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Analyzing Systolic–Diastolic Interval Interaction Characteristics in Diabetic Cardiac Autonomic Neuropathy Progression

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ABSTRACT Cardiac autonomic neuropathy (CAN), one of the major complications in diabetes, if detected at the subclinical stage allows for effective treatment and avoiding further complication including cardiovascular pathology. Surface ECG (Electrocardiogram)-based diagnosis of CAN is useful to overcome the limitation of existing cardiovascular autonomic reflex tests traditionally used for CAN identification in clinical settings. The aim of this paper is to analyze the changes in the mechanical function of the ventricles in terms of systolic–diastolic interval interaction (SDI) from a surface ECG to assess the severity of CAN progression [no CAN, early CAN (ECAN) or subclinical CAN, and definite CAN (DCAN) or clinical CAN]. ECG signals recorded in supine resting condition from 72 diabetic subjects without CAN (CAN-) and 70 diabetic subjects with CAN were analyzed in this paper. The severity of CAN was determined by Ewing's Cardiovascular autonomic reflex tests. Fifty-five subjects of the CAN group had ECAN and 15 subjects had DCAN. In this paper, we propose an improved version of the SDI parameter (i.e., TQ/RR interval ratio) measured from the electrical diastolic interval (i.e., TQ interval) and the heart rate interval (i.e., RR interval). The performance of the proposed SDI measure was compared with the performance of the existing SDI measure (i.e., QT/TQ interval ratio). The proposed SDI parameter showed significant differences among three groups (no CAN, ECAN, and DCAN). In addition, the proposed SDI parameter was found to be more sensitive in detecting CAN progression than other ECG interval-based features traditionally used for CAN diagnosis. The modified SDI parameter might be used as an alternative measure for the Ewing autonomic reflex tests to identify CAN progression for those subjects who are unable to perform the traditional tests. These findings could also complement the echocardiographic findings of the left ventricular diastolic dysfunction by providing additional information about alteration in systolic and diastolic intervals in heart failure.

INDEX TERMS Cardiac autonomic neuropathy (CAN), ECG wave interval parameter, RR interval, QT interval, TQ interval, systolic interval, diastolic interval, systolic-diastolic interval interaction (SDI) parameter.

I. INTRODUCTION

Diabetes mellitus (DM) affects more than 366 million people worldwide [1]. One of the serious clinical complications of DM is cardiovascular autonomic neuropathy (CAN), which gradually results in abnormalities of heart rate control and vascular dynamics [1], [2]. The occurrence of confirmed CAN in diabetes patients is approximately 20%, and increases up to 65% with age and diabetes duration [3]. Ewing *et al.* reported a mortality rate of 53% after five years in a cohort of diabetic patients with CAN, vs. 15% in the

control group (i.e. Diabetic patients without CAN) [4]. The presence and severity of CAN are difficult to diagnose at the subclinical stage due to the absence of overt symptoms. As a result, it creates a potential negative impact on the quality of life of the patients [2], [3]. A high mortality rate due to cardiovascular complications and an increase in diabetes prevalence require accurate and sensitive measures for detecting subclinical CAN.

The Ewing battery is the gold standard for detection and determination of severity of CAN [5]. This battery consists of five cardiovascular autonomic reflex tests, which require physical responses by the patients and the presence of overt clinical autonomic neuropathy. Thus, these tests are not suitable for subclinical CAN detection [6]. Another drawback of these tests is the necessity of active participation by the patients, which is not always possible due to the patient's age, lack of mobility and different pathophysiological conditions such as the presence of arthritis, obesity, and heart or lung disease. Apart from the autonomic nervous system dysfunction, heart rhythm and the associated cardiac electrical conduction and hemodynamic characteristics are also affected by diabetic CAN.

Predominant parasympathetic denervation in the early stages of CAN was found to be associated with altered left ventricular relaxation and filling, increased left ventricular mass, left ventricular hypertrophy and impaired myocardial blood flow regulation [2], [7], [8]. These findings indicate that CAN has a strong association with diabetes-induced systolic and diastolic dysfunction and the associated high mortality and morbidity rate [3], [8], [9], [29]. Doppler echocardiography, tissue Doppler imaging (TDI) and radionuclide imaging techniques are widely used to determine the extent of ventricular autonomic denervation and to assess the level of systolic and diastolic dysfunction [7], [10]. Alternatively, a non-invasive surface ECG signal was used to analyze systolic and diastolic interval abnormalities, which indicate the mechanical abnormalities of left ventricle's function [10]–[12]. ECG based diagnostic tools are widely used, which include the analysis of different ECG wave intervals (i.e. RR interval, QT interval, TQ interval, QRS duration etc.) calculated from surface ECG, which provides information about the changes in cardiac function as well as changes in electrical activity of the heart due to different pathological conditions like diabetic CAN [32].

