakening process in the morning. To confirm the usefulness of the proposed method, the method was applied to Holter recordings from twenty five subjects (ten normal and fifteen T2DM patients).

II. METHODS

Data acquisition and preprocessing

Three channel Holter ECG recordings (*Spiderview: ELA Medical, Cedex France*) were made from ten normal subjects and fifteen patients with the type 2 diabetes (T2DM). Data were digitized with the sampling interval Δt of 8 (ms) and processed offline. Base line drift was eliminated by high pass FIR filtering with the filter length and cutoff frequency set at 1001 and 0.1875 (Hz). These parameters were set empirically by trading off the alteration of T-wave morphology and the base line drift removal. The filter length has been set long enough not to deteriorate the T-wave morphology.

Data Analysis

One of three channels with dominant T-wave amplitude was selected to measure QT intervals. QT intervals are measured by a simple computer algorithm followed by the beat by beat manual correction. The algorithm identifies the starting time of the QT complex as the time when the sign of difference sequence changes by the backward tracking from the R-wave peak. The algorithm traces the signal values from the T-wave peak and identifies the end of the QT complex as the time when the signal value becomes the value less than one standard deviation of the noise level. QT intervals are measured for the beats fallen in predetermined time segments T_k:

$$T_k = [k \cdot T, k \cdot T + \Delta T], k = 1,..., K .$$

That is, the heart beats were sampled for the period ΔT (sec) in evenly spaced time segments. For our analysis, $\Delta T, T$ and K were respectively set at 60 (sec), 3600 (sec) and 24. First the conventional cosinor method has been applied to the QT intervals to obtain basic statistics, *i.e.* the following sinusoid is fitted to the decimated QT interval sequence $x[n], n \cdot \Delta t \in T_k$.

$$q[n] = M + \frac{A}{2}\cos\left(\frac{2\pi(n\cdot\Delta t - t_{ap})}{T_0}\right), n = 1,...,N \quad \ldots(1)$$

Here, M, A and t_{ap} are called mesor, peak to peak cosinor amplitude and acrophase. Mesor and peak to peak amplitude will be useful measures for the diurnal change of the QT intervals. For more detailed characterization of the change, spline smoothing technique is introduced for the analysis. The spline function $s(t)$ is a smoothed curve fitted to the QT interval sequence $x[n], n\cdot\Delta t \in T_k$ to minimize the following cost function to compromise the amount of the fitting error and smoothness of the resulting function.

$$(1-p)\sum_n w_n(s(n\Delta t) - q[n])^2 + w\int\left(\frac{d^2 s(t)}{dt^2}\right)^2 dt \quad \ldots(2)$$

Here w_n is set to 1 for *n* such that $n\cdot\Delta t \in T_k, k = 1,...,K$ and to 0 otherwise. The parameter *w* determines the balance between the fitting accuracy and smoothness. The spline smoothing became the interpolation when *w* is set at 0 where the fitting error became 0 in compensation of losing the smoothness of fitted function. The parameter *w* has been empirically set at 0.398 in this study.

Characteristic parameters named QT circadian transition time (QTCT) and QT circadian transition amplitude (QTCA) are defined and compared between normal subjects and diabetic patients. Smoothed QT interval process $s(t)$ takes high values at night and decreases monotonically in the morning awaking process. QTCT is the time duration of this change and QTCA is defined as smoothed QT value difference in that time duration.

III. RESULTS

Cosinor Analysis

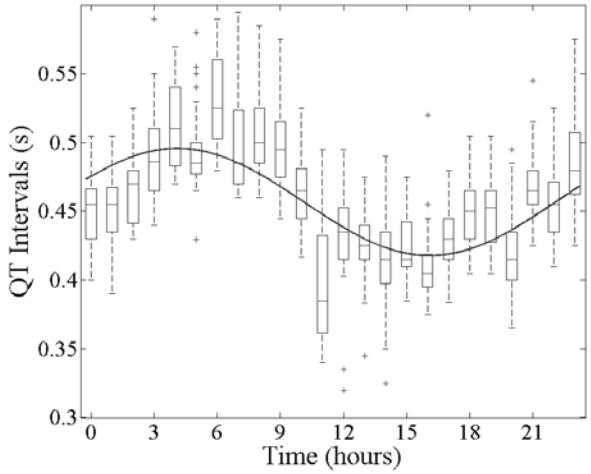
The cosinor analysis has been applied to 24 hour RR, QT and QTc sequences. They all showed circadian changes. Table 1 summarizes differences in the mean RR intervals and peak to peak cosinor amplitude between normal subjects and T2DM patients.

