Long and Short Term QT-RR Interval Co-variability in Type 2 Diabetes

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***Abstract*— This paper examines the long and short term co-variability of QT and RR intervals for diabetic patients to explore if the QT-RR co-variability could yield a noble index for the stratification of clinical severity of the disease. Twenty four hour Holter ECG recordings are made for 19 type 2 diabetic (T2DM) patients and 25 normal subjects. RR and QT intervals are extracted from ECG signals sampled at 200 Hz and their co-variability has been examined. To see the long term QT-RR co-variability, correlation coefficients and mutual entropies between QT and RR intervals have been estimated for original beat to beat intervals and smoothed median interval series of successive one hundred beats. Mutual entropy for both beat-to-beat and smoothed median QT and RR interval series showed statistically significant differences between T2DM and control subjects whereas differences in correlation coefficients showed significant difference only for beat-to-beat intervals. Mutual entropy between both beat-to-beat and smoothed median QT-RR interval sequences showed the equally well separation between T2DM patients and control subjects: Mutual entropy and serial correlation coefficients for beat to beat intervals are respectively 1.42 ± 0.33 (bits), 0.856 ± 0.055 for control and 0.752 ± 0.23 (bits), 0.756 ± 0.10 for T2DM patients. Scatter diagram between RR and QT intervals show apparent nonlinearity which validate this result. Short term QT-RR co-variability has been examined by spline smoothed QTc series and sporadic changes have been observed for the control subjects whereas no such changes are found in diabetic patients. This new phenomenon could be a mean for the clinical characterization of diabetes.**

Keywords—**diabetes, Holter ECG, QT intervals, RR intervals, co-variability, biosignal classification, mutual entropy**

I. Introduction

According to the NIH survey[1], 18.8 million people in the U.S. are diagnosed as diabetes in 2011 and showed approximately one million increase in four years. This large number of diabetes is a serious social problem since diabetes is one of the major causes of the cardiovascular diseases. Thus to develop indices for the diabetic risk assessment is important for preventing the heart attack and improving its prognosis. Because autonomic nervous system dysfunction is one of the prognostic factors of emerging diabetes, QT related indices such as QT dispersion, QT prolongations for diabetes are documented well in the literature[2]-[5] All those studies are on short term ECG characteristics. Recently long term diurnal QT interval changes are studied to associate with insulin resistance and opened a new direction of the study[6]-[7]. Authors proposed a method to better capture the characteristics of diurnal QT intervals based on spline smoothed intervals and found significant differences of QT circadian amplitude (QTCA) between diabetes and control subjects[8]. This report extends this direction of study and examined the RR-QT interval co-variability for the diabetes. QT intervals are monotonically related to RR intervals and the correlation coefficient between QT and RR intervals has been utilized to evaluate the co-variability. We have then introduced mutual entropy in addition to linear correlation coefficient as an index to evaluate the long term co-variability of QT and RR intervals. To examine the characteristics of the short term co-variability of QT to RR intervals, spline smoothing technique has been applied to QTc sequences. By setting appropriate smoothing parameter, we have found that QTc sequences show sporadic changes randomly occur in time for control subjects, while no such change has been observed for diabetes. This finding will be utilized for better characterization of diabetes.

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II. Methods

Data acquisition

Twenty four hour Holter ECG recordings were made from twenty five normal control (NC) subjects and nineteen type 2 diabetic (T2DM) patients (*Cardiomemory RAC-3100: Nihon Kohden, Tokyo Japan*). For beat to beat RR and QT interval extraction high-pass filtered sampled ECG data were utilized. Sampling frequency was set at 200 (Hz). To remove the baseline drifts, FIR high pass filter of order 1001 with cut off frequency of 0.5 (Hz) has been applied to the sampled ECG data. Then RR and QT intervals are measured and unevenly spaced interval sequences $(t_n, I_{RR}[n])$ and $(t_n, I_{QT}[n])$, $n = 1,...,N$ are obtained, where, t_n is defined as:

$$t_n = \frac{TR_n + TR_{n-1}}{2} \qquad (1)$$

Here, TR_n is the n-th T wave occurrence time. $I_{RR}[n]$ and $I_{QT}[n]$ respectively denote n-th RR and QT intervals. Figure 1 show typical RR and QT intervals for control (Fig. 1(a)) and T2DM patient (Fig. 1(b)).

