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Complexity of Heart Rate Variability in Type 2 Diabetes - Effect of Hyperglycemia

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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 pathological cardiac events. In this paper, we examined changes in HRV complexity in association to blood glucose level (BGL) and duration of diabetes. Resting HRV and BGL measurements of 32 healthy controls and 54 type 2 DM (T2DM) patients were analyzed. HRV complexity was assessed using Shannon entropy, sample entropy (SampEn), multiscale entropy (MSE), and multiscale Renyi entropy.**

HRV complexity increased with hyperglycemia indicated by increases in Shannon entropy and MSE and decreases in Renyi entropy for negative orders. Diabetes duration was strongly associated with Renyi entropy which increased for positive orders and decreased for negative orders as a function of disease duration. Shannon entropy, SampEn and MSE did not correlate with disease duration.

I. Introduction

Heart rate variability (HRV) is commonly used in assessing the functioning of cardiac autonomic regulation. The autonomic nervous system (ANS) regulates heart rate (HR) through sympathetic and parasympathetic branches. Roughly speaking, sympathetic activity increases HR and decreases HRV, whereas parasympathetic activity decreases HR and increases HRV [1]. The low frequency (LF, ranging from 0.04-0.15 Hz) component of HRV is influenced by both sympathetic and parasympathetic nervous activities, where the high frequency (HF, 0.15-0.4 Hz) component originates solely from parasympathetic nervous activity [1], [2].

HRV is reduced in diabetes mellitus (DM) patients, suggesting dysfunction of cardiac autonomic regulation. 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 clinical evidence of CAN [2], [3]. For the assessment of CAN using HRV analysis, standard time and frequency-domain methods as well as different nonlinear methods have been proposed [4], [5], [6], [7], [8], [9].

The association between blood glucose level (BGL) and HRV parameters in diabetes have been examined at least in [10], [6], [11], [12], [13]. In [10], the HF component of HRV was reduced in subjects with DM. However, in [11], reduction of the LF component of HRV was observed in diabetics as well as in subjects with impaired fasting BGL. In [12], the LF/HF ratio was shown to be increased during hyperglycaemia in controls and diabetics without CAN. In our previous study focusing on standard time and frequency-domain measures of HRV, a negative correlation between BGL and mean RR interval and decrease in HRV were observed in hyperglycemia [13].

In addition to the standard linear methods, nonlinear analysis of HRV has shown a great potential in cardiovascular research. Related to diabetes, the complexity of short-term HRV was shown to be reduced in patients with type 1 DM (T1DM) [14]. Furthermore, complexity analysis has been used for identifying CAN in [8] and a multiscale Renyi entropy was proposed for identification of CAN in [15].

In this paper, the complexity of HRV in type 2 DM (T2DM) was assessed and its associations with BGL and duration of diabetes were evaluated. The complexity of HRV time series was examined using Shannon entropy (ShanEn), sample entropy (SampEn), multiscale entropy (MSE) and multiscale Renyi entropy. HRV and BGL data from 32 healthy controls and 54 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.

II. Materials and methods

A. Subjects and recordings

After standard exclusion criteria were applied to ensure that any changes in HRV detected were due to the diabetic 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). A resting electrocardiogram (ECG) was recorded over 20 minutes at 400 Hz sampling rate using a lead II configuration (Maclab

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ADInstruments, Australia). The R-wave time instances were extracted from the ECG 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 [16].

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

B. Entropy measures of HRV

In general, entropy is a measure of complexity or unpredictability of a time series. Shannon's entropy is calculated by the equation

$$H(\mathbf{x}) = -\sum_{i=1}^{N} p(x_i) \log_b p(x_i) \tag{1}$$

where the probability density function $p(x_i)$ is the probability that the random variable $\mathbf{x} = x_i$ and b is the base of the logarithm, commonly 2. The probabilities were here estimated simply from RR interval histogram.

