Heart rate variability and complexity in people with diabetes associated cardiac autonomic neuropathy

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***Abstract*— Cardiac autonomic neuropathy (CAN) in diabetes has been called a "silent killer", because so few patients realize that they suffer from it, and yet its effect can be lethal. Early sub clinical detection of CAN and intervention are of prime importance for risk stratification in preventing sudden death due to silent myocardial infarction. This study presents the usefulness of heart rate variability (HRV) and complexity analyses from short term ECG recordings as a screening tool for CAN. Poincaré plot indexes and sample entropy (SampEn) measure of HRV were used for analyzing variability (short and long term) and complexity respectively. Analyses were performed on the different length of HRV records during supine rest. Reduced Poincaré plot patterns and higher SampEn were found in CAN+ group. Significant changes in HRV parameters of CAN+ group during the course of supine rest were found in contrast to control group (CAN-). Our results demonstrated the potential utility of nonlinear HRV parameters in identifying asymptomatic CAN.**

I. Introduction

As many as 22% of people with type 2 diabetes mellitus (DM) suffer from cardiac autonomic neuropathy (CAN) which leads to impaired regulation of blood pressure, heart rate and heart rate variability (HRV). Around 75% of people with diabetes die from cardiovascular disease such as heart attack and stroke [1]. Silent ischaemia is significantly more frequent in patients with than in those without CAN (38% vs 5%) [2]. Early sub clinical detection of CAN and intervention are therefore of prime importance for risk stratification in preventing the potentially serious consequences of CAN especially in people with diabetes.

A noninvasive Ewing test battery [3] specifically designed for identifying CAN is only sensitive for people that are symptomatic. It requires patient cooperation and more importantly is often not able to be performed due to co-morbidities in the patients that would benefit most. These co-morbidities include existing heart or respiratory disease, which is a counter indication for the Valsalva manoeuvre. Use of antihypertensive medication influences the outcome of the lying to standing test that measures blood pressure changes on standing and identifies orthostatic hypotension. The lying to standing heart rate (HR) test is often difficult to perform due to the lack of mobility often found in the elderly.

New methods that are non-invasive and independent of patient cooperation are preferable in the diagnosis of CAN but still require further research to understand their sensitivity and specificity in risk stratification for CAN. The most common method used is heart rate variability analysis [4]. Changes in HRV is regarded as one of the early signs of cardiac autonomic neuropathy [5]. However, conventionally used time and frequency domain parameters of HRV are not always suitable for analysis because of non-stationarity characteristic of ECG recordings and the presence of nonlinear phenomena in the physiological signal's parameter variability. Only a few studies have applied new parameters based on nonlinear dynamics theory to HRV analysis in DM patients [6,7]. Application of new signal processing techniques based on nonlinear dynamics provides supplementary information (i.e., hidden underlying mechanism) about systems involved in cardiovascular function and pathology. The visual analysis of variability by Poincare´ plot [8] and quantification of the unpredictability and complexity of the heart rate using sample entropy [9] are increasingly used because they can be computed from shorter HRV records that are used in community screening.

Therefore, the aim of this study was to ascertain how and which of the variability and complexity parameters of heart rate derived from the Poincare´ plots and sample entropy are different in DM patients with CAN (CAN+) compared with DM patients without CAN (CAN-) as a first step to determining the utility of these parameters in identification of asymptomatic CAN. This study also assessed the minimum length of heart rate signals required for screening CAN+ during supine rest.

II. Methods

A. Subjects and ECG signals

After standard exclusion criteria were applied to ensure that any changes in HRV detected were due to the severity of the diabetes, nine patients with Type 2 diabetes mellitus were included in the study. Four patients were CAN positive (CAN+), whilst the remaining five were CAN-, being without clinical signs and symptoms of CAN. The research protocol was approved by the Charles Sturt University ethics in Human Research Committee (03/164). Exclusion criteria

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included not completing the full five Ewing battery of tests, those with a history of cardiac pathology, and those with less than 85% qualified sinus beats. ECGs were recorded over 20 minutes using a lead II configuration (Maclab version5) and recorded on Macintosh Chart version 4 with a sampling rate set at 400 Hz and a notch filter at 50 Hz. For the Ewing battery, CAN+ was determined with reference to standards reported by Ewing and requiring two or more abnormal results [3].

