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Identification of cardiac autonomic neuropathy in people with diabetes mellitus using short-term ECG recording

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Abstract. Diabetes mellitus is a serious and increasing health problem world-wide. An increased risk for all cardiovascular disease compared to non-diabetic patients including dysfunctional neural control of the heart. The clinical manifestations of cardiac autonomic neuropathy (CAN) include heart rate variability. Poor diagnoses of CAN may result in increased incidence of silent myocardial infarction and ischemia, which can lead to sudden death. This study examined the usefulness of HRV analyses of short ECG recordings as a method for detecting CAN utilizing the traditional Ewing battery as a standard for identification of CAN. Several HRV parameters were assessed including time and frequency domain as well as nonlinear parameters. The advantage of the newer nonlinear HRV measures such as approximate entropy (ApEn) is that they are model independent, suitable for nonlinear processes, and measure aspects of HRV different from the traditional methods such as standard deviation or spectral analysis. Eighteen of 38 individuals with diabetes were positive for two or more of the Ewing battery of tests indicating CAN. Approximate Entropy (ApEn), log normalized total power (LnTP) and log normalized high frequency (LnHF) power were different in CAN^+ to CAN^- individuals ($p < 0.05$). This indicates that nonlinear scaling parameters are able to identify people with cardiac autonomic neuropathy in short ECG recordings.

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Diabetes and its complications

Diabetes mellitus (DM) is a serious and increasing health problem in Australia; with the most common being type 2 – non insulin dependent (NIDDM).[1] This is characterised by insulin deficiency or insulin resistance.[2] It is usually occurs in adults over 40 years old, but is increasingly affecting younger age groups.[3] Patients with type II diabetes have approximately twice the risk for all cardiovascular diseases compared to non-diabetic patients.[4]

DM can cause dysfunction of any or every part of the autonomic nervous system (ANS), leading to a wide range of complications. The most troublesome of these being cardiovascular autonomic neuropathy (CAN), which affects multiple organ systems.[5] The clinical manifestations of CAN include orthostatic hypertension and abnormalities in heart rate variability (HRV), which reflects the variation in the length of the beat-to-beat interval.[6] Undiagnosed CAN may result in increased incidence of silent myocardial infarction and ischemia, which can lead to fatal conditions such as sudden death.[7] The high mortality rate in patients with CAN led to the development of clinical investigations of CAN in people with diabetes. The Ewing battery of tests, introduced by Ewing, is used to identify CAN in diabetics. HRV measured from 24 hours electrocardiogram (ECG) recordings was later used concurrently with the Ewing battery of tests to determine changes in heart rate indicative of abnormal nervous system function.[8-10] 24-hour HRV was able to identify CAN and and even identify asymptomatic cases. The purpose of this study was to examine the usefulness of HRV analyses of short-term ECG recordings as a method for detecting CAN in type II diabetics in comparison with the Ewing battery.

Autonomic Reflex Tests: The Ewing Battery of Tests

One of the most widely used tests for cardiovascular autonomic reflexes, is the Ewing 'battery', which consists of five non-invasive, standard bed-side tests, which examine the changes in heart rate (HR) in response to deep breathing, the Valsalva manoeuvre and standing, plus blood pressure (BP) responses to standing and sustained hand grip. Damage to cardiovascular autonomic nerves can be assessed using the combined results obtained from the five tests.[11] All of these cardiovascular autonomic reflex tests suffer from a common problem, as they require active cooperation from the patients. This affects the accuracy and reproducibility of the results.[12, 13]

Heart Rate and Heart Rate Variability

Heart rate (HR) measures the number of heart beats, usually by counting the number of QRS complexes. The normal HR is determined by dynamic interaction between the spontaneous cardiac impulse generated by the sinoatrial node and the influences of the sympathetic and parasympathetic nervous systems, which work antagonistically. Acceleration of the heart is affected by both the inhibition of parasympathetic influence and the stimulation of the sympathetic nervous system and vice versa. The activity of the heart is also governed by moment-to-moment changes in blood pressure and respiration as well as endocrine influences. All three result in continuous variation in the intervals between beats. HRV reflects the changes in the balance between the different influences such as sympathetic and parasympathetic input, which modulate HR.