Sample entropy is a commonly used entropy measure which is computed as follows [17]. First, embedding vectors of length m are formed from the length N RR interval series

$$u_j = (\mathrm{RR_j}, \mathrm{RR_{j+1}}, \ldots, \mathrm{RR_{j+m-1}}). \tag{2}$$

Next, relative number of vectors u_k for which $d(u_j, u_k) \leq r$ is calculated

$$C_j^m(r) = \frac{\text{nbr of } \left\{u_k \,\middle|\, d(u_j, u_k) \leq r\right\}}{N-m} \quad \forall\, k \neq j. \tag{3}$$

where $d(u_j, u_k)$ is the maximum absolute difference between the vector elements and r is a tolerance value. The values of $C_j^m(r)$ are then averaged to yield

$$C^m(r) = \frac{1}{N-m+1} \sum_{j=1}^{N-m+1} C_j^m(r) \tag{4}$$

and the sample entropy is obtained as

$$\mathrm{SampEn}(m, r, N) = \ln\left(C^m(r)/C^{m+1}(r)\right). \tag{5}$$

Here, the embedding dimension was 2 and the tolerance value was set to 20% of the time series standard deviation (SD).

The multiscale entropy is a fairly new method which captures the complexity of the time series for multiple time scales [18]. In this method, consecutive coarse-grained time series $y_t^{(\tau)}$ (corresponding to scale factor τ) are constructed from the given time series $x_t = (x_1, x_2, \ldots, x_N)$ by averaging x_t within a non-overlapping window of length τ. That is, each element of the coarse-grained time series is calculated as

$$y_j^{(\tau)} = \frac{1}{\tau} \sum_{i=(j-1)\tau+1}^{j\tau} x_i, \quad 1 \leq j \leq N/\tau. \tag{6}$$

The sample entropy measure for each coarse-grained time series is then calculated producing the MSE. MSE was here calculated from $\tau = 1, \ldots, 20$. Scale $\tau = 1$ gives simply the original time series, and thus, MSE for this scale is equal to SampEn.

TABLE I

HRV ENTROPY PARAMETER VALUES (MEDIAN VALUES AND 25TH AND 75TH PERCENTILES) FOR CONTROL SUBJECTS AND T2DM PATIENTS

	HRV group results		
Entropy	Control (N=32)	T2DM (N=54)	
parameter	Median (25th,75th)%	Median (25th,75th)%	p[1]
Shannon entropy	4.85 (4.64,5.01)	4.85 (4.60,4.99)	0.810
SampEn	1.76 (1.62,1.83)	1.81 (1.67,1.94)	0.022
MSE			
$\tau = 10$	0.87 (0.77,0.98)	0.96 (0.80,1.18)	0.011
$\tau = 11$	0.74 (0.66,0.94)	0.93 (0.72,1.08)	0.003
$\tau = 12$	0.73 (0.65,0.83)	0.84 (0.64,1.00)	0.022
$\tau = 13$	0.65 (0.59,0.76)	0.78 (0.64,0.93)	0.003
$\tau = 14$	0.60 (0.51,0.71)	0.71 (0.57,0.84)	0.020
$\tau = 15$	0.53 (0.49,0.65)	0.66 (0.53,0.85)	0.002
Renyi entropy			
$\alpha = -5$	1.006 (1.001,1.019)	1.001 (0.999,1.008)	0.002
$\alpha = -4$	1.004 (1.001,1.012)	1.000 (0.999,1.005)	0.002
$\alpha = -3$	1.002 (1.000,1.007)	0.999 (0.998,1.003)	0.002
$\alpha = -2$	1.000 (0.999,1.003)	0.999 (0.998,1.001)	0.003
$\alpha = -1$	0.999 (0.998,1.000)	0.999 (0.998,0.999)	0.037
$\alpha = 1$	0.997 (0.995,0.997)	0.997 (0.996,0.998)	0.003
$\alpha = 2$	0.996 (0.994,0.997)	0.997 (0.995,0.998)	0.001
$\alpha = 3$	0.995 (0.992,0.996)	0.996 (0.994,0.998)	$<$0.001
$\alpha = 4$	0.995 (0.990,0.996)	0.996 (0.994,0.997)	$<$0.001
$\alpha = 5$	0.994 (0.989,0.995)	0.996 (0.993,0.997)	$<$0.001

