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PERMUTATION ENTROPY ANALYSIS OF HEART RATE VARIABILITY FOR THE ASSESSMENT OF CARDIOVASCULAR AUTONOMIC NEUROPATHY

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INTRODUCTION

Cardiac rhythm is mainly determined by intrinsic properties of the sino-atrial node, together with autonomic nervous systems and endocrine regulation of the heart. The natural interplay between these elements provokes the time interval between heartbeats to constantly change, a phenomenon known as heart rate variability (HRV). Instead, impairment of any of the mentioned modulating components leads to a decrease of HRV, which is related to a reduced adaptive capacity of the cardiovascular system. Assessment of HRV has become a widely applied tool for quantifying autonomic function in different clinical settings. Thus, suitable measures for providing reliable information of the underlying modulation mechanism are needed.

The study of cardiovascular autonomic neuropathy (CAN) is clinically important because of its life threatening consequences [1]. To our knowledge, none of the studies assessing HRV complexity in patients with CAN have considered it from an ordinal perspective. The aim of this work is to explore the potential of permutation entropy (PE) analysis of HRV for the evaluation of neuropathological changes on cardiac autonomic function.

MATERIALS AND METHODS

Subjects

The study involved 24 actively recruited healthy volunteers, 18 type 1 diebetes mellitus patients (T1DM group; females/males: 12/6, age: 30 ± 9 yr) and 14 diabetic patients with CAN (DCAN group; females/males: 7/7, age: 37 ± 9 yr), who were assessed with clinical autonomic tests. Patients and control groups were age and sex-matched. All participants provided informed consent. The study protocol followed principles outlined in the Declaration of Helsinki (1975) and it was approved by the Ethics Committee of the National Institute of Endocrinology, Cuba.

Electrocardiogram (ECG) and RR intervals

The study was conducted between 9:00 h and 12:00 h. Tests were performed in a quiet environment with room temperature at 23–26 °C, after 15 min of acclimatization. Five minutes CM_5-V_5-lead ECG was recorded at rest and seated position under standard conditions, using a Hewlett Packard 78354A electrocardiograph unit and a NI USB-6008 Data Acquisition device (sampling rate:1 kHz). The ECG and the R wave detection by the VFC32 software [2] were visually inspected to avoid artifacts. Tachograms[1] were also visually examined and RR data were filtered.

HRV analysis

Statistical domain methods. HRV statistical analysis was performed using the VFC32 software. The computed measures were mean frequency (MF); difference between the longest and shorter RR interval (W); standard deviation (SD); coefficient of variation (CV); square root of the mean of the sum of the squares of differences between adjacent RR intervals

[1] Plot of the duration of intervals between R peaks of consecutive beats (RR intervals) versus the order of progressive beats.

(rMSSD), and the autonomic stress index (ASI) [3].

Energetic domain methods. For performing spectral analysis of HRV, RR sequences were submitted to a pre-processing procedure. The digital signal processing was implemented in MATLAB (The MathWorks, Inc.)[2]. Ordinal RR series were transformed into proper temporal series after being resampled through an interpolation process using the piecewise cubic Hermite function. The power spectral density (PSD) was estimated by applying the Welch periodogram method and the Fast Fourier Transform algorithm. The PSD was calculated for the low frequency band (LF: 0.04-0.15 Hz), the high frequency band (HF: 0.15-0.4 Hz), as well as the total power (TP: 0.04-0.4 Hz). LF and HF in normalized units (LFnu and HFnu, respectively), and the ratio LF/HF, were also determined [4].

Informational domain methods. Complexity of RR intervals series was quantified by means of Shannon entropy (ShE) and Permutation Entropy (PE) [5].