Clinical Assessment of HRV

HRV is the simplest and best non-invasive method to assess the sympathovagal balance on the heart. [14] HRV is widely used in a variety of research and clinical fields including diabetic neuropathy[15], myocardial infarct (MI) risk assessment, sudden death[16] and congestive heart failure (CHF)[17]. Data can be quantified using diverse methods included those based on time and frequency domain as well as nonlinear measures.[16, 18-20] Both time and frequency domain analysis have some shortcomings and therefore nonlinear analysis such as detrended fluctuation analysis (DFA) and approximate entropy (ApEn) have been increasingly used.[13, 21]

Nonlinear analysis methods differ from the linear methods as they are not designed to assess the magnitude of HRV, but rather measure the scaling and correlation properties of HRV.[16] The non-linear measures DFA and ApEn have been shown to improve risk stratification in patients with cardiovascular disease.[22, 23] DFA produces two scaling exponents: α_1 (short-term) and α_2 (long-term).[18] This study has investigated the usefulness of these measures in detecting CAN in diabetic patients. The same patients were also evaluated with the Ewing battery and the two methods compared.

Methods

79 participants with type 2 diabetes were recruited via advertisement in local papers, radio and television in South-Eastern Australia. The research protocol was approved by the Charles Sturt University Ethics in Human Research Committee (reference numbers 03/103; 03/164). 41 patients were excluded based on history of cardiac pathology. participants who did not complete the full five Ewing battery of tests and those with data of < 85% qualified sinus beats.[24]

Clinical Data Collection Procedures

A medical history questionnaire including age, gender, cardiovascular history, diabetes status, duration of diabetes and types of medications was taken from all participants. ECGs were recorded over 20 minutes using a lead II configuration (Maclab Version 5) and recorded on Macintosh Chart version 3.6 with a sampling rate set at 400 Hz and notch filter at 50Hz. The Ewing battery was administered as described in Ewing 1991.[9]

Processing of ECG Signals

ECG data editing was performed using the MLS310 HRV module (version 1.0, ADInstruments, Australia) from Chart® software package. SoftECG program (version 1.4.10.1, copyright, Herbert Jelinek) was used to analyze nonlinear (DFA and ApEn) data. All ECG data editing included removing high frequency noise using, a 45 Hz low-pass filter and a high pass filter of 3Hz to adjust for wandering baselines in ECG traces. Ectopic beats were selected visually according to the ECG morphology and manually deleted. To compensate for the effect of removing data, linear interpolation was used to replace ectopic beats with normal R-R intervals that occurd immediately before and after the ectopic interval.

HRV Analysis

HRV analyses was performed on 1024 normal beats obtained from the 20 minutes ECG recordings. Details of the methodology for both time and frequency domain analysis has been described previously.[25]

Linear Analysis

Statistical parameters such as standard deviation (SDNN) and root mean square (RMSSD) of the RR intervals were automatically calculated by Chart®. Fourier analysis using the Fast Fourier Transform (FFT) was used to determine the frequency domain parameters of the ECG. Chart® uses a FFT sampling size of 1024 data points, with a 50% overlap function to construct a spectrum. A Hann window was chosen in order to minimise the discontinuity effect introduced at the ends of the ECG traces. In this study all frequency parameters were calculated as well as total power which represents total variance in the ECG signal. Total power in short term recordings consists of the sum of HF, LF and VLF. The measurements of the frequency power components were expressed in both ms^2 and log normalised units.