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

Renyi entropy is a generalization of the Shannon entropy

$$H_\alpha(\mathbf{x}) = \frac{1}{1-\alpha} \log_2 \left(\sum_{i=1}^{N} p(x_i)^\alpha \right) \tag{7}$$

where α is the order of the entropy measure, producing the multiscale entropy. Unlike the Shannon entropy computation, the probabilities are here estimated using the methods outlined in [19]. This involves estimating the probability density function of all other samples x_j and then estimating $p(x_i)$ as the probability given by this density function

$$p(x_i) = \sum_{j=0}^{N} \exp\left(\frac{\mathrm{dist}_{ij}^2}{2\sigma^2} \right) \tag{8}$$

where σ is a parameter controlling the width of the density function and the distance measure is

$$\mathrm{dist}_{ij} = \sum_{k=0}^{\pi} (x_{i+k} - x_{j+k})^2 \tag{9}$$

where π is the pattern length over which comparison occurs. The multiscale Renyi Entropy was calculated from $-5 \leq \alpha \leq +5$, where $\alpha = 1$ is the Shannon entropy and $\alpha = 2$ is the squared entropy.

III. RESULTS

Most of the entropy measures, all except Shannon entropy (ShanEn), showed a clear difference between control subjects and T2DM patients as shown in Table I. SampEn, MSE and Renyi entropy for positive orders ($\alpha \geq 1$) were all lower for controls compared to T2DM patients. In MSE, the difference

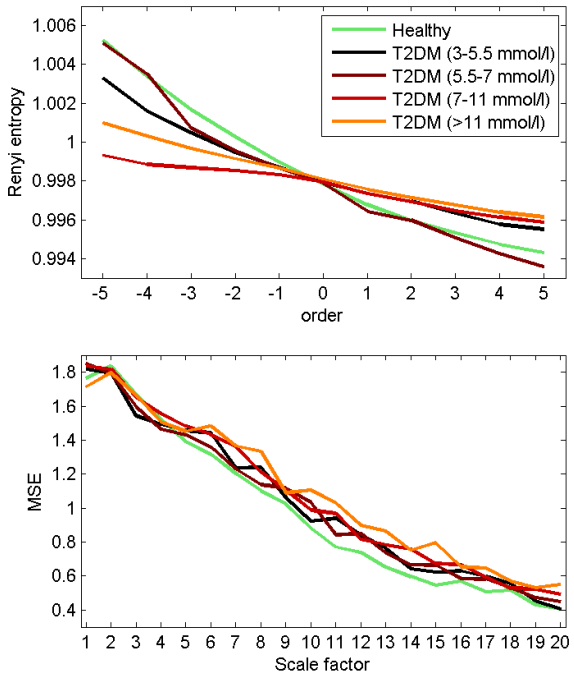

Fig. 1. Renyi entropy and MSE for healthy controls and T2DM patients with normal, elevated and hyperglycemic BGL.

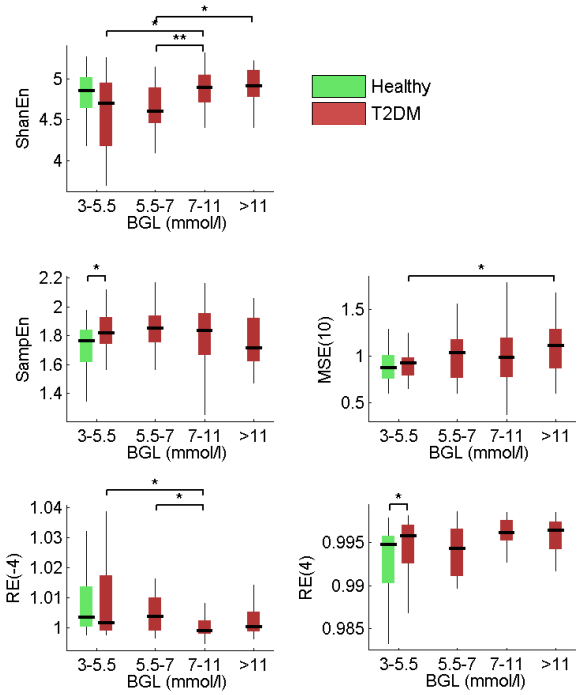

Fig. 2. Box plots of HRV complexity associations with blood glucose level. On each box, the central mark is the median, the edges of the box are the 25th and 75th percentiles, and the whiskers extend to the most extreme parameter values excluding outliers (which are not plotted). Significant differences between all the "boxes" were tested using the Mann-Whitney U test ($*p \leq 0.05$, $**p \leq 0.01$).

between the groups was most significant at scale factors 10-15. Renyi entropy showed group-wise differences also for negative orders.

