Rényi and permutation entropy analysis for assessment of cardiac autonomic neuropathy

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Abstract— **Cardiac autonomic neuropathy (CAN) is a complication of diabetes with a long asymptomatic phase that is associated with high morbidity and mortality. Early identification of CAN in Type 1 diabetes mellitus (T1DM) may be possible using heart rate variability (HRV). However, the power of HRV analysis to identify CAN depends on the selection of suitable features that provide reliable information regarding cardiac autonomic regulation. Our aim was to compare the performance of Rényi entropy (RE) and permutation entropy (PE) for identification of T1DM patients with CAN. RE and PE measures from 235 data points and 5 min of cardiac interbeat interval (RR) sequences were analysed in 18 T1DM patients without CAN, 14 T1DM patients with CAN, and healthy controls matched for age and sex. RE was calculated for different orders α (-5, 5), pattern lengths λ (2, 4, 8), and tolerance σ. For PE analysis λ was set to (3-4) and time delays τ to (1-10). A forward stepwise discriminant analysis was carried out for estimating the classification functions. Accuracy was estimated following a K-fold cross-validation (k = 14). RE calculated for RR sequences of λ = 2, α > 0 showed the best performance for differentiating T1DM patients with CAN ($p < 0.0001$). PE measures showed better performance with ordinal patterns and τ = 4, 5 and 7 for differentiating patients with CAN. RE and PE provide complementary information achieving 100% classification accuracy ($p < 0.0001$ and $p < 0.001$, respectively). This approach might be promising as a sensitive and specific tool for CAN diagnosis in T1DM.**

Keywords— **Rényi entropy, permutation entropy, ordinal patterns, heart rate variability, cardiac autonomic neuropathy**

I. Introduction

Autonomic neuropathy is a common and major chronic complication of diabetes mellitus associated with high morbidity and mortality. Although cardiac autonomic neuropathy (CAN) is the most clinically relevant form of diabetic autonomic neuropathy [1], it is also one of the most overlooked complications of diabetes due to a long asymptomatic phase, thus remaining undiagnosed and undertreated [2, 3].

Identification of early signs of reduced heart rate variability (HRV) associated with CAN [2] requires selecting suitable HRV features that provide reliable information about the underlying autonomic nervous system control mechanisms.

HRV is traditionally quantified using linear measures in the time and frequency domains; however, these methods are not sufficient to characterise the complex dynamics of the heart rate time series, which are characterised by nonstationarity and nonlinearity. Therefore appropriate HRV analysis methods for describing the nonlinear properties of the complex dynamics arising from cardiovascular control are required. Among these nonlinear measures are multiscale entropy features, such as Rényi entropy (RE) and permutation entropy (PE) [4], which provide information on the degree of regularity inherent in a time series.

RE considers the probability of a sequence of values to occur in the HRV data, whereas PE describes the probability of ordinal patterns occurring within the time series. Therefore, these entropy measures may add complementary information when used in combination. Furthermore, both features are promising for CAN assessment [5, 6]. In previous work we have shown that RE has superior discriminatory power to multiscale sample entropy and multi-fractal detrended fluctuation analysis for CAN detection [7]. In the present study we aim at comparing the performance of RE to PE for the identification of CAN in type 1 diabetes.

II. Materials and Methods

A. Subjects

The study involved 24 healthy volunteers, 18 type 1 diabetes mellitus (T1DM) patients without CAN and 14 T1DM patients with CAN (table 1). Patients and controls were matched for age and sex. All participants provided informed consent. The study protocol followed the principles outlined in the Declaration of Helsinki and was approved by the Ethics Committee of the National Institute of Endocrinology, Cuba.

Table 1. Demographic and clinical data. Values are expressed as mean ± standard deviation, number of cases (n) or percentages. T1DM: type 1 diabetes mellitus patients; T1DM-C: control group of T1DM; DCAN: type 1 diabetes mellitus patients with cardiac autonomic neuropathy; DCAN-C: control group of DCAN; F: female; M: male; BMI: body mass index; DD: disease duration; HbA_{1c}: glycosylated hemoglobin.

