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Characterization and classification of Parkinson's disease patients based on symbolic dynamics analysis of heart rate variability

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ABSTRACT

Background: Parkinson's disease (PD) is a chronic and progressive neurodegenerative disorder characterized by deterioration of the substantia nigra, resulting in a deficiency of dopamine. PD is considered a movement disorder associated with numerous non-motor symptoms related to Autonomic Nervous System failures which can precede the motor ones. Therefore, their awareness could be helpful in the diagnosis of PD at an early stage.

Methods: Heart Rate Variability (HRV) is assessed by time and frequency domain indices, and by nonlinear indices based on symbolic dynamics and multiscale symbolic entropy. The features obtained were used to classify between PD patients and control volunteers using a support vector machine. Volunteers performed cardiovascular autonomic reflex tests: active standing, post- hyperventilation and controlled breathing.

Results: Temporal and frequency indices showed significantly lower values in PD patients compared to control volunteers. Symbolic dynamics and multiscale symbolic entropy results suggest a decrease in the complexity of the HRV signal in PD patients, in contrast with a more variable pattern of words for control volunteers. During controlled breathing differences between groups were found with most of the indices computed. Additionally, classification process achieves good separability during cardiorespiratory maneuvers (>95% of accuracy) and features based on symbolic dynamics showed high discrimination between groups.

Conclusions: The results found in this work suggest that the proposed methodological approach can classify PD patients in an early disease stage from healthy controls and give additional information about the cardiorespiratory system, which could be useful for diagnosis and follow up of PD patients.

1. Introduction

The definition of Parkinson's Disease (PD) is the loss or degeneration of the dopaminergic neurons in the substantia nigra. The most common neurodegenerative causes of Parkinsonism are alpha-synucleinopathies and these disorders are defined based upon the protein that accumulates within degenerating neurons. The most common alpha-synucleinopathy in PD patients is Lewy pathology (LP), LP is generated by the misfolding of the protein alpha-synuclein, which makes it insoluble and forms intracellular aggregates in neurons known as Lewy bodies and within cell processes, called Lewy neurites. Misfold alpha-synuclein in PD has not only an abnormal conformation that generates aggregation, but it also has modifications including phosphorylation and oxidative damage [1]. The inflammation induced by alpha-synuclein affects the optimal neuronal functioning, and it is intimately involved in the pathogenetic dysfunction underlying PD. Thus, all this indicates that alpha-synuclein plays a central role in PD's pathogenesis [2].

It has been known for many years that LP extends beyond the substantia nigra and a staging scheme has been proposed [3]. However, subsequent iterations of this scheme proposed that autonomic neurons in peripheral, autonomic ganglia and central autonomic neurons of the spinal cord may be affected before the vagus' dorsal motor neurons [1].

The clinical description of PD consists of four main components, motor symptoms, cognitive changes, neuropsychiatric or behavioral changes and symptoms related to Autonomic Nervous System (ANS) failures [4,5]. The diagnosis of PD is mainly based on the presence of motor symptoms, predominantly tremor at rest, bradykinesia, muscle rigidity and postural instability [4–7]. In addition to these symptoms,

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other motor manifestations have been observed. These include hypomimia, decreased blinking frequency, dystonia, kyphosis, scoliosis, gait impairment, and speech disability. However, pathological and imaging studies suggest that motor symptoms occur when the 50–70 % neurons of the substantia nigra have degenerated [5]; therefore, the disease is diagnosed at an advanced stage.

On the other hand, PD's non-motor symptoms include cognitive changes, neuropsychiatric changes, ANS failures, and sensory and sleep disorders [4–8]. These symptoms have commonly been a neglected feature of PD considering about 90% of patients suffer from these symptoms during the disease [8]. These non-motor symptoms of PD can precede the motor ones for years, even decades [4,5,9]. Therefore, the awareness of the non-motor symptoms is vital because the diagnosis of PD could be performed at an early stage. However, there are no diagnostic tests that allow a definitive diagnosis in the disease's premotor stages. Besides, the diagnosis is difficult because these symptoms are common to other pathologies and not only for PD [8]. Furthermore, the treatment used to diminished motor symptoms may aggravate or cause other symptoms. For example, psychosis, orthostatic hypotension and sleep disorders can be related to levodopa treatment. Then, it is essential to detect and correctly treat non-motor symptoms in order to minimize their impact on the quality of life in PD patients [5].