Frequently used ECG wave intervals derived from a surface ECG are shown in Fig. 1. Inter-beat intervals (i.e. R to R wave interval or RR interval) and their variation provide information about heart rate and the effect of the autonomic nervous system on heart rate changes over time [13]. In addition, systolic and diastolic intervals can also be derived from surface ECG signals [11], [12], [14]. The QT interval can be considered as a surrogate systolic interval within a cardiac cycle of the ECG signal, which is also defined as electrical systole [11], [14]–[18]. The duration and variability of the QT interval indicate the duration and variability of the systolic phase of a cardiac cycle, which

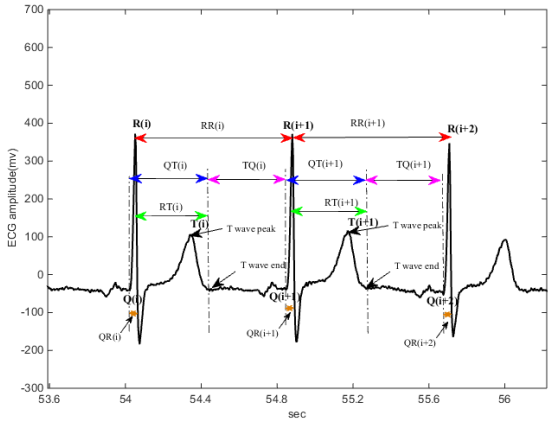

FIGURE 1. Schematic representation of different of ECG wave intervals (*RR*, *RT*, *QT*, *QR* and *TQ* intervals) in two cardiac cycles. The duration of *QR* interval is negligible in comparison to *QT* and *TQ* intervals, which is evident in the figure.

is also affected by the RR interval (i.e. total systolic and diastolic interval duration) and the TQ interval of the previous cardiac cycle [11], [12], [18]. The TQ interval is considered as a surrogate measure for the diastolic interval (i.e. electrical diastole) and directly affects the QT or systolic interval of the next cardiac cycle [11], [12], [16], [19]. The beat-to-beat QT-TQ interval relationship in terms of QT/TQ interval ratio termed as *QTTQ* is described as the systolic-diastolic interval interaction (SDI) or the balance of cardiac contraction and relaxation within one cardiac cycle [12], [16], [20]. Several studies have proposed that the SDI ratio is an indicator of ventricular dysfunction in different cardiovascular disease and increases with increased abnormal cardiac function [16], [20], [21]. Moreover, systolic and diastolic intervals can provide useful information about diastolic dysfunction [10], [20], [21], which is common in diabetic CAN patients [7]. To the best of our knowledge, SDI measures have not been applied before in diabetic CAN analysis.

In this study, we hypothesize that the analysis of the beat-to-beat SDI is a potential tool for diagnosing CAN and CAN progression in diabetic patients. Therefore, the main objective of this study was to detect the presence and severity of CAN by quantifying the beat-to-beat SDI using short-term surface ECG (i.e. 10 min ECG). We have introduced a modified SDI parameter *TQRR*, which indicates how the diastolic interval in every cardiac beat varies with respect to heart rate (i.e. total duration of a cardiac cycle containing the systolic and diastolic intervals). Finally, the performances of the *RR* interval, systolic interval duration (i.e. *QT* interval), diastolic interval duration (i.e. *TQ* interval), the existing and the proposed SDI measures was compared for accuracy in identifying the presence and the severity of CAN in diabetic patients.

II. METHOD

A. STUDY POPULATION

All patients in this study were enrolled in the Diabetes Complications Research Initiative (DiScRi) at Charles Sturt

University [6]. Data were consecutively collected from a total of 223 patients attending the clinic between January and December 2011 and consented to being tested. The research protocol was approved by the Charles Sturt University Ethics in Human Research Committee (03/164) and complies with the declaration of Helsinki.

ECG signals of a total of 142 type 2 diabetes participants were analyzed for this study. Exclusion criteria included the presence of cardiovascular, respiratory, or renal disease or use of antihypertensive or antiarrhythmic medication and any other comorbid conditions that could influence interbeat variability or T-wave characteristics. This ensured that any changes in T-wave morphology (i.e. variability in QT and TQ intervals) and the interbeat or RR interval variability were due to the severity of CAN.

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 and the level of CAN were determined using the suggested reference ranges for the outcome of five cardiac autonomic nervous system function tests as described by Ewing *et al.* [5]. These tests measure changes in heart rate (HR) during postural changes from lying to standing, response of HR in deep breathing, and the Valsalva maneuver, and the change in blood pressure (BP) from lying to standing (fall in systolic blood pressure) and response of BP to sustained handgrip tests (increase in diastolic pressure). The criterion for no autonomic neuropathy (CAN-) was that all five tests had to be within the normal range. The criterion for no autonomic neuropathy (CAN-) was that all five tests had to be within the normal range. For early signs of CAN, one heart rate test had to be abnormal or two borderline. Definite CAN was defined as two or more heart rate tests being abnormal [5]. Table 1 shows the demographics of the subjects used in this study.

TABLE 1. Subject demography of the three groups used in this study.

Group	Total number	Age (years)	Gender (M, F)
CAN-	72	76 ±16	32 M, 40 F
ECAN	55	74 ±12	19 M, 36 F
DCAN	15	78 ± 15	7 M, 8 F

Values of age are given in (mean ± STD) form. M indicates male and F indicates Female subjects.