ECG signals were edited using the MLS310 HRV module (version 1.0, ADInstrument, Australia) from a Chart software package. High frequency noise was removed with a 45 Hz low-pass filter and a 3 Hz high pass filter adjusted for wandering baseline. Ectopic beats were selected visually and deleted manually. Linear interpolation was used to replace ectopic beats that occur immediately before and after the ectopic interval. Intervals between successive R waves of the QRS complex (i.e. instantaneous heart rate (IHR) in beats per min (bpm)=60/R-R intervals in seconds) were calculated. The HRV analysis described in the following sections was performed on various lengths (e.g., from 100~1200) of IHR points to test the minimum length of data required to identify CAN+.

B. Poincaré plot analysis

The Poincaré plot is a popular two-dimensional visualization tool for dynamic systems due to its intuitive display of the dynamic properties of a system from a time series. The length (SD2) and the width (SD1) of the long and short axes of Poincaré plot images represent short and long-term variability of any nonlinear dynamic system [8]. We developed mathematical formulations that relate each measure derived from Poincaré plot geometry to well-understood existing heart rate variability indexes [8]. A strong correlation was found when comparing high frequency power of heart rate signals (modulated by parasympathetic nervous system) to SD1 [13]. SD2 was found to be well correlated with both low and high frequency power (modulated by both the parasympathetic and sympathetic nervous system) [13]. The Poincare´ plot was generated as a scatter plot of current instantaneous heart rate (IHR) against the IHR immediately preceding it. Using the method described by Brennan [8], these plots were used to extract indexes, such as length (SD2) and width (SD1) of the long and short axes of Poincaré plot images.

C. Sample entropy analysis

Sample entropy (SampEn) values of IHR signals from all subjects were calculated. SampEn was developed to reduce the bias caused by the self matching in approximate entropy which is a mathematical approach to quantifying the complexity and regularity of a system [9]. SampEn is defined as the logarithmic likelihood that the patterns of the data that are close to each other will remain close for the next comparison within a longer pattern. SampEn does not use a template-wise approach when estimating conditional probabilities. It only requires that one template find a match of length m+1, then it computes the logarithm of a probability associated with the time series as a whole. Mathematical derivation can be found in previous literature [9]. Parameter **m** which specifies the pattern length was set at 3 and **r** defining the criterion of similarity was set at 17% of the standard deviation of IHR data. Length of data (N) was varied from 100 to 1200 beat number.

D. Surrogate data analysis

To prove any intrinsic relationship of the heart rate control system with SampEn, we followed a method of surrogate data analysis introduced by Theiler *et al.* [15]. For each IHR series of all subjects, 10 surrogate IHR series were obtained by randomly shuffling the original series. Each surrogate data set had an identical IHR distribution (i.e., same mean, SD, and higher moments) as the original data sets and differed only in the sequential ordering of IHR series. SampEn values are computed for 10 surrogate data series. The mean values of the surrogated SampEn were then compared with the SampEn computed for the original IHR data series. It was assumed that the presence of nonlinear structure in the dynamics of the original data exist, given a statistically significant difference is found when comparing the calculated SampEn of the original series and the mean SampEn of the randomly selected surrogate data series. The number of SD (standard deviations) (i.e. d) between the mean of original indexes and the mean of indexes of the surrogate data sets (i.e. d = (original - surrogate)/SD of surrogate) was computed. If $d > 3$, the difference between the original data set and the surrogate data set was considered statistically significant [10].

E. Statistical analysis

Results were expressed as means (±SD). The non-parametric Mann-Whitney U-test was performed to allow for pairwise testing for significant differences of HRV parameters between the two groups. A value of $p < 0.01$ was considered significant. The non-parametric test was used because of non-Gaussian distribution of the variables as ascertained by the Lilliefors test.

III. Results and Discussion

A. Poincaré plot indexes

In order to compare the HRV patterns of CAN+ and CAN- DM patients, two representative examples of IHR time series and its corresponding Poincaré plots taken from each group have been presented in Figures 1A,B,C&D. HRV characteristics of a CAN- subject with mean IHR of 61.75 ± 2.50 bpm, and its corresponding Poincaré plot (Figure 1B) with indexes (SD1 = 2.32, SD2 = 6.67, SD1/SD2 = 0.34) and estimated SampEn of 1.40 are visually different from the HRV characteristics of CAN+ subject with mean IHR 61.49 ± 1.26 bpm, and its corresponding

Poincaré plot (Figure 1D) with indexes SD1 = 1.49, SD2 = 3.24, SD1/SD2 = 0.46 and estimated SampEn = 1.98. Table I summarizes the results from average values of Poincare indexes in the two groups. Although a marked reduction of SD1, SD2, and mean IHR in the CAN+ group were observed, no significant differences were found.