Table 1 Cosinor parameters of RR intervals

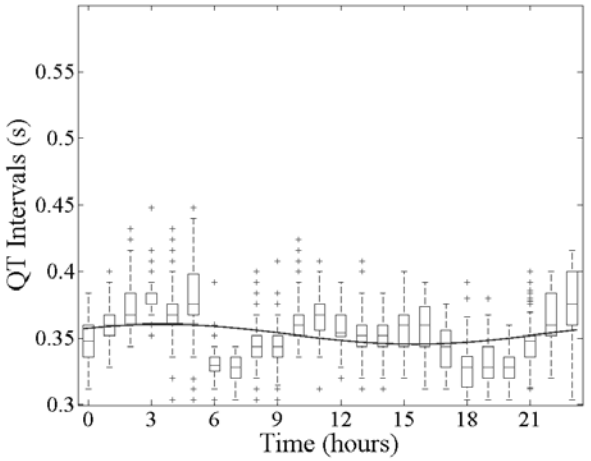
	Mean RR Intervals (ms)	**Peak to Peak Cosinor Amplitude(ms)**
Normal	924.9 ± 60.8	399.6 ± 123.9
T2DM	814.2 ± 121.3 *	214.7 ± 98.4 **

** p<0.01 * p<0.05

It is clearly noted that the mean and cosinor peak to peak amplitude of T2DM patients' RR intervals are significantly lower compared to control subjects. QT intervals and QTc's also showed circadian changes as shown in Fig. 1 and 2.



(a) A Normal Subject



(b) A type 2 diabetic patient

Figure 1. Cosinor curve fit to QT interval sequences

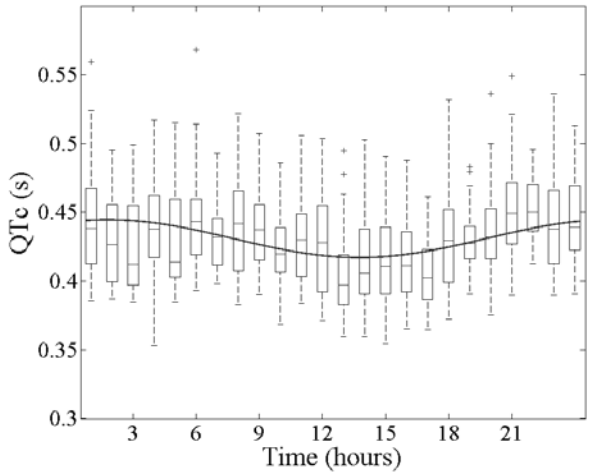


Figure 2a. Cosinor curve fit to QTc sequences (A Normal Subject)

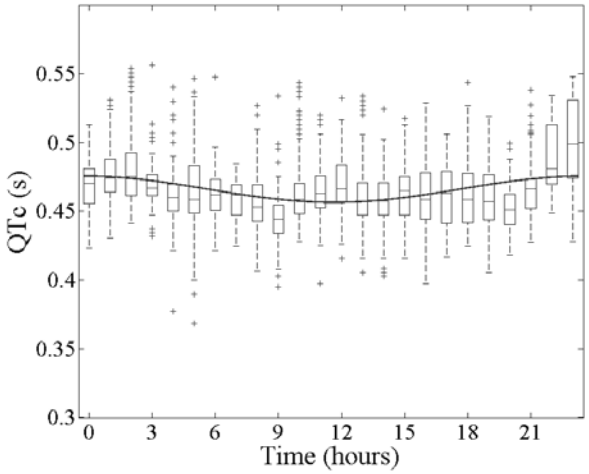


Figure 2b. Cosinor curve fit to QTc sequences (A type 2 diabetic subject)

Table 2 Cosinor parameters of QT and QTc intervals

		Mean Interval (ms)	Peak to Peak Cosinor Amplitude (ms)
QT	Normal	440.3 ± 24.8	88.6 ± 20.7
	T2DM	421.6 ± 34.4	52.5 ± 19.3 **
QTc	Normal	452.5 ± 17.4	29.9 ± 10.0
	T2DM	470.8 ± 23.5	20.6 ± 10.2 †

** $p < 0.01$, † $p = 0.057$

Table2 show significant differences in QT cosinor amplitude parameter. However, cosinor single sinusoidal fit is not always appropriate as is clearly noted in Fig. 1(b) where actual changes show higher complexity. To capture fine characteristic circadian changes in QT and QTc intervals, the spline analysis is applied to the data.