B. ECG SIGNAL PRE-PROCESSING FOR DIFFERENT WAVE INTERVAL DETECTION

Twenty-minute long Lead II ECG traces of all participants were recorded in a supine resting condition after a 5-minute rest period to equilibrate the heart rate with Macintosh Chart version 7 and a sampling rate set at 400 Hz. A digital notch filter at 50 Hz was applied to reduce the electrical interference. High frequency noise was removed with a 45 Hz low pass filter and a 3 Hz high pass filter adjusted for wandering baseline before RR and QT interval detection. Lead II was chosen as it provides the best T-wave morphology and the strongest R peaks. Ectopic beats were selected visually and deleted manually. Linear interpolation was used to replace ectopic beats immediately before and after the ectopic interval. The patients from whom an ECG recording of at least 20 minutes was not available and in those with ECGs less than 85% normal beats were excluded from the study. ECG signals were edited using the MLS310 HRV module (version 1.0, ADInstruments, Australia) included with the LabView software package.

C. RR AND QT INTERVAL DETECTION FROM SURFACE ECG

RR and QT intervals were detected from a 10-minute ECG segment of every subject. We analyzed the first 10-minute segment of the 20 min recording, as some ECGs contain noisy portions towards the end of the recording period, which is problematic for the proper detection of QT intervals. RR and QT intervals were detected using a semi-automated template-matching algorithm proposed by Berger *et al.* [22], which provides reliable results associated with ventricular repolarization variability in many clinical studies [23]. The template matching method requires the operator to define a template QT interval by selecting the beginning of the QRS complex and the end of the T wave for one beat of the ECG signal. The algorithm then finds the QT interval of all other beats by calculating how much each beat must be temporally stretched or compressed to best match the template interval. The QT interval (i.e. systolic interval) was calculated as the difference between the Q wave onset and T wave end (i.e. QT_{end} interval) in a cardiac cycle.

D. CALCULATION OF ECG TQ INTERVAL

From the detected QT and RR interval time series, we also calculated the TQ interval (i.e. diastolic interval) and formed three time series for variability analysis. These three beat-to-beat time series are represented as:

$$\begin{aligned} QT &= \{QT(i), i = 1, 2, \ldots\ldots N\}, \\ RR &= \{RR(i), i = 1, 2, \ldots\ldots N\}, \text{ and} \\ TQ &= \{TQ(i), i = 1, 2, \ldots\ldots N\}, \end{aligned}$$

Where N is the total number of intervals within the 10 min ECG segment. The TQ interval is calculated by subtracting the QT interval from the RR interval within the same cardiac beat by neglecting the QR intervals (Fig. 1). Any RR interval time series $RR(i)$ can be expressed as:

$$\begin{aligned} RR(i) &= RT(i) + TQ(i) + QR(i+1) \\ &\Rightarrow RR(i) = QT(i) - QR(i) + TQ(i) + QR(i+1) \end{aligned} \tag{1}$$

The RR interval can be considered as the combination of RT, TQ and QR intervals. Since the QR interval duration is negligible in comparison to the RT or QT interval,

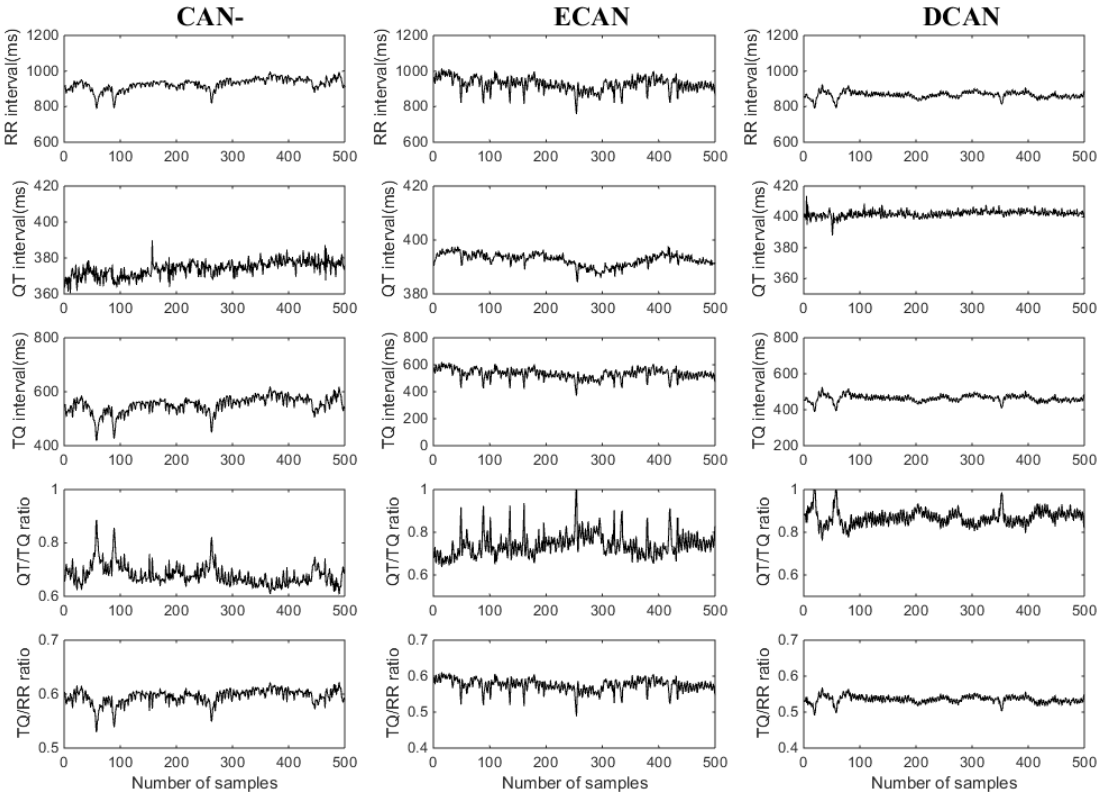

FIGURE 2. **Variation of RR interval, QT interval, TQ interval, *QTTQ* and *TQRR* time series of a single subject in three groups.**