Autonomic dysfunction in PD patients has been extensively studied through heart rate variability (HRV). However, different tests under different conditions have been approached, which difficult the correlation between results. In this case, protocols for signal acquisition are varied, including rest in a temporal range from 5 to 30 min [10–13], active standing position [14,15], tilt test [16–19] respiratory maneuvers [12,13,15,18,20] and 24-h ambulatory ECG recording [21–23]. Regarding respiratory maneuvers, these including deep breathing at six breaths per minute with a duration of 1 min. [12] to 6 min. [15] and Valsalva maneuver [12,18,20]. By the other hand, it is important to point out that during deep breathing and with PD patients since an early stage of the disease, only Delgado et al. [15] and Maetzler et al. [13] have reported significative differences with respect to young and age matched healthy controls respectively. Additionally, Linden et al. [19] reported heart rate differences during deep breathing between the control group and long term diagnosed patients with Idiopathic Parkinson's disease.

Furthermore, the methodological approaches mainly consider time and frequency indices, such as the mean of HR, SDNN, RMSSD, LF, HF, LF/HF [11–13,15,18,20–24], some efforts have explored baroreflex sensitivity [18,20,25] and non linear indices as DFA, fractal dimension and approximate entropy [12], symbolic dynamics [14,26,27], or instantaneous measurements based on point process [10]. Most of the efforts that explore HRV in PD use spectral indices and some authors have reported differences between PD patients and healthy controls [13,15,18,21,22,24]. Moreover, other metrics such as non-linear indices have not been extensively studied in PD. For example, the symbolic dynamics of HRV seems to be more accurate to discriminate autonomic dysfunction compared with HRV frequency domain between healthy and PD patients [14]. Additionally, a comparison of symbolization strategies was previously performed, showing similar trends of symbolic indices between PD patients and a healthy group with different symbolization strategies even though symbolic indices exhibited a diverse statistical power in separating groups and experimental conditions [27]. However, inside the symbolic dynamics other strategies, as Renyi entropy and probabilistic approaches based on the occurrence of the words, can be used. In addition, it is important to comment that in literature most of the studies discuss the separability of the populations based on the statistical power, but the statistical power could not lead to a good separability, for this reason, exploring classification approaches could be interesting in this regard. In the last years, the classification methods have been relevant, supporting the medical decision process, the applications range from early diagnosis to treatment of diseases. Notably, in PD there are solely a few works that performed classification between PD patients and healthy control participants using cardiovascular signals [10]. However, in the light of the easy recording of cardiac signal as ECG or HRV, it is useful to explore their potential in the classification of PD patients for screening proposes, besides of the potential of cardiovascular signals in the early diagnosis of PD [16] and clinical implications in the treatment.

On the other hand, the regularity or irregularity of symbol sequences from symbolic dynamics can be characterized by entropy-based measures and considering the advantage of multiscale analysis, a multiscale symbolic entropy method can be approached. A multiscale symbolic entropy was recently proposed to analyze human gait signals [28] and patients with vasovagal syncope [29] obtaining additional information about the dynamics of signal complexity.

As it can be observed from the previous description, there is enormous variability in protocols applied and the results in the different studies are not always consistent. Another vital variable to consider is the condition of PD patients that were included in the studies, for example, disease duration, disease stage according to different scales and the treatment that is followed, since these parameters significantly influence the obtained results.

One of the main quests in the research around PD is the early detection; therefore, the use of simple and attainable tools as HRV analysis to reach this objective is essential. Therefore, it is necessary to study other protocols and methods to understand the ANS state in PD patients better. This paper proposes the HRV analysis in PD patients with traditional indices and symbolic dynamics from a single and multiscale perspective to classify them from control volunteers using a well-known support vector machine (SVM) classifier.