Spline smoothing Analysis

Fig. 3(a)(b) show examples of spline smoothing fit to decimated QT interval sequences. Fine morphology of the circadian changes is captured by this technique.

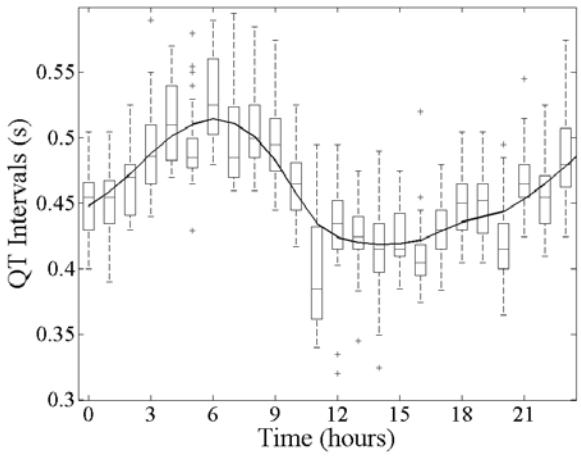


Fig. 3a Spline smoothed QT intervals (Normal)

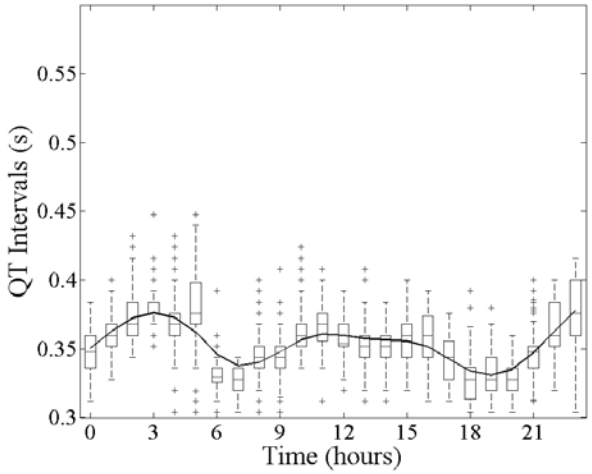


Fig. 3b Spline smoothed QT intervals (T2DM)

Fig. 4 shows examples of spline smoothing fit to QTc interval sequences. Circadian changes are apparent though not prominent as QT interval sequences.

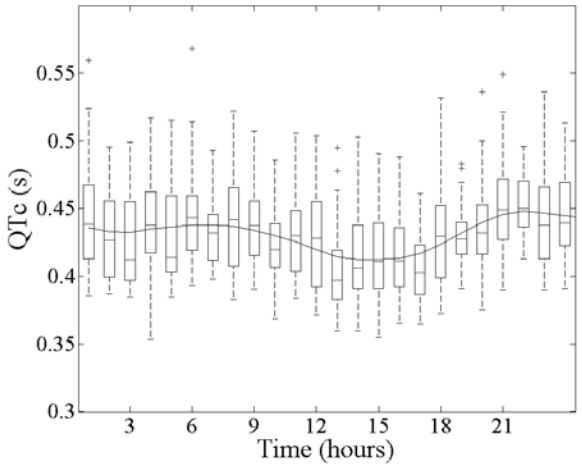


Fig. 4a Spline smoothed QTc intervals (Normal)

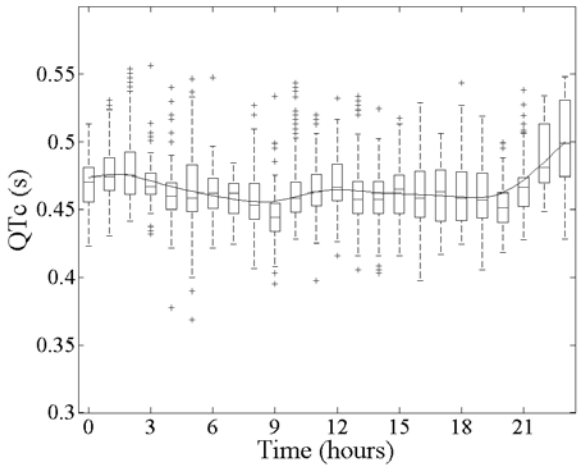


Fig. 4b Spline smoothed QTc intervals (T2DM)