the effect of variability due to the $QR(i)$ or $QR(i+1)$ interval is considered negligible on the overall RT or QT variability (Fig. 1) and we can assume that $QR(i) = QR(i+1)$. Hence, the beat-to-beat TQ interval can be calculated using the equation:

$$TQ(i) = RR(i) - QT(i) \tag{2}$$

E. BEAT TO BEAT SYSTOLIC AND DIASTOLIC INTERVAL INTERACTION (SDI) PARAMETERS

Existing beat-to-beat systolic-diastolic interval interaction (SDI) is defined as the ratio of the QT and TQ interval [12], [20] and can be expressed as follows

$$QTTQ(i) = \frac{QT(i)}{TQ(i)} \tag{3}$$

Where, i=1...N and N is the total number of detected QT and TQ intervals within the 10 min ECG signal.

In this study, we proposed another SDI measure for quantifying beat-to-beat systolic-diastolic interval interactions, namely $TQRR(i)$, which was calculated as $\frac{TQ(i)}{RR(i)}$. The relationship between the proposed $TQRR$ parameter and $QTTQ$ can be shown using the following equation:

$$TQRR(i) = \frac{TQ(i)}{RR(i)} = \frac{TQ(i)}{QT(i)+TQ(i)} = \frac{1}{1+\frac{QT(i)}{TQ(i)}}$$
$$\approx f(\frac{QT(i)}{TQ(i)}) = f(QTTQ(i)) \tag{4}$$

Therefore, $TQRR$ can indicate the beat-to-beat systolic-diastolic interval interaction variations similar to $QTTQ$ as shown in (4) and it actually complements $QTTQ$ in describing synchronized mechanical function (i.e. systole and diastole) of the left ventricle. In the current study, we denote $QTTQ(i)$, and $TQRR(i)$, which characterize the beat-to-beat systolic-diastolic interval interaction within each cardiac cycle, as SDI measures.

Both the mean (mRR, mQT, mTQ) and standard deviation (SDRR, SDQT, SDTQ) of different ECG wave intervals were calculated and compared between the three CAN groups to explore how these parameters change with CAN progression. The variability of the ECG wave intervals was measured as the standard deviation of the corresponding time series. The mean of all SDI measures was also studied and depicted as $mSDI_{QT\text{-}TQ}$ and $mSDI_{TQ\text{-}RR}$ respectively. Variability of the SDI parameters was determined by calculating the variances of the $QTTQ(i)$ and $TQRR(i)$ parameters, which were denoted as $vSDI_{QT\text{-}TQ}$ and $vSDI_{TQ\text{-}RR}$ respectively.

F. 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 Dunn-Sidak post hoc analysis were carried out for comparison among the three groups (CAN−, ECAN, and DCAN) to evaluate statistical

TABLE 2. Values of the mean and standard deviation of different ECG wave interval (*RR*, *QT* and *TQ*) parameters in CAN-, ECAN and DCAN groups.

ECG wave interval parameters	CAN-(72)	ECAN (55)	DCAN (15)	p value
mRR (ms)	931.16 ± 118.87	914.74 ± 124.65	903.39 ± 129.98	0.545
SDRR (ms)	44.79 ± 17.01	33.25 ± 12.80#	23.38 ± 8.52*	2.55e-7
mQT (ms)	365.91 ± 25.72	387.39 ± 24.57#	392.35 ± 30.13*	1.34e-5
SDQT ms	4.14 ± 1.84	3.99 ± 2.04	3.28 ± 1.87	0.147
mTQ (ms)	565.71 ± 104.12	527.35 ± 109.44	511.03 ± 109.28	0.063
SDTQ (ms)	43.58 ± 16.64	32.32 ± 12.58#	22.91 ± 8.26*	3.33e-7

All values are shown as mean ± STD
* indicates CAN- group is statistically significantly different from DCAN group
# indicates CAN- is significantly different from ECAN group for the particular wave interval feature.

significant differences. A value of $p < 0.05$ was considered significant. All the statistical calculations were carried out in MATLAB R2012b.

III. RESULTS

The beat-to-beat variations of the derived RR, QT, TQ intervals and SDI measures (i.e. *QTTQ* and *TQRR*) derived from the ECG segments of three subjects from the three groups (i.e. CAN-, ECAN and DCAN) are shown in Fig. 2. Visually, both RR and TQ interval showed a progressive decrease with CAN progression whereas the QT interval increased in the CAN positive groups with respect to the CAN- group. The variability of the RR and TQ is also noticeably decreased with the severity of CAN. The value of *QTTQ* gradually increases with the severity of CAN with a decrease in variability indicating the increase in the probability of arrhythmogenesis. Whereas both the magnitude and variability of *TQRR* decreases with CAN progression (Fig. 2).

