Effect of Hyperglycemia on Cardiac Autonomic Function in Type 2 Diabetes

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Abstract

Heart rate variability (HRV) is reduced in diabetes mellitus (DM) patients, suggesting dysfunction of cardiac autonomic regulation which has been associated with increased risk for cardiac events. In this paper, we examined the associations of blood glucose level (BGL) and duration of diabetes with autonomic nervous system (ANS) function assessed by HRV analysis. Resting HRV and BGL measures of 32 healthy controls and 54 type 2 DM (T2DM) patients were analyzed. HRV data were analyzed using time-domain, frequency-domain and nonlinear methods.

HRV parameters showed a clear difference between controls and T2DM patients. BGL correlated negatively with mean RR interval. In addition, a decrease in HRV was observed in hyperglycemia, most clear changes shown in triangular interpolation of RR interval histogram (TINN), root mean square of successive RR interval differences (RMSSD) and Poincaré plot index SD1. Duration of diabetes was clearly associated with decreased HRV, shown by decreases in standard deviation of RR intervals (SDNN), HRV triangular index (HRVi), TINN, LF power and Poincaré plot index SD2. Glycemic values were not associated with disease duration.

1. Introduction

Heart rate variability (HRV) is a commonly used tool to assess the functioning of cardiac autonomic regulation. Autonomic nervous system (ANS) regulates heart rate (HR) through sympathetic and parasympathetic (vagal) branches. Roughly speaking, sympathetic activity increases HR and decreases HRV, whereas parasympathetic activity decreases HR and increases HRV [1]. Two apparent components of HRV are the low frequency (LF, ranging from 0.04-0.15 Hz) component mediated by both sympathetic and parasympathetic nervous activities and the high frequency (HF, 0.15-0.4 Hz) component mediated almost solely by parasympathetic nervous activity [1, 2].

HRV is reduced in diabetes mellitus (DM) patients, suggesting dysfunction of cardiac autonomic regulation which has been associated with increased risk for cardiac events. Early assessment of cardiac autonomic neuropathy (CAN) and intervention are important for risk stratification and early treatment in preventing sudden cardiac death in diabetic patients. While HRV is recognized to carry early diagnostic value regarding CAN, reduction of HRV has been observed also in patients without evidence of CAN [2]. For the assessment of CAN using HRV analysis, standard time and frequency-domain methods as well as different nonlinear methods have been proposed [3, 4].

Several studies on the association between blood glucose level (BGL) and HRV have been conducted in order to better understand the autonomic dysfunction related to diabetes, both with and without CAN. In general, HRV has been observed to be reduced in diabetic patients [5–7]. In [6], the HF component of HRV was reduced in subjects with DM. However, in [7], reduction of the LF component of HRV was observed in diabetics as well as in subjects with impaired fasting BGL. Furthermore, HRV has been shown to be inversely associated with BGL, indicated by negative correlations between both LF and HF component powers and BGL [7]. In addition, the LF/HF power ratio was shown to be increased during hyperglycaemia in controls and diabetics without CAN [8].

The aim of the present study was to examine the associations of blood glucose level (BGL) and duration of diabetes with autonomic nervous system (ANS) function assessed by HRV analysis. HRV and BGL data from 32 healthy controls and 54 type 2 DM (T2DM) patients were analyzed. Some of the subjects were measured more than once (1-5 visits per subject during 2002-2011, on average 2 visits per subject) resulting in 158 measurements. The HRV data were analyzed using a wide variety of time-domain, frequency-domain and nonlinear methods.

2. Materials and methods

2.1. Subjects and recordings

After standard exclusion criteria were applied to ensure that any changes in HRV detected were due to the dia-

betic status, 32 healthy controls and 54 type 2 diabetes mellitus patients who were participants of a health screening clinic at Charles Sturt University were included in the study. Some of the subjects were measured more than once (1–5 visits per subject during 2002–2011, on average 2 visits per subject) resulting in a total of 158 measurements. None of the diabetic patients showed clinical evidence of CAN.