2. Materials and methods

2.1. Study population and protocol

In this study 24 volunteers were considered, patients diagnosed with PD and healthy adult volunteers as a control group. The group of patients with PD consists of 12 volunteers, six males and six females with a mean age of 67.50 ± 10.06 years and a mean diagnosis time of 5.09 years. These patients were diagnosed by clinical experts, who assigned a severity scale of the illness according to the Hoehn-Yahr Scale. Besides, to the PD, patients have chronic diseases such as Diabetes, Hypertension, and Hypothyroidism. The features of the patients with PD are specified in Table 1. The control group comprises 12 volunteers, six males and six females, with a mean age of 51.2 ± 6.7 years. None of these volunteers had clinical symptoms of autonomic and cardiovascular disorders, or was under medication. The institutional Ethics Committee approved the study, and the volunteers gave their written informed consent to participate.

Data acquisition was performed in the Hospital "Ignacio Morones Prieto", in San Luis Potosí, México. Electrocardiogram (ECG) signal was acquired with the BIOPAC® MP150 system at a sampling frequency of 500 Hz during cardiovascular autonomic reflex tests [12,30,31], considering the following conditions:

- **Control**: Resting stage where patients remained in a supine position for 5 min.
- **Active Standing (AS)**: A progressive posture change implemented the orthostatic phase; the volunteer remained standing for 5 min. Due to the age of participants and the study's limitations, volunteers were supported at the time of standing to accomplish the maneuver as fast as possible.
- **Post-Hyperventilation (PH)**: Stage of 5 min duration after a minute performing an hyperventilation at 35 breaths per minute.
- **Controlled Breathing (CB)**: Stage in which volunteers performed controlled breathing at 0.1 Hz for 4 min.

During the respiratory maneuvers the volunteers were supported

Table 1
Demographic and clinical features of Parkinson's disease patients.

Volunteer	Sex	Age	Hoehn-Yahr Scale	Chronic diseases	Treatment
1	M	53	1	None	Pramipexole, selegiline, venlafaxine
2	M	75	2	Diabetes	Levodopa, gabapentin
3	M	78	–	Barrett's esophagus	Levodopa, pramipexole
4	M	83	2	Hypertension, Hypothyroidism	Levodopa
5	M	54	–	None	Levodopa
6	M	73	1	None	Levodopa
7	F	67	1	Diabetes, Hypertension, Hypothyroidism	Pramipexole, gabapentin
8	F	71	–	Osteoporosis	Levodopa, pramipexole
9	F	54	1	Hypertension, Hypothyroidism	Pramipexole
10	F	63	1	Hypertension, Hypothyroidism	Pramipexole
11	F	75	1	Hypertension	Levodopa, selegiline, amantadine
12	F	64	–	Diabetes, Hypertension	Levodopa, pramipexole

with a visual stimulus to facilitate control of their breathing. Time series of successive beat to beat intervals (RR intervals) were computed from ECG as the time difference between consecutive R waves, which were detected according to [32]. RR intervals were manually reviewed and pre-processed with an adaptive filter in order to remove artifacts and/or ectopic beats [33].

2.2. Signal analysis

Linear and non-linear methods were used to study the cardiovascular system's characteristics to understand its dynamics in PD patients. In this context, classical linear indices and symbolic dynamics jointly with multiscale entropy were explored. A block diagram of the proposed method is shown in Fig. 1. Firstly, temporal and frequency indices were carried out as linear indices. Secondly, non-linear indices based on symbolic dynamics were performed with words formed by a sequence of symbols from an alphabet. Thirdly, a combination of multiscale entropy and symbolic dynamics was computed. Additionally, a classification process between healthy controls and PD patients was carried out employing a SVM.