Table 2 summarizes the values of these wave interval parameters for the three groups. The DCAN group had the lowest mean RR interval, mRR, (903.39 ± 129.98 ms) compared to the ECAN (914.74 ± 124.65 ms) and CAN- (931.16±118.87 ms) groups, which indicates the presence of a higher heart rate in the CAN positive groups during the resting condition (i.e., resting tachycardia). However, values of mRR were not significantly different among the three groups. SDRR, one of the time domain Heart Rate Variability (HRV) measures, decreased gradually with the increase in severity of CAN but was only significantly different between CAN- and ECAN, and CAN- and DCAN groups. Mean raw QT interval (mQT) showed an increase with progression of CAN and differentiated ECAN and DCAN significantly from the CAN- group, whereas mRR and mTQ intervals could not. The gradual decrease in the mean TQ interval or diastolic interval from CAN- to DCAN gave an indication of increased stress on heart function and incomplete relaxation of the ventricles with CAN progression. The variations of RR intervals (SDRR) and TQ interval (SDTQ) time series are significantly different in both ECAN and DCAN groups from CAN-, whilst SDQT did not differentiate between any of the three groups. Moreover, the value of SDQT is quite small in comparison to SDRR and SDTQ. None of the ECG wave interval parameter changes (i.e. Mean and standard deviations of RR, QT or TQ intervals) was significantly different among the severity of CAN. These variability patterns are shown in Fig. 3(A) and 3(B).

The values of SDI parameters are given in Table 3 and their variations in the three groups are displayed in Fig. 3 (C-D). The mean SDI measure (i.e. $mSDI_{QT\text{-}TQ}$) gradually increased with the increase in severity of CAN. On the other hand, $mSDI_{TQ\text{-}RR}$ progressively decreased with the CAN progression and is lowest in the DCAN group, which demonstrated the gradual reduction in the mean diastolic interval (i.e. mTQ) in the CAN positive groups (CAN-: 565.71 ± 104.12 ms, ECAN: 527.35 ± 109.44 ms and DCAN: 511.03 ± 109.28 ms).

Variances of the SDI parameters ($vSD_{QT\text{-}TQ}$ and $vSDI_{TQ\text{-}RR}$) showed a decreasing pattern with severity of CAN. The variance of *QTTQ* ($vSDI_{QT\text{-}TQ}$) was found to be higher than the variance of *TQRR* measure in three groups. $vSDI_{TQ\text{-}RR}$ could successfully detect the progression of CAN by differentiating the early and definite levels 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 ECAN and DCAN groups, whereas $vSDI_{QT\text{-}TQ}$ was only found to be different between the CAN- and DCAN group.

IV. DISCUSSIONS

In this study, we analyzed the changes in beat-to-beat variations for different ECG wave intervals (i.e. RR, QT and TQ intervals) and systolic-diastolic interval interaction parameters with the progression of CAN in diabetic subjects. The findings of this study validated our hypothesis that beat-to-beat SDI parameters derived from short term ECG recording can efficiently detect and distinguish the groups with different levels of CAN from the group having no CAN. The results of this study also suggest that the systolic-diastolic interval interaction based features performed better than the time domain HRV based methods in identifying the progression of CAN in diabetes from short-term (i.e. 10 min) ECG recordings.