PE is based on the representation of time series in a symbolic phase space. Given any discrete time series $X = \{x_1, x_2, \ldots, x_{n-1}, x_n\}$ of length *n*, partitions are taken for each time *t* as *d*-dimensional vectors ($d \geq 2$) of values of *X*. These realizations of *X* are not needed to be consecutive and might be separated $\tau \geq 1$ units each from the other, viz: $t \rightarrow \left(x_t, x_{t+\tau}, \ldots, x_{t+\tau(d-2)}, x_{t+\tau(d-1)}\right)$. A symbolic sequence is then built by mapping these vectors to ordinal patterns. Values in partition vectors are arranged in increasing order and a permutation vector (or motif) of their indexes with respect to (0,1,…,d-1) is obtained. Parameters *d* and τ are called *embedding dimension* and *time delay*, respectively [6]. In this work we have set parameter d = {3,4} and limited τ to range between 1 and 10 for performing calculations, as we only had available short term records.

(Normalized) PE is defined as the Shannon entropy associated to the distribution corresponding to the frequencies of appearance of each pattern *i* in the series, P(d,τ,i) –in probabilistic terms:

$$PE(d,\tau) = -\frac{1}{\log_2 d!}\sum_{i=1}^{d!} P(d,\tau,i)\log_2\left[P(d,\tau,i)\right]$$

Possible motifs for our signals are shown in Table 1, as well as the indexes used to identify them [7].

Table 1: *Complete set of ordinal patterns and indexes, i, for d = 3 and d = 4.*

d=3		**d=4**							
i	Motif	*i*	Motif	*i*	Motif	*i*	Motif	*i*	Motif
1	012	*1*	0123	*7*	1023	*13*	2013	*19*	3012
2	021	*2*	0132	*8*	1032	*14*	2031	*20*	3021
3	102	*3*	0213	*9*	1203	*15*	2103	*21*	3102
4	120	*4*	0231	*10*	1230	*16*	2130	*22*	3120
5	201	*5*	0312	*11*	1302	*17*	2301	*23*	3201
6	210	*6*	0321	*12*	1320	*18*	2310	*24*	3210

Statistical analysis

The complete statistical processing was performed using STATISTICA (StatSoft, Inc.). Kolmogorov-Smirnov test was used to assess normality. A comparative analysis between groups was performed using a t-test. Correlations were assessed by using Pearson's correlation coefficients. P-values < 0.05 were considered as significant.

RESULTS

Only two PE measures significantly differed between diabetic patients without CAN and control groups: PE(3,7) and PE(4,9). When comparing between DCAN and controls the majority of PE indicators showed lower values in DCAN, overall. However, only PE(3,4), PE(3,5), PE(3,7), PE(4,4), PE(4,5) and PE(4,7) significantly differed between DCAN patients and its control group (results not shown here). Results for τ = 5 where those with higher distinguishing power.

[2] Unless otherwise indicated all calculations were performed using MATLAB.

Table 2: *Correlation matrix between permutation entropy and standard heart rate variability measures*

