Analysing Cardiac Autonomic Neuropathy in Diabetes using Electrocardiogram derived Systolic-Diastolic Interval Interactions

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Abstract

Systole and diastole are the fundamental periods of the cardiac cycle and their relative duration is used to evaluate heart function in various physiological and pathological conditions. In clinical practice, systolic-diastolic interval is generally measured using echocardiography. However, recent studies have shown that the QT and TQ intervals of the electrocardiogram (ECG) signal can be used as surrogate systolic and diastolic intervals respectively and the ratio of beat-to-beat QT-TQ intervals can be used as the systolic-diastolic interval interaction (SDI) parameter. In this study, we propose a new parameter, beat-to-beat TQ-RR ratio, to investigate the SDI. Performance of both QT-TQ and TQ-RR based SDI measures were analyzed using a case study to detect and monitor the progression of cardiac autonomic neuropathy (CAN) in diabetes. ECGs recorded in supine resting condition of 72 diabetic subjects with no CAN (CAN-) and 70 diabetic subjects with CAN were analyzed in this study. Fifty-five subjects of the CAN group had early level of CAN (ECAN) and 15 subjects were at the severe or definite stage of CAN (DCAN). The results show that variability of the TQ-RR based SDI measure can significantly ($p<0.001$) differentiate all three groups (CAN-, ECAN and DCAN) and the level of CAN. In contrast, the variability of the QT-TQ based SDI measures showed significant difference only between CAN- and DCAN groups. This result suggested that TQ-RR based SDI analysis was more sensitive in tracking progression of CAN than the QT-TQ based approach, which is crucial for the early detection of CAN.

1. Introduction

The concept of measuring the diastolic and systolic duration to evaluate cardiac function has been validated using the interval between aortic leaflet closure and mitral leaflet separation on M-mode echocardiography, the most common tool for assessment of ventricular function (1). Besides echocardiography, intervals derived from surface electrocardiogram (ECG) have also been reported to measure systolic and diastolic intervals (2-5). Frequently used ECG wave intervals derived from the surface ECG are shown in Figure 1. Inter-beat intervals (i.e. R to R wave interval or RR interval) and their variation provide information about heart rate and the effects of the autonomic nervous system on heart rate changes over time (6). The duration and variability of the QT interval indicates the duration and variability of the ventricular repolarization process and is crucial for analyzing arrythmogenesis (7). The QT interval can also be considered as a surrogate systolic interval within a cardiac cycle of the ECG signal (2-4). Alternatively, the TQ interval is considered as a surrogate measure for the diastolic interval and directly affects the QT or systolic interval of the next cardiac cycle. The beat-to-beat $QT - TQ$ interval relationship can be described as the systolic-diastolic interval interaction or the balance in the heart's contraction and relaxation operation within one cardiac cycle (8). Several studies have proposed that the systolic to diastolic interval ratio is an indicator of ventricular dysfunction in cardiovascular disease and increases with increased abnormal cardiac function (3, 9-11). Therefore, surface ECG based systolic-diastolic time interaction analysis may also provide useful information about diastolic dysfunction associated with CAN and assist CAN diagnosis.

In this study, we hypothesize that analysis of beat-to-beat systolic-diastolic interval interaction is a potential tool for diagnosing CAN in diabetic patients. The main objective of this study was, therefore, to determine an association between the presence and severity of CAN classified using the Ewing battery (12) and the beat-to-beat systolic-diastolic interval interactions using surface ECGs in diabetes subjects with either no CAN, mild, moderate or severe CAN. Besides the existing beat-to-beat systolic-diastolic time interaction parameter denoted by $QTTQ$, which was proposed by Fossa et al. (8), we

have introduced a novel parameter, namely $TQRR$, which shows the variation of the diastolic interval in every cardiac beat with respect to heart rate changes. Finally, the performances of systolic-diastolic interval interaction parameters were compared in identifying the presence and severity of CAN in diabetic patients.

2. Data & methods

2.1. Data

All patients in this study were enrolled in the Diabetes Complications Research Initiative (DiScRi) at Charles Sturt University (13). The research protocol was approved by the Charles Sturt University Ethics in Human Research Committee (03/164) and complies with the declaration of Helsinki. All patients gave written informed consent for this study.

A total of 142 type 2 diabetes participants had ECG data recorded and the ECGs analyzed for this study. Participants were divided into three groups: i) diabetes without CAN (CAN-), ii) diabetes with early CAN (ECAN), and iii) diabetes with definite CAN (DCAN). Seventy-two participants were CAN-, 55 in the ECAN and 15 in the DCAN group. Presence of CAN was determined using the suggested reference range for the outcome of five cardiac autonomic nervous system function tests as described by Ewing (12) .