Temporal indices included mean, standard deviation and the root mean square differences of successive RR intervals (RMSSD). In the frequency domain, the RR intervals were resampled to 2 Hz and the power spectral density was obtained by means of an autoregressive model [34], whose order was selected according to the Akaike criterion in the range of 6 to 14. Before computing the spectral density, the offset was removed. Power in the high frequency band (HF, $0.15 < f < 0.4$ Hz), low frequency band (LF, $0.04 < f < 0.15$ Hz), very low frequency band (VLF, $f < 0.04$ Hz), LF/HF ratio and normalized spectral components (LF %, HF%) were calculated. For illustration, see Fig. 1.

2.2.1. Symbolic dynamics

The RR intervals were transformed into a sequence of symbols, called alphabet. The alphabet was generated based on the following rule:

$$s_i = \begin{cases} 0: & \mu < x_i \leqslant (1+a)\mu \\ 1: & (1+a)\mu < x_i < \infty \\ 2: & (1-a)\mu < x_i \leqslant \mu \\ 3: & 0 < x_i \leqslant (1-a)\mu \end{cases} \quad \forall i = 1,2,3\ldots \tag{1}$$

where μ denotes the mean of the RR intervals, x_i represents each sample of RR intervals and a is a scalar that helps to define the ranges in which x_i is assigned [33]. In this work, tests were performed with a from 0.03 to 0.08. However, $a = 0.05$ was selected because this value showed a better

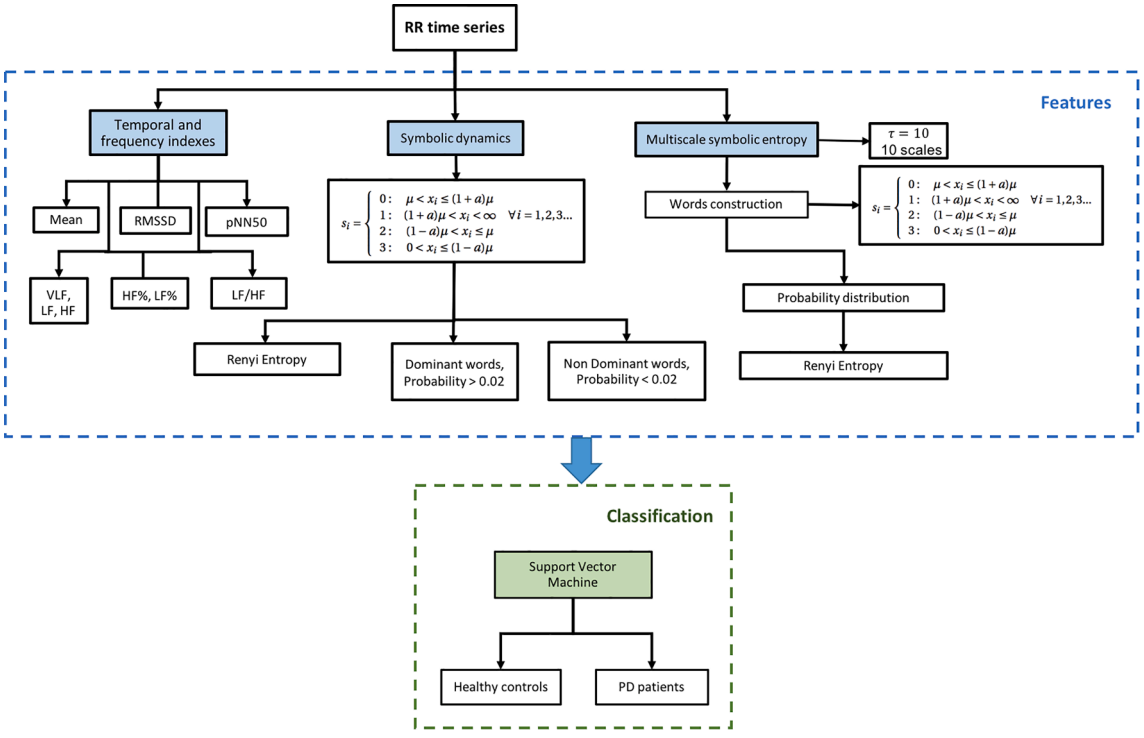

Fig. 1. Block diagram of the proposed methodology.

discrimination between groups. This selection of a value agrees with other HRV analyses, since the idea behind this value is related to common rest variability of RR intervals [33,35,36]. Once s_i is obtained, words of three consecutive symbols are formed. Then the sequence of words was created by overlapping two symbols, leading to a maximum of 64 different words w_i. Fig. 2 shows an example of the coding procedure.