Blood glucose was measured clinically using an Accu-Chek Advantage II glucometer (Roche Australia P/L). Resting electrocardiogram (ECG) was recorded over 20 minutes at 400 Hz sampling rate using a lead II configuration (Maclab ADInstruments, Australia). The R-wave time instances were extracted from the ECG by using an adaptive QRS detection algorithm and the RR interval time series were formed. The very low frequency trend components were removed from the RR series by using a smoothness priors method [9]. Furthermore, the non-equidistantly sampled RR series were interpolated (4 Hz cubic spline interpolation) to have evenly sampled data for spectral analysis. Respiratory frequency was derived from the ECG and utilized in HF component estimations.

The study was approved by the Charles Sturt University Human Ethics Committee and written informed consent was obtained from all participants.

2.2. Heart rate variability analysis

A selection of time-domain, frequency-domain and nonlinear measures of HRV were considered. The computations of these parameters were performed following the guidelines given in [2].

The time-domain parameters considered were the mean RR interval, standard deviation of RR intervals (SDNN), root mean square of successive RR interval differences (RMSSD), percentage of successive RR intervals differing more than 50 ms (pNN50), HRV triangular index (HRVi), and baseline width of the RR interval histogram evaluated through triangular interpolation (TINN).

The frequency-domain parameters considered were LF and HF component powers as well as total spectral power. The powers of LF and HF components were computed both in absolute units and in normalized units. In addition, the LF/HF power ratio was computed. The RR spectrum, from which the frequency-domain parameters were extracted, was computed using a parametric spectrum estimation method based on autoregressive (AR) modelling. In this approach, an AR model of order 16 was fit into the RR series data and the spectrum is obtained from the estimated model coefficients. One advantage of this approach is that the spectrum can be decomposed into distinct components, i.e. the LF and HF components can be decomposed [10]. The HF component was obtained as a sum of spectral components centred within 0.15–0.5 Hz. The upper limit of HF band was increased to 0.5 Hz because the respiratory frequency of some subjects was over 0.4 Hz. Subjects with respiratory frequency below 0.15 Hz were excluded.

In addition to time- and frequency-domain methods, 4 commonly used nonlinear methods were applied on the RR data. These were 1) Poincaré plot which is a scatter plot of successive RR intervals and produces 2 standard deviation measures, SD1 describing short term variability and SD2 describing long term variability [11]; 2) sample entropy (SampEn) which measures signal complexity or irregularity [12]; 3) detrended fluctuation analysis (DFA) which measures correlations within the signal for both short term fluctuations (α_1, within range 4-16 beats) and long term fluctuations (α_2, within range 16-64 beats) [13]; and 4) correlation dimension (D2) which is also a measure of signal complexity and is expected to give information on the minimum number of dynamic variables needed to model the underlying system [14]. In SampEn computation, the embedding dimension was 2 and the tolerance 0.2 times SDNN, whereas in D2 computation the embedding dimension was 10.

3. Results

Most of the HRV parameters showed a clear difference between control subjects and T2DM patients as can be seen from Table 1. Heart rate is increased and HRV overall decreased in T2DM patients. However, there is no difference in LF/HF component ratio between controls and diabetics.

The effect of glycemia on different HRV parameters was then evaluated within the T2DM patients for whom BGL varied between 3.3–17.6 mmol/l. Correlations of BGL with different HRV parameters are shown in Table 1. Mean RR interval correlated negatively with BGL, i.e. heart rate was increased in hyperglycemia. Overall, HRV showed mild negative correlation with BGL, i.e. HRV was reduced in hyperglycemia. In order to observe the effect of BGL on HRV, the data was divided into three groups with different glycemic levels (3–6, 6–10 and 10–18 mmol/l). The most significant and consistent changes were found in mean RR, RMSSD, TINN and SD1 (see Figure 1 A). In addition, DFA slope α_2 showed a positive correlation with BGL.

Secondly, the effect of diabetes duration on different HRV parameters was evaluated. Mean RR did not correlate with disease duration, but HRV reduced as a function of disease duration (Table 1). The most significant decreases were observed in SDNN, HRVi, TINN, absolute LF power and SD2 (see Figure 1 B). The decrease in HRV took place mainly during the first 10–15 years of the disease as can be seen from the figure. Glycemic values were not associated with disease duration (r=-0.048; p=0.629).