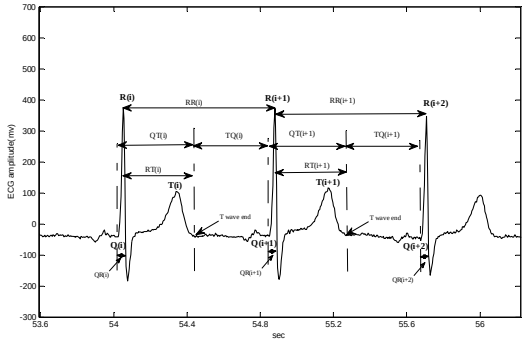

Figure 1. Schematic representation of different ECG wave intervals (RR, RT, QT, QR and TQ intervals) of two cardiac cycles. The duration of the QR interval is negligible in comparison to QT and TQ intervals, which is evident in the figure.

2.2. ECG signal and interval detections

Twenty minute long Lead II ECG traces (LabView software, ADInstruments, Australia) of all participants were recorded in a supine resting condition with a sampling rate set at 400 Hz. Lead II was chosen as it provides the best T-wave morphology and the strongest R peaks.

RR and QT intervals of 10 minute ECG segments to allow for noise and movement artifacts at the beginning and end of the 20-minute recording period were detected for each subject using a semi-automated template-matching algorithm proposed by Berger et al (14). The QT interval was calculated as the difference between Q wave onset and T wave end point (i.e. QT_{end} interval).

From the detected QT and RR interval time series, we also calculated the TQ interval by subtracting the QT interval from the RR interval within the same cardiac beat by neglecting the QR intervals (Figure 1). Since the QR interval duration is negligible in comparison to the RT or QT interval, the effect of variability due to $QR(i)$ or $QR(i+1)$ interval is considered negligible on the overall RT or QT variability (Figure 1) and assume that $QR(i) = QR(i+1)$. Hence, the beat-to-beat TQ interval can be calculated using the equation:

$$TQ(i) = RR(i) - QT(i) \tag{1}$$

2.3. Beat-to-beat systolic and diastolic interval interaction parameters

An existing beat-to-beat systolic-diastolic interval interaction measure is defined as the ratio of QT and TQ interval (8), which can be expressed as follows:

$$QTTQ(i) = \frac{QT(i)}{TQ(i)} \tag{2}$$

Where, i=1...N and N is the total number detected intervals. In this study, we proposed a new beat-to-beat interval interaction parameter for quantifying beat-to-beat systolic-diastolic interval interaction namely $TQRR(i)$, which was calculated as $\frac{TQ(i)}{RR(i)}$.

The relationship between the proposed $TQRR$ with $QTTQ$ measures can be shown using the following equations:

$$TQRR(i) = \frac{TQ(i)}{RR(i)} = \frac{TQ(i)}{QT(i) + TQ(i)}$$
$$= \frac{1}{1 + \frac{QT(i)}{TQ(i)}} \approx f\left(\frac{QT(i)}{TQ(i)}\right) = f(QTTQ(i)) \tag{3}$$

Therefore, $TQRR(i)$ signify the actual beat-to-beat variation of the $QTTQ$ (i.e. systolic-diastolic interval interaction) as both can be represented as a function of the beat-to-beat $QTTQ$ parameters (Eqn. (4)). $QTTQ(i)$ and $TQRR(i)$, which characterizes the beat-to-beat systolic-diastolic interval interaction within each cardiac cycle, form the systolic-diastolic interval interaction (SDI) measures.

Variability of the SDI parameters were determined by

calculating the variances of $QTTQ(i)$ and $TQRR(i)$, which were denoted as $vSDI_{QT\text{-}TQ}$ and $vSDI_{TQ\text{-}RR}$ respectively.

2.4. Statistical analysis

Results were expressed as mean ± std. Lilliefors test was applied to evaluate the normality of ECG wave intervals and SDI measures before statistical comparison. Non-parametric Kruskal–Wallis test and Bonferroni post hoc analysis were carried out for comparisons among the three groups (CAN−, ECAN, and DCAN) to evaluate statistical significant differences. A value of $p < 0.05$ was considered significant. All the statistical calculations were carried out in MATLAB R2012b.