The complexity of the sequence of symbols was computed utilizing the Renyi entropy [33,37]:

$$H_q = \frac{1}{1-q}\ln\sum_{i=1}^{64} p(w)^q \tag{2}$$

where $p(w)$ refers to the probability of each word. The advantage of Renyi entropy against Shannon entropy is that q value can give relevance to words with higher or smaller probabilities. If $q > 1$, the H_q is determined mainly by words with higher probabilities, whereas if $q < 1$, the entropy will be weighted by words with a smaller probability of occurrence. The Renyi entropy is defined for positive $q \neq 1$ and converges to the Shannon entropy in the limit $q \to 1$. For any value $q \geqslant 0$ the generalized entropies H_q are equal to zero for certain events described by the distribution $Q_1 = \{1, 0, \ldots, 0\}$, and achieve their maximum $In(N)$ for the uniform distribution. The generalized entropies are correlated; e.g., for the distributions Q_k the entropies are equal to $In(k)$ independently of the value of q [38]. In this study, q values higher and smaller than one were assessed and the value which shows the most significant differences is reported. Additionally, dominants words were considered as the words with a probability of 0.02 or higher and non-dominants words with a probability less than 0.02. A comparison between common dominants words that appear in both groups was performed and the dominants words in control volunteers that are non-dominant words in PD patients were analyzed.

2.2.2. Multiscale symbolic entropy

Given a time series $\{x_n\}$, consecutive coarse-grained time series corresponding to the scale factor τ is constructed [39]. First, the initial time series is divided into non-overlapping windows of length τ; second, the data points inside each window are averaged. In general, each element is calculated according to Eq. (3):

$$y_j^\tau = \frac{1}{\tau}\sum_{i=(j-1)\tau+1}^{j\tau} x_i, \quad 1 \leqslant j \leqslant \frac{N}{\tau}. \tag{3}$$

Then the new time series $\{y_j^\tau\}$ is transformed into a sequence of symbols by Eq. (1). The algorithm was performed considering the τ scale from 1 to 10 and the dynamic of the symbol sequence was assessed by Renyi entropy. This method is illustrated in Fig. 3.

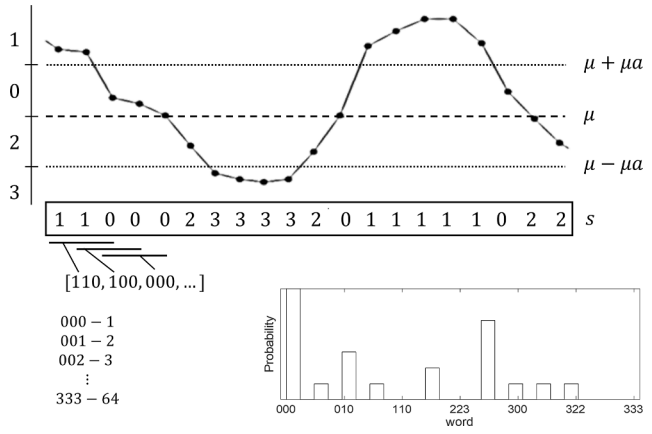

Fig. 2. Description of the symbols extraction and coding procedure from RR intervals.

2.3. Statistical analysis

A Lilliefors normality test was performed to identify if the indices of healthy and PD data from each maneuver come from a normal distribution. According to the results of the normality test, the differences between the AS, PH and CB maneuvers concerning the control were evaluated using a one-way repeated measures ANOVA for each index per group, with maneuvers as the repeated factor and with post hoc comparisons based on the Bonferroni method. The differences between the PD patients and the control volunteers were evaluated at each maneuver and index by applying unpaired two-sample Student's t-test in those scales that follow a normal distribution, and for the values that did not have a normal distribution, the Wilcoxon test was performed. Statistically significant differences were considered with $p < 0.05$.