The principle of Poincare plot construction is taken from nonlinear dynamics theory, but indexes used for its quantification are essentially linear [8]. However, this plot can provide supplementary information about beat to beat HRV structure which cannot be obtained by conventional time and frequency domain analysis [11]. From the Poincaré plot indexes, CAN+ subjects had all measures reduced [Table I]. The decreased long term HRV (represented by the length SD2) and decreased beat to beat HRV (represented by the width, SD1) was expected in CAN+ patients as the reduction of Poincaré plot indexes (SD1, SD2) was confirmed in other studies with parasympathetic nervous system dysfunction [12,14].

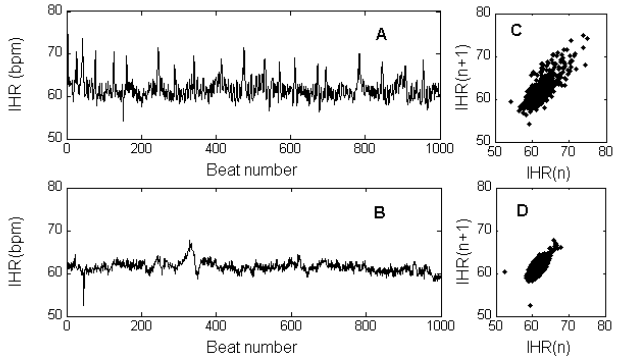

Fig. 1. Top panels show IHR time series from a control (CAN-) subject (A) and its corresponding Poincaré plot (C). Bottom panels show IHR time series from a DM subject with CAN+ (B) and its corresponding Poincaré plot (D).

SD1/SD2 represents the ratio of short term and long term variability. The larger SD1/SD2 ratio for the CAN+ subjects reflects that a greater percentage of its overall variance is beat-to-beat variance. No significant difference was found between the SD1/SD2 values of two groups. However, SD1/SD2 values of IHR in the CAN- group remain stable irrespective of IHR data length (as shown in Fig. 2). During the rest, there is gradual sympathetic inhibition and parasympathetic activation in humans. Our results ascertained that in CAN- group the sympathovagal balance (represented by SD1/SD2) remained stable during the length of supine rest. In contrast, the CAN+ group showed higher SD1/SD2 values during the first 400 beats and then decreases during the course of time (Fig. 2). The possible explanation of this finding may be that the individuals in the CAN+ group exhibit slower parasympathetic activation and/or sympathetic withdrawal during supine rest as a manifestation of cardiac dysregulation.

B. SampEn values of IHR of CAN+ and CAN-

To explore the complexity of the heart rate variability, the sample entropy of the IHR signals was calculated. It is interesting to note that the difference between SampEn values in the two groups was highly significant ($p < 0.01$). Lower values of SampEn reflect more regular time series while higher values are associated with less predictable (more complex) time series. The higher SampEn values of CAN+ group indicates an increase in irregularity and randomness in the IHR of CAN+. Mean SampEn values of 400 IHR points are summarized in Table I. SampEn of IHR in CAN+ group remained higher irrespective of IHR data length (as shown in Fig. 3). Significant differences between the two groups were found at the length of 400,600, 800 and 900 beats. On the other hand, SampEn of the CAN- group remained stable and lower irrespective of IHR data length. Fluctuations in SampEn values over the period of the test in CAN+ group might indicate the impairment of the cardiovascular control system. Mechanisms involved remain to be investigated. The use of surrogate data was aimed at destroying the underlying control mechanism (time series structure in beat to beat heart rate) and to increase the degree of randomness. Mean values of surrogate SampEn of IHR data in the CAN+ group (Table I) was found to be no more significantly ($p > 0.05$) different than surrogate SampEn in the CAN- group. Also, mean values of surrogate SampEn were found to be significantly (d>3) higher than that of original SampEn values of IHR data in both groups reflecting the effects of randomness. Therefore, it can be suggested that fluctuations in beat to beat heart rate dynamics are not randomly executed rather it is modulated by a cardiac regulation system which remains stable in CAN- but changes with neuropathy in CAN+.