In *Fig. 3a* and *3b* QT intervals show systematic decreasing pattern in the morning corresponding to the subject's transition from the state of being asleep to awake. We term the duration and amplitude of this apparent state transition QT circadian transition time (QTCT) and amplitude (QTCA). They are compared in *Table 3* and Fig. 5

Table 3 Comparison of characteristic QT circadian parameters

	QTCT (hours)	QTCA(ms)
Normal	7.1 ± 2.4	102.2 ± 21.5
T2DM	4.9 ± 1.2 *	53.8 ± 18.7 ***

** p< 0.001 ** p<0.01, * p<0.05

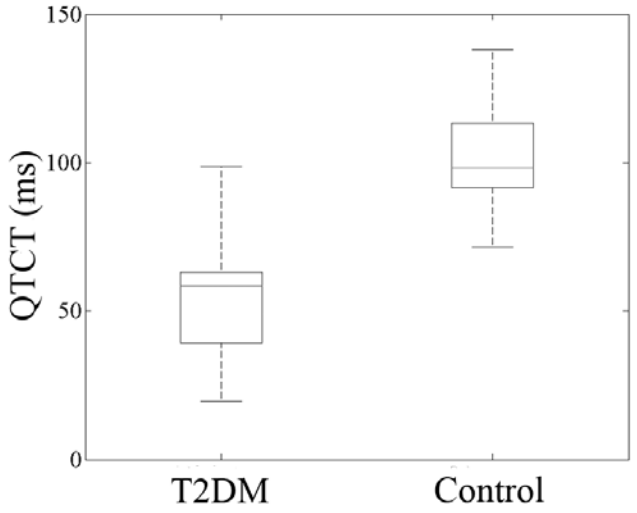


Fig. 5 Comparison of QTCA between T2DM and control subjects

Fig. 5 mimics the difference in QTCA between T2DM patients and control subjects.

IV. Discussion and Conclusion

A method of characterizing circadian changes in QT intervals is presented. Because of the large variability of QT intervals circadian changes of QT intervals are usually examined by taking the ensemble average over the subject population[5]. The proposed method, by setting an appropriate parameter value of *w*, enables us to estimate the mean time course of circadian changes for an individual subject. The parameter *w* is determined by trading off the fitting accuracy and smoothness of the fitting function. The parameter is currently determined empirically. Optimization of the parameter *w* setting an appropriate criteria is an open problem.

We haven't observed systematic changes of QTc intervals in the sleep-awake transition time. However in some T2DM cases, we have observed a paradoxical increase of QTc interval right after the starting time of QT decrease.

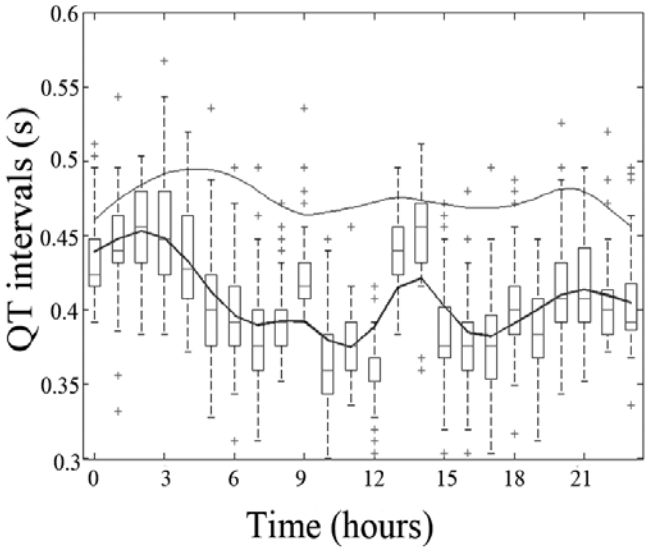


Fig. 6 Comparison between QT intervals nd QTc's (A T2D patient; Thick line: QT intervals, Thin line QTc's)

Fig. 6 shows the case. QTc intervals apparently show delayed change compared to QT intervals. This phenomenon is reported in the early work of circadian study of QT intervals [5] indicating that the statistical properties of QT intervals provide additional information to the one obtained by the RRI intervals alone.

Tanaka *et al.* showed the amount of circadian change namely circadian amplitude of QT intervals positively correlates with insulin resistance of the diabetic patients utilizing the simple cosinor method [4]. The proposed method may be useful to strengthen this kind of assertion with more precise characterization of properties of the QT related circadian change

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