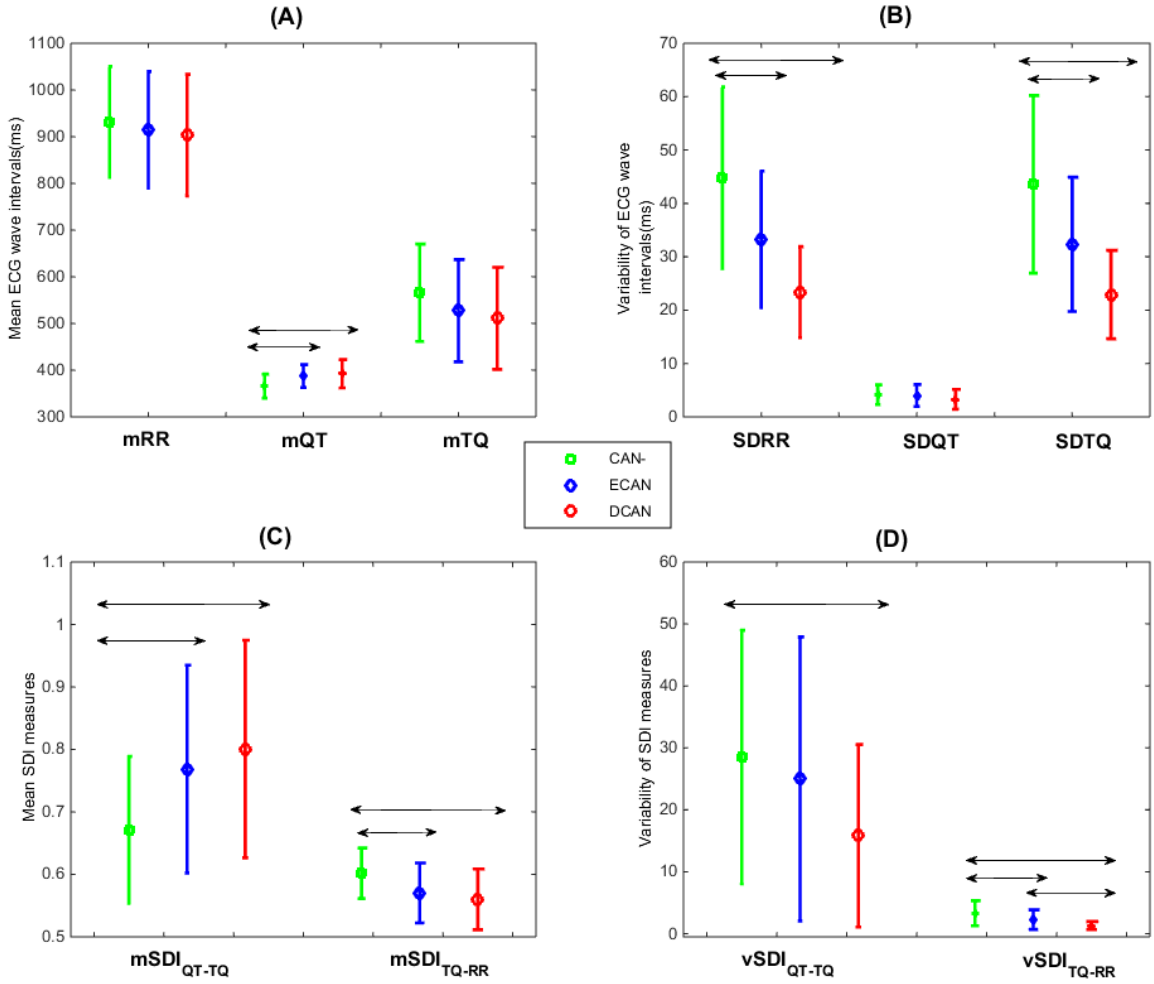

FIGURE 3. Error bar (mean ± STD) plots showing the trends in the variability of different ECG wave intervals (A, B) and SDI parameters (C, D) within the three groups. The arrow between the groups for a particular feature indicates that it can differentiate the groups with statistical significance. From Fig. 3(D), it is obvious that only the variability measures of beat–to-beat SDI parameter ($vSDI_{TQ\text{-}RR}$) can significantly differentiate all the three groups (CAN-, ECAN and DCAN) thus identifying the presence and progression of CAN.

TABLE 3. Values of mean and variance of beat-to-beat SDI parameters in CAN-, ECAN and DCAN groups.

SDI parameters	CAN-(72)	ECAN (55)	DCAN (15)	p value
$mSDI_{QT\text{-}TQ}$	0.67 ± 0.11	0.77 ± 0.16#	0.80 ± 0.17*	1.01e-4
$vSDI_{QT\text{-}TQ}$	28.52 ± 20.46	24.99 ± 22.92	15.80 ± 14.72*	0.011
$mSDI_{TQ\text{-}RR}$	0.60 ± 0.04	0.57 ± 0.04#	0.55 ± 0.04*	9.52e-5
$vSDI_{TQ\text{-}RR}$	3.30 ± 2.02	2.28 ± 1.56#	1.32 ± 0.61*^	6.21e-6

All values are shown as mean ± STD
* indicates CAN- and DCAN groups are statistically different
# indicates CAN- and ECAN groups are statistically different
^ indicates the statistically significant difference between ECAN and DCAN group for the particular SDI measure.

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 (Fig. 1) assuming that this interval has negligible effect on QT variability (QTV). However, this modification has been reported in many studies where the RT interval instead of the QT interval was used to represent ventricular repolarization variability in a cardiac cycle [24], [25] and applied successfully in the current study for analyzing diastolic interval variability in cardiac autonomic neuropathy classification.

TQRR was found to be a more sensitive parameter than *QTTQ* to track progression of CAN in diabetes, which indicates that changes in diastolic interval is more sensitive with CAN related alteration of the mechanical abnormality of ventricular relaxation. *TQRR* indicates the variation of the diastolic interval within a cardiac cycle, whereas

QTTQ describes the balance between the systolic and diastolic interval within a cardiac cycle. Previous studies have shown that left ventricular diastolic dysfunction (LVDD) is related to diabetic CAN and better reflected in altered HRV than in QTV [7], [28], [29]. The change of SDQT is not significant between the CAN groups while both SDRR and SDTQ changes gradually with CAN progression. *TQRR* includes the effect of normalization with respect to heart rate and indicates the rate corrected diastolic interval variation which has also been reported very sensitive in coronary artery disease analysis [33]. Moreover, due to the nonlinear relationship between the heart rate and diastolic interval, changes in heart rate due to CAN related alteration in ANS are more evidently reflected with the variation in diastolic rater than in the systolic time interval [35]. Therefore, these findings prove the increased sensitivity of *TQRR* in CAN progression detection rather than *QTTQ*.

Significant findings of this study are discussed in the following sub-sections.

A. RELATIONSHIP BETWEEN HEART RATE AND DIASTOLIC DYSFUNCTION IN CAN

CAN was found to be associated with left ventricular diastolic dysfunction (LVDD) in both type 1 and type 2 diabetes patients [7]–[9]. LVDD is characterized by impaired left ventricular (LV) relaxation due to LV concentric remodeling and increased LV mass even with normal ejection fraction (EF) [7], [10]. LVDD was found to be prevalent in diabetic CAN patients [9], [30] and related to increased resting heart rate and a RR variability decrease, due to the relative predominance of sympathetic nervous system activity at the earlier stages of CAN as a result of parasympathetic denervation [3], [7], [30]. Incomplete relaxation of the ventricles, which could be interpreted from the alteration (i.e. decrease) in diastolic interval duration [10]–[12], is found in diabetic CAN subjects and associated with higher heart rate (i.e. decreased RR interval) during supine rest [3], [7] indicating the coupled relation between heart rate and diastolic interval. Left ventricular hypertrophy, which is a result of LVDD has been shown to be a powerful predictor of cardiovascular disease (CVD) mortality similar to CAN related heart rate variability changes in diabetes [1]–[3], [7]. Therefore, analysis of the interaction between diastolic interval (i.e. TQ interval) and heart rate (i.e. RR interval) and their variability from surface ECG could provide useful information for CAN diagnosis.