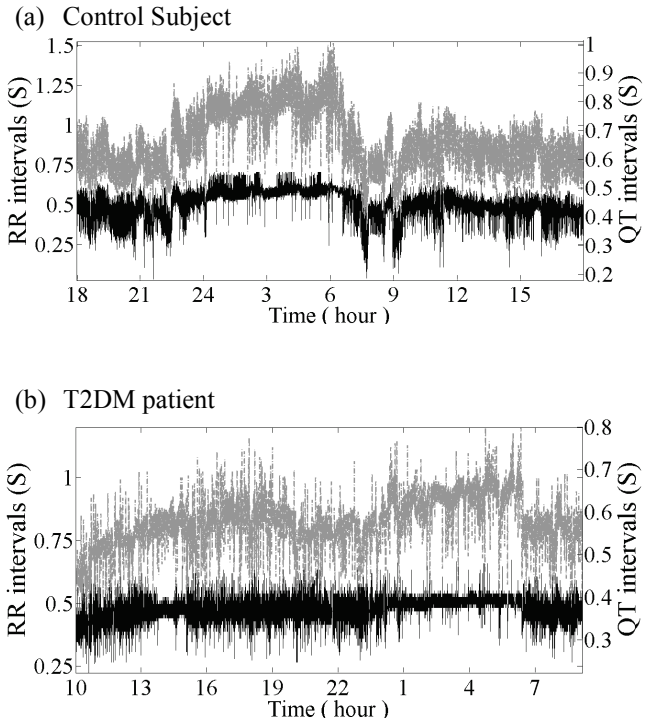


Fig. 1 Typical beat to beat RR and QT intervals
(Upper grayed trace: RRIs; Lower black trace QTIs)

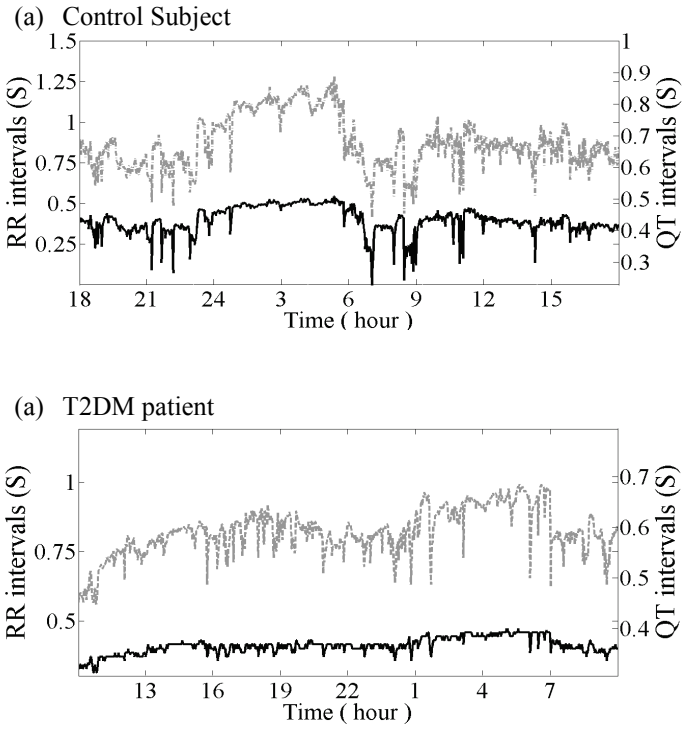


Fig. 2 Typical smoothed median RR and QT intervals
(Upper grayed trace: RRIs; Lower black trace QTIs)