Indices	T1DM	T1DM-C	DCAN	DCAN-C
F/M (n)	12/6	12/6	7/7	7/7
Age (yrs)	29.61 ± 8.79	29.67 ± 8.24	36.57 ± 9.13	36.21 ± 8.58
BMI (Kg/m^2)	24.59 ± 2.90	23.44 ± 2.53	24.99 ± 3.80	23.73 ± 2.45
DD (yrs)	15.35 ± 10.36	-	23.43 ± 12.70	-
HbA_{1c} (%)	7.15 ± 1.90	-	7.95 ± 1.28	-

B. ECG recordings and RR intervals

The study was conducted between 9:00 am and 12:00 noon in a quiet environment with room temperature ranging between 23–26 °C. Five minute CM_5-V_5-lead ECG was recorded at rest and in a seated position under standard conditions, using a Hewlett Packard 78354A electrocardiograph unit and a NI USB-6008 Data Acquisition device (sampling rate was 1 kHz) after 15 min of acclimatization. The ECG and the R waves were visually inspected using the VFC32 software[1] to ensure a sinusoidal rhythm. Tachograms[2] were examined and RR data were filtered as described in [8].

C. HRV analysis

Rényi entropy: RE $H(\lambda, \alpha)$ is a generalization of Shannon entropy to include measures of different orders:

$$H(\lambda, \alpha) = \frac{1}{1-\alpha} log_2 \left(\sum_{i=1}^{n} p_i^{\alpha} \right) \quad (1)$$

where p_i is the probability of each sequence of RR intervals of length λ and the exponent α is the order of the entropy measure. This is the parameter that is varied to produce a multiscale entropy. The probability of a sequence of RR intervals was estimated by measuring the similarity of the sample i with all other samples of the same length λ in the whole sequence. Each sequence was regarded as a point in a λ-dimensional space, and its probability was estimated using a Gaussian kernel centred on each such point. Then p_i is given by the density function:

$$p_i = \sum_{j=0}^{n} exp\left(\frac{-dist_{ij}^2}{2\sigma^2} \right) \quad (2)$$

where σ is the Gaussian dispersion or tolerance and $dist$ is the Euclidean distance between sample i and all other samples j, in λ-dimensions:

$$dist_{ij} = \sum_{k=0}^{\lambda} \left(x_{i+k} - x_{j+k} \right)^2 \quad (3)$$

Here, x_{i+k} is one RR sample out of sequence of length λ, the pattern length over which comparison occurs. The density method for estimating probabilities is superior in terms of providing a measure that can discriminate different classes of CAN [9, 10]. The multiscale RE was calculated from 235 data points of cardiac interbeat interval (RR) sequences for α = {-5, 5}, λ = {2, 4, 8}, and different values of $\sigma = \{0.0001, 0.0002,\ 0.0005, 0.001, 0.002, 0.005, 0.01\}$.

Permutation entropy: PE is based on the representation of time series in a symbolic phase space. Given any discrete time series $X = \{x_1, x_2, \dots, x_{n-1}, x_n\}$ of length n, partitions are taken for each time t as λ-dimensional vectors ($\lambda \geq 2$) of values of X. These realizations of X were then separated into ($\tau \geq 1$) units, viz.: $t \rightarrow \left(x_t, x_{t+\tau}, \dots, x_{t+\tau(\lambda-2)}, x_{t+\tau(\lambda-1)} \right)$.

A symbolic sequence is then built by mapping these vectors to ordinal patterns. Values in partition vectors were arranged in increasing order and a permutation vector (or motif) π of their indexes with respect to $(0, 1, \dots, \lambda - 1)$ was obtained. Parameters λ and τ are the *embedding dimension* and *time delay*, respectively. In this work, we computed PE from 5-minute RR sequences for $\lambda = \{3, 4\}$ and $\tau = (1, \dots, 10)$.

Normalized PE is defined as the Shannon entropy associated to the distribution of the frequencies of appearance of each pattern i in the series, $P(\lambda, \tau, i)$ -in probabilistic terms:

$$PE(\lambda, \tau) = -\frac{1}{log_2 \pi!} \sum_{i=1}^{\pi!} P(\lambda, \tau, i) log_2 [P(\lambda, \tau, i)] \quad (4)$$

Possible motifs for our signals are shown in table 2, as well as the permutation indexes used to identify them [11].