B. CHANGES IN HRV PARAMETERS IN CAN

Although the changes in the mean RR interval were not significant between groups, it indicated the presence of an increased resting heart rate (i.e. decreased *RR* interval) in the CAN positive subjects as reported in several previous studies [1]–[3], [26]. Some recent studies have suggested that the higher heart rate in diabetic CAN subjects is associated with higher cardiac output and left ventricular hypertrophy due to incomplete relaxation of the ventricles, which might lead to diastolic heart failure without overt heart disease [7], [28], [29]. Therefore, the increased resting heart rate, observed in our study as a decrease in mRR, suggests that DCAN subjects may be more prone to develop heart failure associated with resting tachycardia than subjects without CAN [2], [3].

Heart rate variability measured by SDRR decreases from CAN- to DCAN, with CAN- being significantly different from ECAN and from the DCAN group. This corroborates previous research findings that reported a decrease in heart rate variability with increasing heart rate in diabetic subjects with CAN [1]–[3], [26]. However, SDRR was not sensitive to CAN progression, as it could not differentiate the ECAN from the DCAN group (Table 2, Fig. 3(B)). Thus, SDRR detected changes in heart rate associated with parasympathetic denervation at the subclinical stages of CAN and definite impairment of the autonomic modulation of the heart rate, but not the gradual changes associated with the progression from ECAN to DCAN [1].

C. CHANGES IN ELECTRICAL SYSTOLIC AND DIASTOLIC INTERVAL DURATIONS IN CAN

The mean systolic interval (mQT) gradually increased with the severity of CAN and significantly differentiated CAN- from ECAN and DCAN groups. QT interval prolongation in ECG recordings was reported in several studies as an indicator of the presence of CAN [3], [7], [31], which supports our current findings. One of the interesting findings of this study is that the gradual decrease in the mean amplitude and variability of diastolic interval, (i.e. mTQ and SDTQ), with CAN progression, although the decrease in mean value is not statistically significant. The increase in systolic interval and decrease in the diastolic interval with an increase in heart rate found in the CAN positive patients (i.e. ECAN and DCAN group subjects) could indicate that they are more prone to arrhythmogenesis than the CAN- group [12], [14].

In contrast to SDQT (i.e. variability of the systolic interval), SDTQ showed a similar decreasing trend with CAN progression as SDRR. It also differentiated CAN positive groups from the CAN- group. These results are aligned with some previous findings [18], [27], [28], which indicated that changes in diastolic interval variability is highly correlated with RR interval variability (i.e. SDRR) but not with systolic interval variability, which showed minimal changes with alteration of ANS modulation on heart rate in healthy subjects. Therefore, a significant decrease in SDTQ similar to the SDRR results might be associated with an impaired ANS control in CAN positive subjects. However, these parameters were unable to identify the progressive impairment of ANS control of the heart associated with CAN.

D. CHANGES IN BEAT TO BEAT SYSTOLIC-DIASTOLIC INTERVAL INTERACTION (SDI) PARAMETER IN CAN

Beat-to-beat SDI parameters are simple ECG based measurement of systolic-diastolic interval interactions that can provide useful information about the diastolic dysfunction in

diabetic CAN patients [7], [11], [20]. $mSDI_{QT\text{-}TQ}$ indicates the mean interaction between systolic and diastolic intervals and was found to increase with severity of CAN. The increase in *QTTQ* observed is due to the progressive increase in the QT interval and decrease in TQ interval, which indicates that the heart is taking more time for the systolic phase and limits the proper recovery time of ventricles affecting proper filling of blood for the next ventricular contraction cycle [9]–[11]. This leads to increased cardiac stress and further progression of cardiac pathology such as impairment of ventricular repolarization and arrhythmia with CAN progression [10], [12]. Furthermore, a higher systolic to diastolic interval ratio was also reported as an indication of impaired ventricular function in subjects with cardiac disease and a sign of arrhythmogenesis [12], [20], [21]. These findings suggest that DCAN patients may be more susceptible to arrhythmogenesis and heart failure than diabetes subjects without CAN and can be identified efficiently by analyzing the beat-to-beat SDI. The gradual decrease in $mSDI_{TQ\text{-}RR}$ with CAN progression also supports our findings of the continuing decrease in both RR and TQ intervals. Although none of these mean SDI parameters could differentiate between the ECAN and DCAN group, these indices can provide valuable information about changes in ventricular function that may lead to left ventricular diastolic dysfunction (LVDD) [8]–[10], [12].