Nonlinear Analysis

RR interval data was transferred to SoftECG for DFA and ApEn analyses. Details of DFA algorithm have been described previously.[18, 26] DFAα_1 and DFAα_2 are the slopes for box sizes 4 to 11 beats and 12 to 64 beats, respectively. ApEn measures regularity and complexity of time series data. ApEn is calculated using fixed values of two input variables – (m,r). A common choice of m = 2 and r = 20% of the standard deviation of the data set.[20]

Statistical Analysis

Statistical analyses were performed using *Microsoft Excel* add-in 'Analyse-It' (Version 1.71), Analyse-It Software, UK). The normality of data was tested prior to statistical analysis using the Shapiro–Wilk test. If data was not normally distributed ($p<0.05$), natural log (ln) was used to transform the data. If transformation did not normalize the data, a non-parametric Kruskal-Wallis test was used. Fisher's exact probability test was performed using KyPlot (Version 4.0, Klyen lab, UK) to compare clinical variables such as gender, % of hypertension and smoking. Diabetics were divided into two groups CAN^+ and CAN^- using Ewing battery. The differences for these

groups was assessed using a student t-test. Equal variance was confirmed using Bartlett's test in KyPlot.

results

TP, Ln(HF) and ApEn were significantly lower ($p<0.05$) in CAN^+ compared to CAN^- diabetics (table 1). A general trend of lower HRV parameters was observed in CAN^+ diabetics in comparison to CAN^-, which is in agreement with previous publications.[12, 27]

TABLE ~~1~~a). *HRV parameters of CAN^+, CAN^- diabetic and control after exclusion.*

	CAN^+	**CAN^-**
Number of participants	18	20
Age	65.3 ± 6.8	62.0 ± 12.3
Gender (M/F)	8/10	6/14
Duration of diabetes (years)	9.4 ± 6.3	5.3 ± 4.7
SDNN	30.7 ± 15.7	35 ± 12
RMSSD	18 ± 11.4	24 ± 12.5
Total Power	972 ± 1116	1249 ± 891
Ln(Total Power) #	6.4 ± 1.1	7.3 ± 1.1
VLF (ms^2)	591 ± 820	632 ± 414
Ln(VLF)	5.9 ± 1	6.2 ± 0.3
LF (ms^2)	215 ± 259	330 ± 364
Ln(LF)	4.9 ± 1.4	5.4 ± 1
HF (ms^2)	151 ± 189	263 ± 315
Ln(HF) #	4.2 ± 1.6	5.1 ± 1
LF/HF	2.4 ± 2.5	1.63 ± 1.2
DFA α_1	1.14 ± 0.3	1.05 ± 0.3
DFA α_2	1.1 ± 0.2	1 ± 0.2
DFA 32	68.2 ± 38.6	72.4 ± 27.9
ApEn #	0.99 ± 0.3	1.18 ± 0.2

All values are presented as mean ± S.D. Significant difference (# $P<0.05$)

discussion

Linear parameters all appeared lower in CAN^+ compared to CAN^-, but only for Ln(HF) was the difference significant.. These results suggest that CAN^+ patients (by Ewing's criteria) have less parasympathetic and sympathetic modulation compared to patients who are CAN^-. LF/HF ratio was higher in CAN^+ compared to CAN^-, indicating a possible shift towards sympathetic dominance. ApEn, was significantly different between CAN^+ and CAN^- indicating a decrease in complexity of the HR in CAN^+. The CAN^+ group as identified by the Ewing battery had diabetes on average for 9 years compared to CAN^- with an average of 6 years. This suggests that CAN is progressive and is more severe, later in the course of diabetes when the Ewing battery is more likely to pick up autonomic neuropathy.

Results in this study provide further understanding of the changes in HRV parameters in diabetics with autonomic dysfunctions. A general trend of lower HRV parameters found in this study between diabetics and controls support previous findings. Overall, this research study indicated that HRV analysis alone is effective in detecting CAN using short 20 minute ECG traces. In future studies, ranking subjects according to early, mild and severe CAN detected by Ewing battery to HRV analyses could further suggests the effectiveness of HRV analyses for early detection of CAN in diabetics.

This study establishes that at least one non-linear measure (ApEn) is as sensitive as linear measures in detecting CAN using short ECG recordings. Determination of ApEn can have diagnostic value in a population-based study and may contribute to traditional HRV measures.

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