D. Statistical analysis

Statistical analysis was performed using STATISTICA (StatSoft, Inc.). Normality was assessed by the Kolmogorov-Smirnov test. Comparative analyses were performed using the Mann-Whitney U- or t-tests and correlations assessed by Spearman R coefficients. A forward stepwise discriminant

[1] Machado A and M. Estévez (2008), University of Havana
[2] Plot of the duration of RR intervals versus the order of progressive beats

analysis was carried out for estimating classification functions and separate cases. Accuracy was estimated following a K-fold cross-validation testing strategy (k = 14). P values < 0.05 were considered as significant and adjusted for multiple comparisons.

Table 2 Permutation indexes i and motifs π of length $\lambda = 3$ and $\lambda = 4$

$\lambda = 3$		$\lambda = 4$							
i	π	i	π	i	π	i	π	i	π
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

III. Results

There was no significant difference in RE or PE between T1DM patients without CAN and healthy individuals. RE showed significant differences between diabetes patients with CAN compared to healthy controls for samples of sequence length $\lambda = 2$ only, regardless of σ values (table 3). The best results were achieved with $\alpha = 5$ (Mann-Whitney U test $p < 0.00002$).

PE measures showed significantly lower values in the DCAN group for $PE(3,4)$, $PE(3,5)$ $PE(3,7)$, $PE(4,4)$, $PE(4,5)$ and $PE(4,7)$ compared to controls (Mann-Whitney U test $p < 0.008$) (table 3). Probabilities of ordinal patterns $P(\lambda,\tau,i)$ computed from these (λ,τ) values were analysed, with best significant results obtained for $P(3,4,4)$, $P(3,4,6)$, $P(3,5,6)$, $P(4,4,24)$, $P(4,5,22)$ and $P(4,5,24)$ between DCAN group and controls (t-test $p < 0.0004$) (table 3).

RE measures with $\lambda = 2$ showed moderate correlation with $PE(3,4)$ ($R = 0.55$), $PE(3,5)$ ($R = 0.60$) and $P(3,4,6)$ ($R = 0.66$) in the control group. In the DCAN group, RE measures correlated with $PE(4,5)$ ($\alpha = -5$: $R = 0.56$), $P(3,5,6)$ ($\alpha = -5$: $R = 0.63$; $\alpha = 5$: $R = 0.68$), and $P(4,5,24)$ ($\alpha = -5$: $R = 0.64$; $\alpha = 5$: $R = 0.55$).

Among the three discriminant models computed from RE $H(2,5)$ with $\sigma = 0.01$, PE measures, and ordinal pattern statistics, the best accuracy was accomplished for the model including probabilities of ordinal patterns (table 4). However, a 100% classification accuracy was achieved by combining RE and ordinal pattern statistics.

Table 3. Rényi entropy (RE), permutation entropy (PE) and ordinal patterns (OP) data. Only descriptive statistics of significant features for the identification of diabetic cardiac autonomic neuropathy (DCAN) are shown. Values are presented as median ± interquartile range for RE and PE, and as mean ± standard deviation for OP. The numbers in brackets after: RE H, indicate the values of parameters (λ,α), where λ is the sequence length and α is the exponent; PE, indicate the values of parameters (λ,τ), where τ is the time delay; probabilities of OP P, indicate the values of parameters (λ,τ,i), where i is the permutation index. Statistic: Z-value for RE and PE, and t-value for OP.