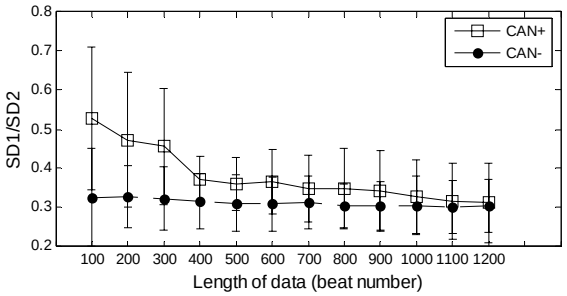

Fig.2 Mean and standard deviation of SD1/SD2 values of IHR signals of CAN- and CAN+ patients over the various data lengths, N(range:100-1200 beat number).

C. Relationship between SD1/SD2 and SampEn

The relationship of the SD1/SD2 ratio with SampEn (shown in Fig. 4) makes intuitive sense, because the SD1/SD2 describes a relationship between microscopic and macroscopic variability reflecting a fractal like relationship. On the other hand, SampEn extracts the complexity information, a nonlinear behaviour. The relationship between the two apparently nonlinear measures of HRV

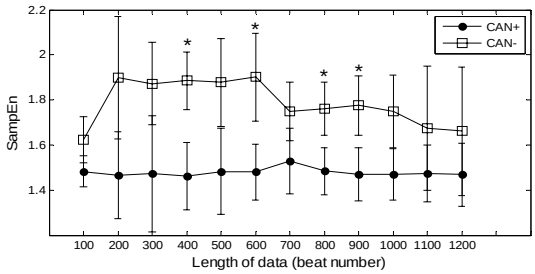

Fig.3 Mean and standard deviation of SampEn values of IHR signals of CAN- and CAN+ patients over the various data lengths, N(range:100-1200 beat number).*means significant (p <0.01) difference.

should be unchanged or stable irrespective of the length of IHR data in normal autonomic nervous function. However, any dysfunction in the autonomic nervous system over a successive length of time is a breakdown of such a constant relationship as can be seen in Fig. 4 for CAN+ patients. We speculate that such a relationship could be an indirect measure of dynamical stability of autonomic nervous system function underlining the possible benefit in cardiac dysregulation diagnosis.

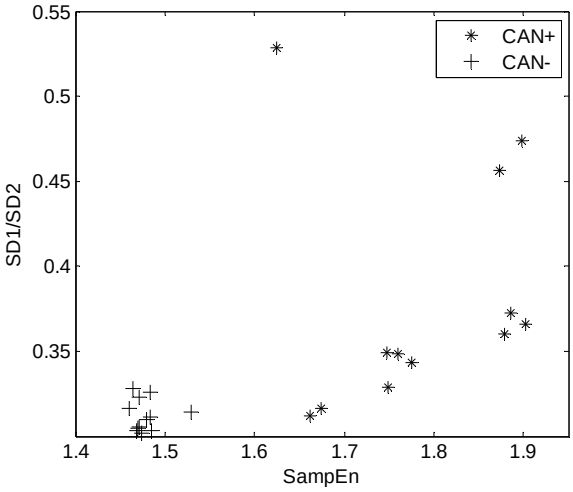

Fig. 4. Relationship between mean SD1/SD2 and mean SampEn of IHR signals of CAN- and CAN+ patients group over the various data lengths, N (of IHR data (range:100-1200 beat number with an increment of 100 beats).

In conclusion, the results of the investigation indicate possible dysfunction of autonomic control of heart rate in DM patients with CAN+. HRV analysis using short term ECG traces could be effective in detecting CAN. Further research on a large sample size is required to further elucidate the findings of this study and effectiveness of HRV analyses for early detection of mild and severe CAN in diabetic patients.

TABLE I
MEAN AND SD OF HRV PARAMETERS OF IHR POINTS (N=400) OF FOUR CAN+ AND FIVE CAN- SUBJECTS

	CAN+ (mean±SD)	CAN- (mean±SD)
SampEn (original)	1.88±0.12*	1.46±0.14
SampEn(surrogate)	2.39±0.26#	2.28±0.08#
SD1 (bpm)	1.98±0.74	2.14±0.32
SD2(bpm)	5.44±2.19	6.92±1.09
SD1/SD2	0.37±0.05	0.31±0.07
IHR(bpm)	70.92±9.06	68.14±7.95

* significant (p<0.01) difference between CAN+ and CAN-. # The values of d [see section IID for details] were found to be greater than 3 between SampEn (original) and SampEn (surrogate) values the two groups.

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