Fig. 1 (b) shows that QT interval trend for T2DM patient is not responsive to RR interval change. Higher co-variability is clearly observed in control cases compared to T2DM patients. In addition to the beat to beat interval sequences, smoothed interval trends are analyzed. Namely, the median interval sequences of one hundred successive QT and RR intervals are calculated for the co-variability analysis. Fig. 2 show smoothed median interval sequences out of the typical beat to beat QT and RR interval sequences shown in Fig. 1. The smooth trend components are extracted by this process. The median may have advantage to examine the RR and QT interval co-variability when the data include sporadic large measurement errors. These RR and QT interval data are utilized for long term RR and QT interval co-variability whereas QT_c intervals sequences $(t_n, I_{QT_c}[n])$ were also utilized for the short term interval co-variability. The standard Bazzet scaling has been applied to obtain QT_c interval sequences.

Data Analysis

In order to evaluate twenty four hour long term RR and QT interval co-variability, serial correlation coefficient c_{RQ} and mutual entropy I_{RQ} between RR and QT intervals have been estimated for each subject.

$$c_{RQ} = \frac{\sum_{n=1}^{N}\left(I_{RR}[n]-\overline{I_{RR}[n]}\right)\left(I_{QT}[n]-\overline{I_{QT}[n]}\right)}{\sqrt{\sum_{n=1}^{N}\left(I_{RR}[n]-\overline{I_{RR}[n]}\right)^2}\sqrt{\sum_{n=1}^{N}\left(I_{QT}[n]-\overline{I_{QT}[n]}\right)^2}} \quad (2)$$

$$I_{RQ} = \sum_{I_{RR}}\sum_{I_{QT}} \log_2 \frac{p\left(I_{RR}, I_{QT}\right)}{p\left(I_{RR}\right)p\left(I_{QT}\right)} \quad (3)$$

To examine the short term RR and QT interval co-variability, spline smoothed QT_c interval sequence $\tilde{I}_{QT_c}(t_n)$ has been examined. The sequence $\tilde{I}_{QT_c}(t_n)$ is obtained by minimizing the functional:

$$p\sum_n (\tilde{I}_{QT_c}(t_n) - I_{QT_c}[n])^2 + (1-p)\int\left(\frac{d^2\tilde{I}_{QT_c}(t)}{dt^2}\right)^2 dt \quad (4)$$

Here, $I_{QTc}[n] = I_{QT}[n]/\sqrt{I_{RR}[n]}$. Later in the result section, appropriate selection of the smoothing factor p mimic the sporadic short term changes in QT and RR co-variability. The factor value p has been set empirically. at 5.9×10^{-10} .

III. RESULTS

Long term co-variability

Table I and Figure 3 compares correlation coefficients between RR and QT intervals for control subjects and T2DM patients. Serial correlation coefficient between RR and QT beat to beat intervals showed significantly smaller value for T2DM patients compared to control subjects whereas median smoothed intervals didn't show statistically significant difference. It is apparent that the correlation coefficients generally show higher values for smoothed data.

TABLE I. COVARIABILITY OF RR AND QT INTERVALS (CORRELATION COEFFICIENTS)

	Control	T2DM
Beat-to-Beat	0.856 ± 0.055 *	0.756 ± 0.104 *
Median Smoothed	0.930 ± 0.023	0.906 ± 0.049

(*: p<0.001)

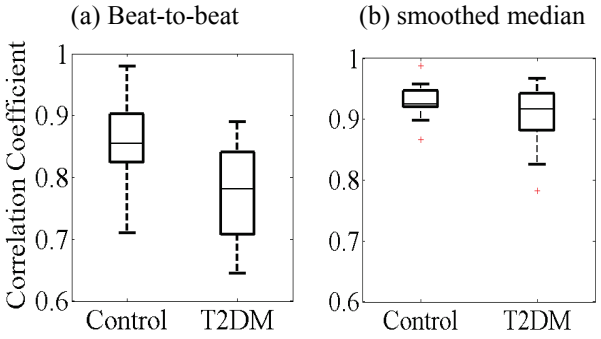


Fig. 3 Co-variability between RR and QT intervals (correlation coefficients)

Table II and Figure 4 show the same comparison between RR and QT intervals using mutual entropy.