2.4. Classification

In the context of Biomedical Engineering, the development of systems to automatically recognize a medical condition based on some measurable physiological information is of fundamental importance. In the more general case, m physiological measures $x_i, i = 1, 2, \ldots, m$ are used, and they build up a feature vector $x = [x_1, x_2, \ldots, x_m]^T$, where T stands for transposition and each vector is related to a single volunteer. It is important to note that there will be variations between volunteers with the same medical condition and our objective is to define a mathematical model that is able to work with these variations and to assign a new vector into the right medical condition based only on the measurable physiological information. In our case, the possible medical conditions are healthy and PD, and the feature vectors are composed of the linear and nonlinear measures computed from the RR intervals. To find the classification model, we used the well-known method called SVM, since this is commonly used in many research areas and has already been used for healthy/PD classification with interesting results [10]. Since the database has a reduced number of volunteers, we decided to use the Leave-One-Out Cross Validation (LOOCV) scheme to train the SVM classifiers and the SVM used a linear kernel. Before the LOOCV, each data was normalized with zero mean and unit variance using the whole training set. The mean and variance vectors of the training set were used to normalize the test vector. At each LOOCV iteration, sigma and soft margin parameters were determined using Bayesian optimization. Accuracy, sensitivity and specificity were computed and used as performance measures. Feature selection was carried out by searching the n-tuple that maximizes performance measures through a support vector machine recursive feature elimination (SVM-RFE) procedure [40]. SVM-RFE is implemented by training an SVM with a linear kernel to get a ranked list of all features, and the performance was quantified through the area under the ROC curve (AUC). The classification procedure was made independently for each maneuver.

3. Results

3.1. Temporal and frequency indices

Fig. 4 shows an example of the RR intervals fluctuations obtained from healthy (right panel) and PD (left panel) conditions. The RR intervals show a reduced oscillatory pattern for PD patients with respect to the control volunteers, and this happens for the three maneuvers (rows 1 to 3, columns 1 and 3). The spectrum of RR intervals of PD patients during the control maneuver (row 1) shows an inhibited high frequency component. In the controlled breathing case, for control volunteers, we can observe how the spectrum is entirely concentrated in the respiratory frequency (frequency = 0.1 Hz), while for PD, the spectrum presents dispersion regardless the main peak is well located. Please note that the RR intervals are detrended and the spectra are normalized with respect

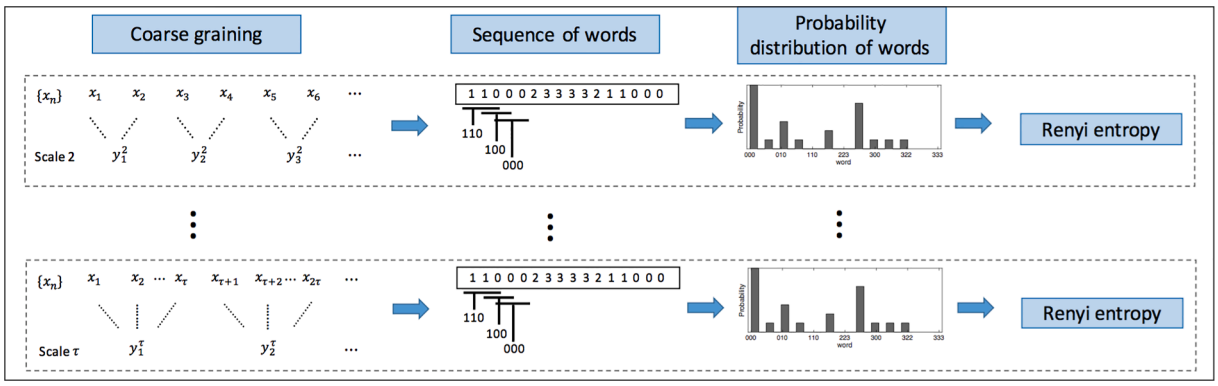

Fig. 3. Description of the Multiscale Symbolic Entropy implementation.