PE(d,τ)	MF	W	SD	CV	ASI	ShE	rMSSD	LF	HF	TP	LFnu	HFnu	LF/HF
PE(3,1)	**-0,50**	0,16	0,05	-0,16	-0,12	-0,23	0,34	-0,21	0,07	-0,03	**-0,45**	**0,37**	**-0,39**
PE(3,2)	-0,31	-0,02	-0,11	-0,20	0,03	-0,27	0,15	-0,26	0,08	-0,12	**-0,42**	**0,41**	**-0,43**
PE(3,3)	-0,14	-0,14	-0,07	-0,30	-0,08	-0,20	-0,06	-0,03	-0,09	-0,06	0,04	-0,03	0,04
PE(3,4)	-0,22	**0,45**	**0,55**	**0,59**	**-0,48**	**0,58**	**0,36**	**0,54**	0,19	**0,46**	0,33	-0,21	0,25
PE(3,5)	**-0,45**	0,22	0,18	0,06	-0,24	0,10	0,32	0,00	0,21	0,17	-0,28	**0,43**	**-0,42**
PE(3,6)	0,13	-0,04	-0,02	0,11	0,10	0,07	-0,12	0,24	-0,08	0,10	**0,56**	**-0,41**	**0,45**
PE(3,7)	0,19	-0,19	-0,14	0,04	0,12	0,08	-0,15	-0,01	-0,15	-0,11	0,25	-0,15	0,17
PE(3,8)	-0,13	0,12	0,13	0,22	-0,02	0,16	0,19	0,01	0,16	0,07	-0,10	0,20	-0,20
PE(3,9)	-0,32	0,25	0,33	0,23	-0,33	0,18	0,32	0,34	**0,37**	0,31	0,13	-0,04	0,03
PE(3,10)	**-0,35**	0,27	0,16	0,08	-0,23	-0,01	0,32	0,11	0,21	0,16	-0,03	0,09	-0,09
PE(4,1)	**-0,48**	0,17	0,07	-0,19	-0,18	-0,22	0,35	-0,15	0,05	0,00	-0,27	0,21	-0,23
PE(4,2)	**-0,40**	0,02	-0,04	-0,13	-0,05	-0,18	0,26	-0,24	0,23	-0,05	**-0,51**	**0,57**	**-0,58**
PE(4,3)	-0,07	-0,14	-0,06	-0,22	-0,04	-0,18	0,03	0,01	0,08	-0,01	0,00	0,09	-0,05
PE(4,4)	-0,18	**0,36**	**0,51**	**0,54**	**-0,46**	**0,56**	0,31	**0,55**	0,21	**0,45**	**0,36**	-0,23	0,28
PE(4,5)	**-0,37**	0,08	0,10	0,03	-0,16	0,02	0,27	-0,04	0,24	0,06	**-0,36**	**0,49**	**-0,50**
PE(4,6)	0,18	-0,13	-0,07	0,07	0,14	0,05	-0,10	0,09	-0,07	0,00	0,34	-0,23	0,26
PE(4,7)	-0,02	-0,13	-0,16	-0,08	0,06	-0,06	0,08	-0,14	0,08	-0,10	-0,04	0,20	-0,15
PE(4,8)	-0,28	0,14	0,12	0,14	-0,13	0,07	0,30	-0,05	0,33	0,11	**-0,39**	**0,48**	**-0,48**
PE(4,9)	-0,19	0,26	0,33	0,30	-0,27	0,25	0,31	**0,35**	**0,40**	0,34	0,08	0,05	-0,05
PE(4,10)	-0,22	0,23	0,09	0,08	-0,17	-0,03	0,30	0,07	0,24	0,14	-0,08	0,13	-0,12

There is revealed a pattern of correlations between PE measures and standard HRV analysis features that is nearly invariant for the time delays in the study. This can be seen on Table 2, in which significant correlation coefficients appear in bold style. Results illustrate that PE(3,4), PE(4,4) and, in less extent, PE(3,5) and PE(4,5) are significantly correlated with most HRV measures.

Starting on the set (d,τ) = {(3,4),(3,5),(3,7),(4,4),(4,5),(4,7)}, which provided a good PE differentiation between DCAN patients and healthy controls, probabilities of appearance of corresponding ordinal patterns P(d,τ,i) were studied as well. In this way, P(3,5,[1,2,3]), P(3,6,5), P(3,7,6) P(4,4,[5,10,14,17,22]), P(4,5,[7,11,14]) and P(4,6,[8,24]) were the variables that most significantly differed between DCAN and control groups (Figs. 1 and 2). Overall, it can be seen that patterns involving values in a completely descendent order, such as P(3,τ,6) and P(4,τ,24), have the highest probability of occurrence in DCAN patients -and fair high values in controls. This situation provokes other patterns to be hardly accessible for the diseased system. A better differentiation between both populations is achieved in the cases referred (please compare with the behaviour of the probabilities of occurrence of τ = 6 patterns in Fig. 1).