Table 1. HRV parameter values (median values and 25th and 75th percentiles) for control subjects and T2DM patients. For T2DM patients, HRV parameter correlations (Pearson's correlation coefficients and corresponding p-values) with BGL and duration of diabetes

	HRV group results			**HRV correlates**			
	Control (N=32)	T2DM (N=54)		BGL		T2DM duration	
HRV parameter	Median (25th,75th)%	Median (25th,75th)%	p[1]	r	p	r	p
Mean RR (ms)	971 (912,1066)	874 (797,973)	< 0.001	-0.331	< 0.001	0.058	0.560
SDNN (ms)	21.6 (18.4,26.9)	16.5 (12.3,23.2)	< 0.001	-0.097	0.332	-0.423	< 0.001
RMSSD (ms)	22.5 (17.6,26.4)	17.0 (11.4,23.0)	< 0.001	-0.141	0.157	-0.304	0.002
pNN50 (%)	1.47 (0.54,5.07)	0.44 (0,2.59)	< 0.001	-0.050	0.613	-0.203	0.040
HRVi	6.44 (5.79,7.60)	4.87 (3.89,6.96)	< 0.001	-0.068	0.492	-0.428	< 0.001
TINN (ms)	130 (105,155)	100 (70,135)	< 0.001	-0.210	0.033	-0.406	< 0.001
LF power (ms^2)	222 (115,331)	113 (56,208)	< 0.001	-0.068	0.497	-0.397	< 0.001
HF power (ms^2)	203 (119,269)	94 (49,205)	< 0.001	-0.007	0.946	-0.253	0.010
Tot. power (ms^2)	455 (328,686)	264 (145,528)	< 0.001	-0.046	0.645	-0.367	< 0.001
LF power (n.u.)	53.8 (37.4,64.3)	54.4 (37.6,64.8)	0.849	0.087	0.383	-0.069	0.491
LF/HF ratio	1.16 (0.60,1.80)	1.19 (0.60,1.84)	0.841	0.073	0.465	-0.128	0.196
SD1 (ms)	15.9 (12.4,18.7)	12.0 (8.1,16.3)	< 0.001	-0.141	0.157	-0.304	0.002
SD2 (ms)	26.2 (22.1,33.3)	20.0 (14.8,28.5)	< 0.001	-0.071	0.476	-0.449	< 0.001
SampEn	1.76 (1.62,1.83)	1.81 (1.67,1.94)	0.022	-0.167	0.092	0.171	0.085
DFA, α_1	0.98 (0.79,1.12)	1.01 (0.76,1.17)	0.587	0.145	0.144	-0.123	0.216
DFA, α_2	0.34 (0.29,0.41)	0.43 (0.34,0.51)	< 0.001	0.200	0.043	0.056	0.576
D2	0.22 (0.09,0.59)	0.07 (0.00,0.27)	< 0.001	-0.034	0.735	-0.185	0.061

[1] Mann-Whitney U test for the difference between control subjects and T2DM patients.

4. Discussion

The association of autonomic nervous system function assessed by HRV analysis with blood glucose level and duration of diabetes in T2DM patients was examined.

An increase in HR and a decrease in HRV were observed in hyperglycemia. Most consistent changes as a function of BGL were observed in mean RR interval, RMSSD, TINN and SD1, suggesting reduced parasympathetic regulation of heart rate in hyperglycemia. In addition, the DFA slope α_2 increased in hyperglycemia, but the accuracy of this parameter is questionable when estimated from short-term HRV recordings.

The duration of diabetes had a very clear effect on HRV, i.e. HRV reduced as a function of disease duration. Most consistent decreases were observed in SDNN, HRVi, TINN, LF power and SD2, suggesting that the decrease in HRV as a function of disease duration was dominated by decrease in the LF component. This would indicate that the reduction of HRV in diabetes is mainly due to reduced sympathetic regulation of heart rate. In addition, the LF component of HRV is substantially affected by baroreflex activity [15] which is known to be reduced in diabetes.