$vSDI_{QT\text{-}TQ}$ measures the variation of systolic-diastolic interval interaction in every cardiac cycle and was found to be significantly different only between the CAN- and DCAN group. Whereas, $vSDI_{TQ\text{-}RR}$ could detect the presence and the progression of CAN, distinguishing 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 intervals rather than QT and TQ intervals with autonomic denervation in CAN. Moreover, the complex interactions between QT and TQ intervals may not change significantly at the earlier stages of CAN but show pronounced modification in advanced stages of CAN. However, the changes in the interactions of TQ with RR intervals were evident in the early stages as well as with the advancement of CAN and also reported to be more sensitive in the detection of early diastolic dysfunction in myocardial ischemia [33]. This may then explain why $vSDI_{QT\text{-}TQ}$ could not detect ECAN from the CAN- group, but differentiated CAN- from DCAN whilst the other SDI measure (i.e. $vSDI_{TQ\text{-}RR}$) could differentiate between all three groups successfully. 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 ANS denervation in CAN patients [1]–[3]. Thus the gradual degradation of ANS 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.

$vSDI_{TQ\text{-}RR}$ was the only feature found in our study that showed a significant difference between the ECAN and DCAN group in addition to differentiating the ECAN and DCAN groups from the CAN- group, and thus proven as a sensitive marker for detecting the presence and progression of CAN in diabetic subjects. The pathophysiological basis of CAN progression from ECAN to DCAN is a function of increasing hyperglycemia and free radical damage to the autonomic nervous system [1], [30]. Initially the parasympathetic fibers are affected as that have a tonic influence on heart rate and thus decrease heart rate variability and increase ventricular repolarization variability with a more pronounced, but phasic sympathetic influence [1], [30], [31]. At the definite stage of CAN, sympathetic fibers are also damaged due to free radical activity, which leads to changes in the heart rate (HR) and ventricular repolarization (VR) characteristics due to both parasympathetic and sympathetic modulation of the HR and VR being abnormal [31], which might be reflected better in $vSDI_{TQ\text{-}RR}$ parameter compared to others. This study results also indicate the increase in systolic interval and the decrease in the diastolic interval with CAN progression, which detect the alteration of normal mechanical relaxation of the ventricles affecting diastolic function.

The proposed beat-to-beat SDI parameter outperformed other HRV parameters and ECG wave interval features in identifying the progression of CAN in diabetes from short-term ECG recordings. Beat-to-beat QT, RR and TQ interval analysis technique used in this study also overcome the problem of determining subject specific heart rate correction formula, effect of hysteresis on QT-RR interaction and the incompetent gross variability measures for describing the heart rate and ventricular repolarization variability [12].

E. THE FEASIBILITY OF USING SDI PARAMETERS IN CLINICAL HEALTHCARE

The current research provides several advantages for clinical health care. The first is that the SDI method can be used in place of the Ewing test battery, which has several counter indications including the presence of cardiorespiratory disease [6]. Second, the Ewing battery is not accurate if applied for identification of subclinical CAN and in obese or movement restricted patients. The SDI method requires the patient to be in a supine resting position only whilst recording the ECG. Third, SDI provides additional information about cardiac systolic and diastolic functions as well as CAN severity in addition to HRV analysis from the ECG trace. This information complements the echocardiographic techniques for analyzing systolic and diastolic heart failure and therefore can be used for determining a patient group who actually should be referred for echocardiography. This ECG based technique will definitely help providing a cost effective health care service whose demand is increasing due to increase in cardiac imaging related Medicare cost and inaccessibility of echocardiographic services in every clinical setting [35].

In clinical settings the possible sources of error associated with an ECG are the presence of noise due to power line interference, muscle artifact noise due to movement of the

patient and baseline wondering noise. These must be filtered out before the analysis can be undertaken. In addition, ECG segments of only normal sinus rhythm (i.e. without any ectopic beats) should be considered for this analysis. Our proposed measures are validated using 10 min single lead ECG (Lead II) recordings. The unpublished results of this study also indicated that the performance of the proposed measures was found equally useful in 5 min ECG segments, which is a standard in the clinical setting and both *QTTQ* and, *TQRR* showed similar good performance in analyzing CAN detection and progression. Therefore, further validation is necessary in shorter ECG recording durations (i.e. 2-5 min) and in different ECG recording leads (i.e 12 lead ECG). As the efficiency of the proposed measures depend on the proper detection of RR, QT and TQ intervals we believe that ECG leads having a clearly detectable high amplitude T wave (Lead I, Lead II, Precordial leads V1-V6) in a 12 lead ECG system might show similar performance.

Our future study will include the analysis of sensitivity of SDI measures with varying recording duration (ranging from 1 to 10 minutes) and validate its applicability in 12 lead ECG signal. Also the effect of methodological difference of QT interval detection (i.e. manual measurement technique like slope intercept method vs. template matching algorithms) will be considered.

V. CONCLUSION

Identification of cardiac autonomic neuropathy is an important part of the clinical assessment in diabetic patients. Systolic and diastolic interval analyses have been shown to be associated with CAN progression, (i.e. transition from CAN- to early CAN to definite stage) whereas HRV based analysis cannot determine CAN progression. This study has introduced a novel feature associated with the beat-to-beat SDI variability (TQ/RR) that can successfully detect the presence and identify the progression of CAN. An association of SDI with progression of CAN is thought to be useful in further exploring the CAN related vulnerability in arrhythmogenesis and heart failure, which might help the physician to determine an efficient treatment plan for the patient if diagnosed at an early stage of CAN.

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