TABLE II. COVARIABILITY OF RR AND QT INTERVALS (MUTUAL ENTROPY (bits))

	Control	T2DM
Beat-to-Beat	1.423 ± 0.333 **	0.752 ± 0.237 **
Median Smoothed	2.189 ± 0.308 **	1.503 ± 0.332 **

(**: p<0.0001)

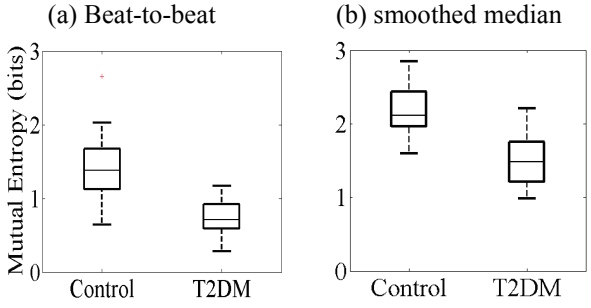


Fig. 4 Co-variability between RR and QT intervals (Mutual entropy)

Both beat-to-beat and the median smoothed intervals showed highly significant differences in the co-variability. Higher class separation capability by use of mutual entropy will be due to the nonlinear association of QT to RR intervals. Figure 5 show typical scatter diagrams between QT and RR intervals for a control subject and T2DM patient, which mimic their nonlinear relation.

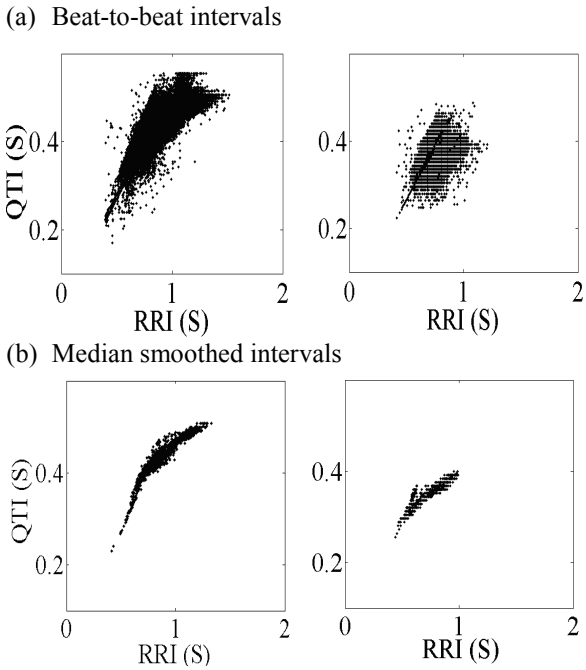


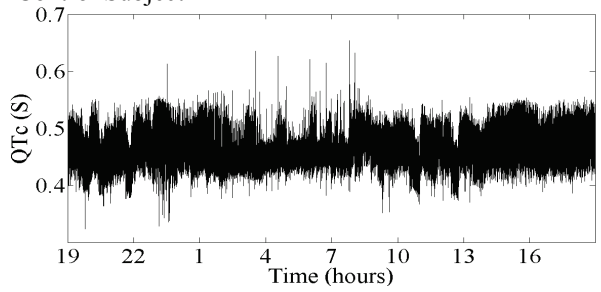
Fig. 5 Nonlinear relation between RR and QT intervals for control subjects (left panels) and T2DM patients (right panels)

In addition to clear non-linear scattering patterns, it is also noted in Fig. 5 that the beat-to-beat variability range for T2DM patients is lower than that for control subject. The tendency remains true for smoothed median data. Overall smaller variability in the scatter diagram observed in smoothed median data compared to the beat-to-beat scatter diagram is the technical methodological consequence and does not show the effectiveness of the index.