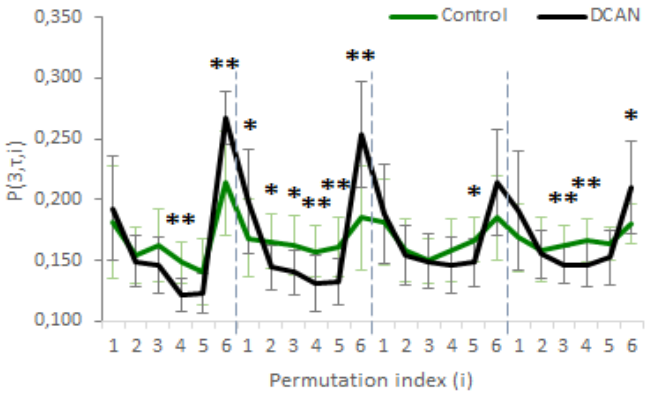

Figure 1: *Mean probabilities of existence of ordinal patterns, d=3. Symbols * and ** denote t-test p<0.05 and p<0.01, respectively. Dashed lines are defining regions for τ = [4,5,6,7], in that order. For illustrative purposes it was included τ = 6.*

DISCUSSION

In this study, we explore the potential of PE analysis of short-term HRV complexity for assessing cardiac autonomic function in type 1 diabetic patients with and without CAN. To our knowledge, there are no published works assessing cardiac autonomic function by means of PE. The growing and widespread use of this method for HRV analysis relies on its robustness and simplicity, as well as in the fact

that it takes into account time causality and it is not needed any prior knowledge about the nature of the data under consideration.

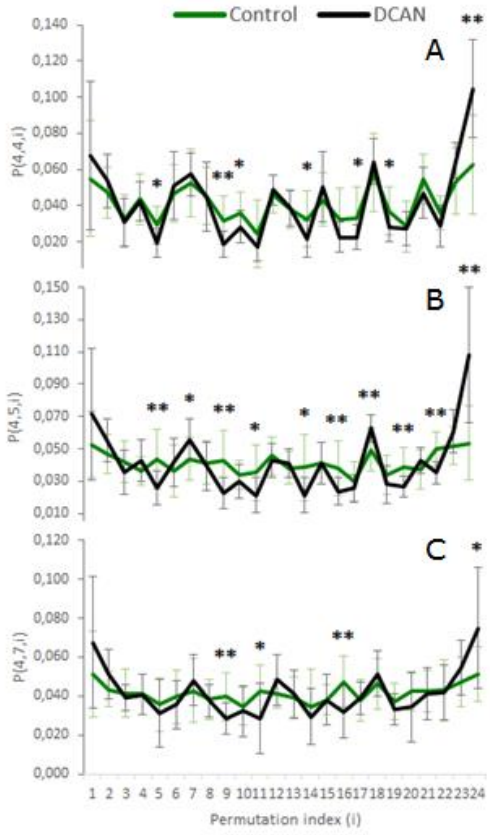

*Figure 2. Mean probabilities of existence of ordinal patterns, d=4. Only results for τ = 4 (A), τ = 5 (B) and τ = 7 (C) are shown. Symbols * and ** denote t-test p<0.05 and p<0.01, respectively.*

No outstanding results were obtained when compared patients without CAN to controls. Several PE measures were significantly reduced in patients with CAN. This suggests a decreased responsiveness of the cardiac control mechanisms to external and internal stimuli, and thus a weakened strength of feedback interactions, which are expected to determine the dynamics of the system.

Correlation analysis showed that PE(d,4) is related to all measures of overall HRV (W, SD, CV, ASI, ShE and TP). PE(d,5) is the only variable that correlates with measures of short-term HRV. PE(d,7) did not show correlation with any of the standard HRV measures. It also turned out that the correlation matrix seems to (almost) repeat for equal values of τ, evidencing the importance of studying temporal scales of the system under consideration.

Consequently with the results obtained for PE, some of the motifs computed also differed significantly in their probabilities of appearance between DCAN patients and normal subjects. Some ordinal patterns become hardly accessible for the system in DCAN patients, while others become more reachable. We posit that this behavior is due to a lower level of complexity in the series, induced by physiological perturbations originated in the diseased system.

Our results supports PE as an adequate and promising method to be consider in clinical settings. Indeed, further research is imperative for evaluating the diagnostic value of this measure in order to disclose its full potential as an early biomarker of cardiovascular autonomic dysfunction.

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