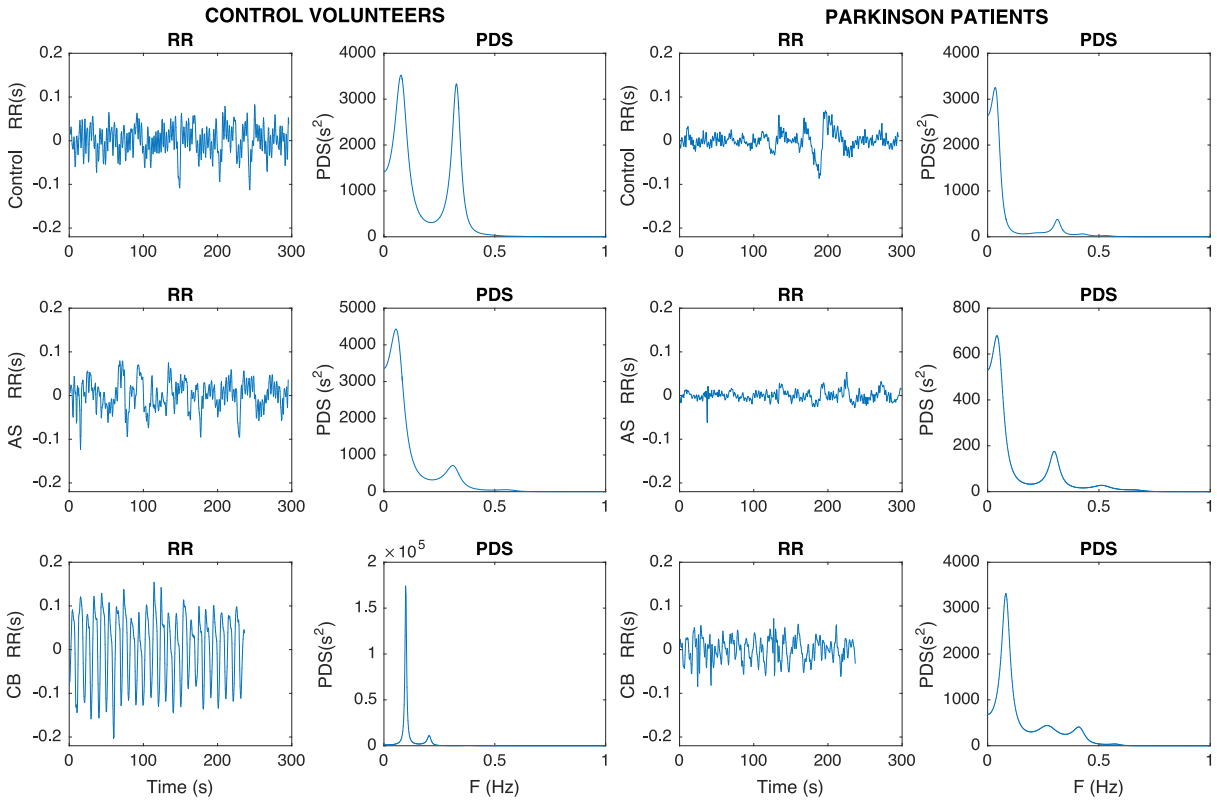

Fig. 4. Temporal and spectral relationship of RR intervals for control and PD volunteers (columns) during control, active standing (AS) and controlled breathing (CB) maneuvers (rows).

to the total power.

Table 2 shows the mean and standard deviation for temporal and frequency indices of control volunteers and PD patients, where each column represents the assessed maneuvers. For control volunteers, all the maneuvers showed significant differences concerning the control stage in LF% and HF% indices, while in the case of PD patients this significant difference was only observed during controlled breathing. Regarding differences between groups, PD patients showed a statistically significant minor value of RMSSD during control, active standing, and controlled breathing. Additionally, LF and HF also showed a statistically significant decreased behavior.