The effect of glycemia on HRV complexity was then evaluated within the T2DM patients for whom BGL varied between 3.3–17.6 mmol/l. In order to observe the effect of BGL on HRV entropy, the data was divided into four groups with different glycemic levels (3–5.5, 5.5–7, 7-11 and $>$11 mmol/l, which correspond to clinically relevant cut-off values). The median values of Renyi entropy and MSE for these four T2DM groups as well as for the healthy controls are shown in Fig. 1.

Boxplots showing the observed associations between HRV entropy measures and blood glucose level are shown in Fig. 2. MSE for scale factor 10 and Shannon entropy were both increased in hyperglycemia. Renyi entropy decreased for negative orders and increased for positive orders in hyperglycemia, the figure showing Renyi results for orders -4 and 4. Sample entropy showed no difference in association with BGL.

Secondly, the effect of diabetes duration on different HRV entropy parameters was evaluated and the results for different entropy measures are shown in Fig. 3. Shannon entropy, sample entropy and MSE did not show any significant changes in association with diabetes duration. However, the Renyi entropy increased for positive orders and decreased for negative orders as a function of the disease duration as can be seen from Fig. 3 where Renyi entropy is presented for orders -4 and 4. The most significant change in Renyi entropy took place around 10 years (disease duration 5-10 years vs. 10-15 years).

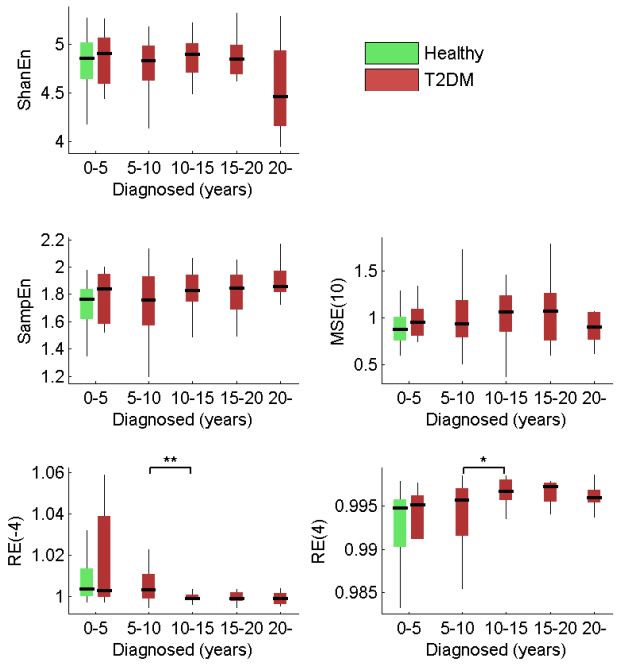

Fig. 3. Box plots of HRV entropy associations with duration of diabetes (box descriptions as in Fig. 2). Significant differences between successive "boxes" were tested using the Mann-Whitney U test ($*p \leq 0.05$, $**p \leq 0.01$).

IV. Discussion

The association of HRV complexity, assessed through different entropy measures, with blood glucose level and duration of diabetes in T2DM patients was examined.

HRV complexity was observed to increase in hyperglycemia. This was shown as increases in Shannon entropy and MSE as a function of BGL. Multiscale Renyi entropy for positive orders mildly increased in association with BGL even though the changes were not significant between the selected BGL ranges. For negative orders the Renyi entropy decreased in hyperglycemia. Sample entropy did not show any significant changes in association with glycemic level. In our previous study where standard linear measures of HRV were assessed, an increase in heart rate and decrease in HRV were observed in hyperglycemia [13]. The decreased HRV is related to reduced intensity of the periodic LF and/or HF components of HRV which can partly explain the increased complexity observed in this study.

Secondly we evaluated the effect of diabetes duration on the different HRV entropy parameters. Renyi entropy increased for positive orders and decreased for negative orders as a function of disease duration. The most significant change in Renyi entropy happened around 10 years of disease duration. The other entropy measures assessed in this study did not show any significant changes in association to disease duration.

In conclusion, the results of this study indicate that HRV entropy measures, especially the multiscale Renyi entropy, can be used for assessing elevated glycemic values and the unfavorable effects of high blood glucose on cardiac autonomic function in T2DM patients.

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