In conclusion, the results of this study indicate that elevated glycemic values have an unfavorable effect on cardiac autonomic function and this effect is pronounced in long-term T2DM patients.

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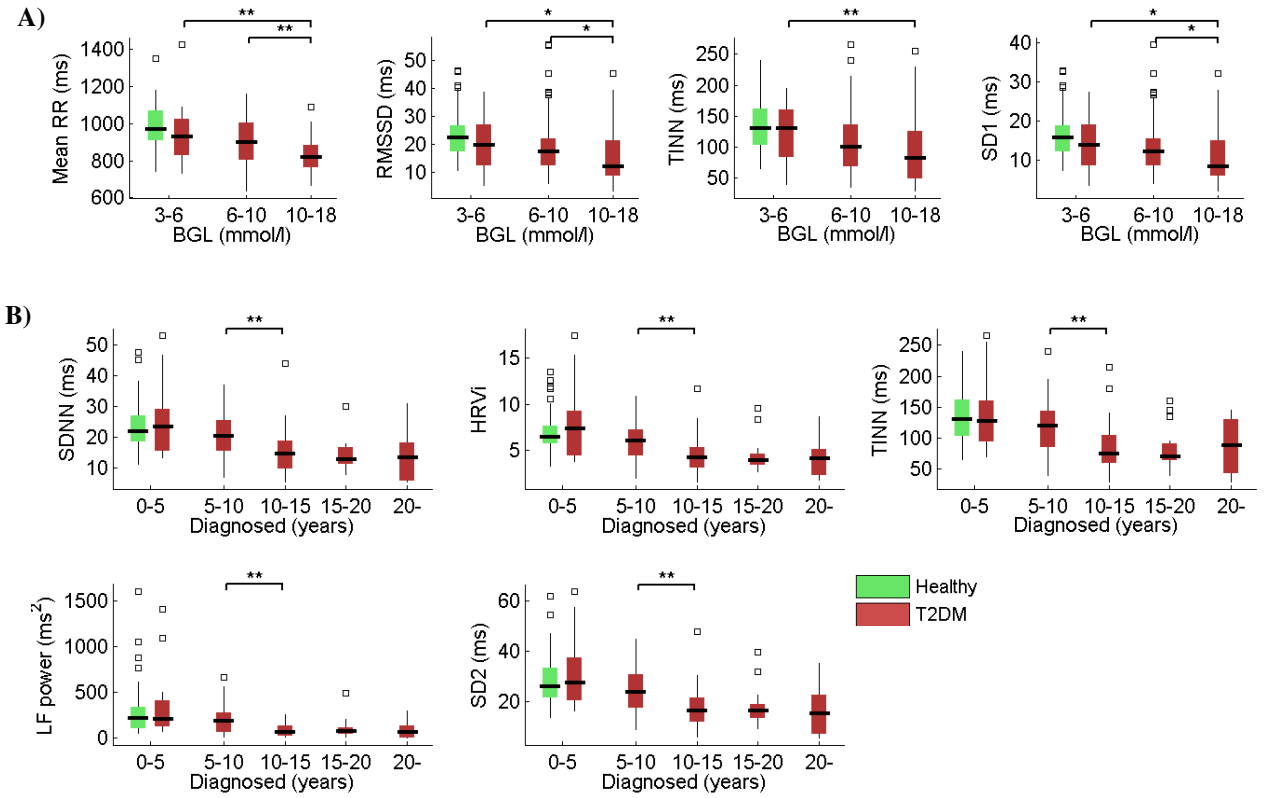

Figure 1. Box plots of the most significant HRV associations to blood glucose level (A) and duration of diabetes (B). On each box, the central mark is the median, the edges of the box are the 25th and 75th percentiles, and the whiskers extend to the most extreme parameter values excluding outliers which are plotted separately. Significant differences between all the "boxes" (A) or between successive "boxes" (B) were tested using the Mann-Whitney U test (*$p \leq 0.05$, **$p \leq 0.01$).

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