3. Results

The values of SDI parameters are given in Table 1 and displayed in Figure 2. Variances of the SDI parameters ($vSD_{QT\text{-}TQ}$ and $vSDI_{TQ\text{-}RR}$) showed a decreasing pattern with severity of CAN. The values of $vSDI_{QT\text{-}TQ}$ were found to be higher than the other two variability measures. $vSDI_{TQ\text{-}RR}$ could successfully detect the progression of CAN in addition to identifying the presence of CAN. This is evident from the results, which showed highly statistical significant differences ($p<0.001$) between the three groups and also between the CAN- and ECAN as well as ECAN and DCAN groups, whereas $vSDI_{QT\text{-}TQ}$ could only differentiate between the CAN- and DCAN group.

Table 1: Mean ± SD (standard deviation) values beat-to-beat SDI parameters in CAN-, ECAN and DCAN groups.

Subject groups	SDI parameters	
	$vSDI_{QT\text{-}TQ}$	**$vSDI_{TQ\text{-}RR}$**
CAN- (72)	28.52 ± 20.46	3.30 ± 2.02
ECAN(55)	24.99 ± 22.92	2.28 ± 1.56#
DCAN(15)	15.80 ± 14.72*	1.32 ± 0.61*^
p value	0.011	6.21e-6

* indicates significant difference between CAN- and DCAN group
\# indicates significant difference between CAN- and ECAN group
^ indicates significant difference between ECAN and DCAN group

4. Discussions

In this study, we analyzed the changes in beat-to-beat systolic-diastolic interval interaction (SDI) parameters with the progression of CAN in diabetic subjects. In our analysis, we considered TQ interval instead of TR interval as the surrogate diastolic interval by neglecting the QR interval within a cardiac cycle (Figure 1), which is included in the electromechanical diastolic interval calculated from an ECG. However, this modification has been reported in many studies to represent ventricular repolarization variability in a cardiac cycle (15, 16) and applied successfully in this study for cardiac autonomic neuropathy classification.

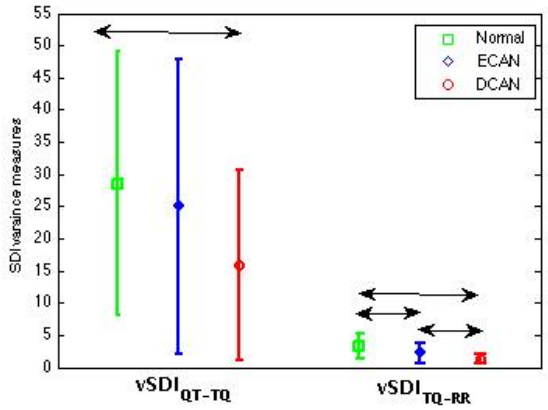

Figure 2. Error bar (mean ± sd) plots showing the trends in the variations SDI parameters within the three groups. The arrow between the groups for a particular feature indicates that it can differentiate the groups with statistical significance.

Beat-to-beat SDI parameters are simple ECG based measurements of systolic-diastolic interval interactions that can provide useful information about the diastolic dysfunction in diabetic CAN patients (11, 17). $vSDI_{QT\text{-}TQ}$ measures the variation in systolic-diastolic interval interaction in every cardiac cycle and was found to be significantly different between CAN- and DCAN. Whereas, $vSDI_{TQ\text{-}RR}$ could detect the presence and the progression of CAN, which distinguished between CAN-, ECAN and DCAN groups with very high statistical significance. This indicates that the changes in the variability of SDI parameters are more pronounced as interaction between TQ and RR rather than QT and TQ intervals. The complex interactions between QT and TQ intervals may change significantly at the advanced stage of CAN compared to earlier stages. Previous study has reported decrease in RR variability (SDRR) with severity of CAN (18). In our study, the variability of all SDI measures also decreased gradually similar to the decrease in SDRR with the severity of CAN, which might occur due to the gradual autonomic denervation in CAN patients (18). Thus the gradual degradation of autonomic control on heart rate and the subtle pathophysiological changes occurring with CAN progression might be reflected more in the beat-to-beat TQ-RR interactions, which enable these indices to classify the progression of CAN.

Therefore, $vSDI_{TQ\text{-}RR}$ were the more sensitive markers for detecting the presence and progression of CAN in diabetic subjects. This result also proved that the

proposed beat-to-beat systolic-diastolic interval interaction parameter ($vSDI_{TQ-RR}$) outperformed the existing parameter ($vSDI_{QT-TQ}$) in identifying the progression of CAN in diabetes from short-term ECG recordings.

5. Conclusion

Identification of cardiac autonomic neuropathy in the early stages of disease is an important part of the clinical assessment in diabetic patients. This study has introduced a novel feature associated with the beat-to-beat systolic-diastolic interval interaction variability, derived from short-term surface ECG recording that can efficiently detect the presence and identify the progression of CAN.

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