Short term co-variability

Above long term analysis shows T2DM patients have low co-variability between RR and QT intervals over twenty four hour period and the differences are statistically significant. To examine the short term time varying properties of the co-variability, QT_c interval sequence $I_{QTc}[n]$ has been analyzed. Fig. 6 shows typical examples of the sequence for a control subject (a) and T2DM patient (b). Time varying co-variability is not obvious by the eye inspection of these raw data. Figure 7 shows spline smoothed QT_c interval sequence $\tilde{I}_{QTc}(t_n)$. By appropriate setting of smoothing factor p, occasional sporadic decreases

(a) Control Subject



(b) T2DM patient

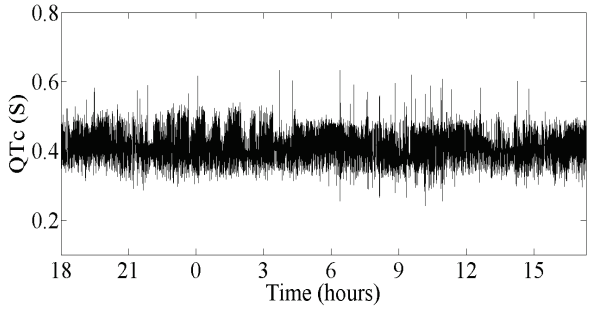


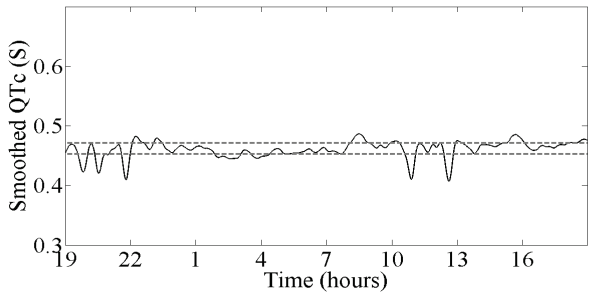
Fig. 6 Typical beat to beat QTc sequences

in smoothed QT_c sequence $\tilde{I}_{QTc}(t_n)$ are observed mainly for control subjects as shown in Figure 7. Smoothing factor p has been set so as to maximize the differences in the range of $\tilde{I}_{QTc}(t_n)$ between control and T2DM patients. The range were 0.105 ± 0.029 (S) for control subjects and 0.038 ± 0.018 (S) for T2DM subjects. The difference was statistically significant ($p<0.0001$).

IV. Discussion and Conclusion

Long and short term co-variability between QT and RR intervals for T2DM patients has been examined. Mutual entropy showed the co-variability of T2DM patients is significantly smaller than that for control subjects. This observation is true in both cases utilizing beat-to-beat and smoothed median QT and RR intervals. Correlation coefficient showed significant difference only for beat-to-beat intervals. Better separation by mutual entropy comes from non-linear relation between QT and RR intervals. Thus the mutual entropy is recommended to be utilized as an index for the better characterization of T2DM patients. Our preliminary analysis showed negative correlation between the mutual entropy and the total cholesterol indicating the mutual entropy could be a useful index for the risk assessment and stratification of T2DM patients. Short term sporadic QTc change caused by the different plasticity of QT and RR intervals showed the significant difference in the QTc range which may also be a novel index for the Diabetic risk assessment. Further validation is necessary to confirm the observation described and to find the physiological implication by relating the indices with physiologic quantities such as insulin resistance or total cholesterol.

(a) Control Subject



(b) T2DM patient

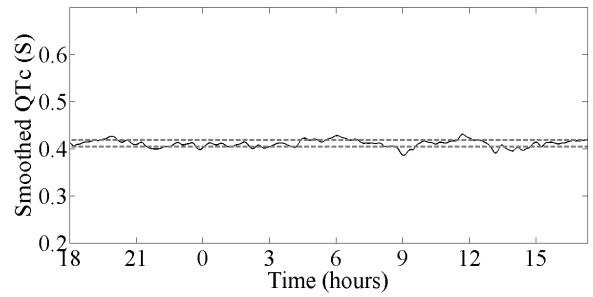


Fig. 7 Typical spline smothed QTc sequence (Horizontal bars show mean $\pm$ 2σ range)

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