Feature	DCAN	Control	Statistic	p-value
H(2,-5)	1.018 ± 0.021	1.001 ± 0.002	4.18124	0.000029
H(2,5)	0.936 ± 0.044	0.984 ± 0.016	-4.27313	0.000019
PE(3,4)	0.971 ± 0.015	0.988 ± 0.015	2.94065	0.003275
PE(3,5)	0.979 ± 0.018	0.994 ± 0.008	3.40013	0.000674
PE(3,7)	0.989 ± 0.014	0.996 ± 0.006	3.53797	0.000403
PE(4,4)	0.950 ± 0.021	0.972 ± 0.025	2.66497	0.007700
PE(4,5)	0.963 ± 0.031	0.981 ± 0.012	2.98660	0.002821
PE(4,7)	0.977 ± 0.018	0.984 ± 0.011	2.75686	0.005836
P(3,4,4)	0.122 ± 0.014	0.148 ± 0.017	4.41163	0.000159
P(3,4,6)	0.267 ± 0.022	0.213 ± 0.043	-4.21300	0.000268
P(3,5,6)	0.253 ± 0.044	0.185 ± 0.042	-4.19553	0.000280
P(4,4,24)	0.105 ± 0.027	0.062 ± 0.027	-4.12352	0.000339
P(4,5,22)	0.035 ± 0.007	0.050 ± 0.011	4.46966	0.000136
P(4,5,24)	0.108 ± 0.042	0.054 ± 0.023	-4.28317	0.000223

Table 4. Classification accuracy of discriminant models based on Rényi entropy (RE), permutation entropy (PE) or probabilities of ordinal patterns (OP) for cardiac autonomic neuropathy identification. OP, RE represents a procedure combining the discriminant power of RE and OP.

Feature	Sensitivity	Specificity	Accuracy	F	p-value
RE	71%	93%	82%	49.192	0.000000
PE	57%	93%	75%	8.2008	0.000625
OP	93%	100%	96%	12.599	0.000014
OP, RE	100%	100%	100%	-	-

IV. Discusion

In this work, we compared two approaches that yield multiscale entropy measures, and evaluated their potential for the identification of CAN in type 1 diabetes patients.

Results regarding a better performance of RE with positive values of α in the identification of CAN are consistent with our prior work [9, 10]. However, our previous findings supported that greater sequence length ($\lambda \geq 8$) improves RE performance for CAN assessment in type 2 diabetes rather than the current short sequence length [10]. Shorter sequence lengths better reflect cardiac vagal modulation rather than a sympathetic effect. Since ECGs were recorded in a supine position, a predominance of vagal activity is expected regardless of sequence length. Longer sequences for analysis include more of a sympathetic component and may better reflect impairment of sympatho-vagal tone.

Further research is required to reveal whether this difference in RE performance according to pattern length might be

suggesting clinical-pathologic dissimilarities between cardiac dysautonomia occurring in type 1 and type 2 diabetes mellitus.

We did not find significant differences between T1DM patients without CAN and controls for any of the HRV features analysed. The lack of a significant difference might reflect a still emergent cardiac autonomic dysfunction that does not affect substantially HRV dynamics due to a moderate disease duration in our cohort (15.35 ± 10.36 yrs), in addition to good diabetes management.

In previous work, we found that $PE(3,4)$ was correlated to the standard deviation (SD) and other measures of overall HRV, whereas $PE(3,5)$ and $PE(4,5)$ provided information on the sympatho-vagal balance in the healthy system [6]. However, these and other correlations were rather weak, supporting that PE provides additional information to that obtained using standard methods of HRV analysis. RE has also been shown to add new information when computed for negative values of α [10]. Since length of recording has an important impact on CAN classification [12], further research should aim at comparing the optimal data length of these algorithms for the identification of CAN.

RE performed at a higher accuracy in the identification of patients with CAN as compared to PE or probabilities of ordinal patterns P, although a combination of P reached the highest level of accuracy. Importantly, since RE and ordinal pattern statistics provide complementary information, the classification of cases based on these measures achieved an accuracy of 100%. Thus, a multidimensional space combining nonredundant HRV features holds promise in providing a sensitive and specific tool for CAN diagnosis.

V. Conclusions

RE performed at a higher accuracy in the identification of CAN as compared to PE. The combination of RE and ordinal pattern statistics reached the highest level of accuracy. This approach might be promising as a sensitive and specific tool for CAN diagnosis in T1DM. Additional research on a larger sample size is required to further elucidate the effectiveness of the proposed procedure for CAN detection.

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Conflict of Interest

The authors declare that they have no conflict of interest.

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