3.2. Symbolic dynamics

The number of apparitions of a particular word reflects its importance in the time series construction. The time series tends to be more complex or rich in information if it is composed of many words' participation with the same occurrence. To evaluate this characteristic of the RR intervals during healthy and pathologic conditions, the histogram of occurrence of words was obtained in each volunteer, which later it was normalized with the total number of words. In this way, we have a normalized version of the histogram that can be visualized as a probability distribution. Thus, we can evaluate the importance of each word in the construction of the coded time series. Two types of words were defined, called dominants and non-dominants. The dominant words were those words that appear in mean with at least 0.02 of probability. From here, two analyses were performed: a) to compare the words that are dominant in both groups at each maneuver and b) to evaluate the dominant words in the control group that became non-dominant in the pathologic one. The opposite was also evaluated, the dominant words in the pathologic group that became non-dominant in the control one.

Table 2
Mean and standard deviation of temporal, frequency and nonlinear indices.

Control volunteers	Control	Active Standing	Post-Hyperventilation	Controlled Breathing
Mean (s)	0.852 ± 0.153	0.733 ± 0.120	0.783 ± 0.129	0.815 ± 0.141*
RMSSD (s)	0.023± 0.011†	0.018 ± 0.008†	0.021 ± 0.009	0.034 ± 0.014†
VLF ($1x10^3$) (ms^2)	68.51 ± 108.72	101.07 ± 123.42†	135.81 ± 77.33†	30.57 ± 17.54†
LF ($1x10^3$) (ms^2)	138.02 ± 167.58†	194.76 ± 178.04†	182.02 ± 110.08†	668.37 ± 458.78*†
HF ($1x10^3$) (ms^2)	68.95 ± 62.67†	38.17 ± 27.87†	49.15 ± 35.94†	65.32 ± 53.05†
LF %	62.18 ± 16.08	80.32 ± 11.18*	78.71 ± 11.23*	91.32 ± 3.17*
HF %	37.82 ± 16.08	19.67 ± 11.18*	21.29 ± 11.23*	8.68 ± 3.17*
LF/HF	2.41 ± 2.31	5.52 ± 3.09	4.82 ± 2.75	11.93 ± 4.43*
Renyi	4.75 ± 0.43†	4.81 ± 0.31†	4.75 ± 0.25†	4.79 ± 0.16†
Parkinson Patients				
Mean (s)	0.806 ± 0.214	0.754 ± 0.191	0.783 ± 0.171	0.783 ± 0.175
RMSSD (s)	0.015 ± 0.012	0.013 ± 0.013	0.019 ± 0.018	0.018 ± 0.012
VLF ($1x10^3$) (ms^2)	30.81 ± 35	28.83 ± 34.28	42.67 ± 50.51	13.19 ± 16.94
LF ($1x10^3$) (ms^2)	73.98 ± 137.76	72.16 ± 142.27	132.91 ± 262.23	127.45 ± 160.56
HF ($1x10^3$) (ms^2)	25.32 ± 38.85	21.21 ± 44.54	30.74 ± 60.65	15.04 ± 20.35
LF %	66.26 ± 19.13	70.9 ± 12.79	71.68 ± 17.70	85.46 ± 12.09*
HF %	33.74 ± 19.13	29.1 ± 12.79	28.32 ± 17.70	14.54 ± 12.09*
LF/HF	2.65 ± 1.59	3.39 ± 2.61	5.76 ± 7.07	11.14 ± 8.22 *
Renyi	3.76 ± 0.76	3.7 ± 0.71	4.29 ± 0.70	4.14 ± 0.64

* Post hoc comparison vs Control $p < 0.05$.
† Unpaired two-sample Student's t test, Control vs PD volunteers $p < 0.05$.
Renyi entropy of the word distribution with $q = 0.25$.

In the first row, Fig. 5 shows the comparison of dominant words in both groups at the different maneuvers as mean and standard deviation. The white circles stand for the control group and black circles represent the pathologic one. The diamonds are the cumulative sum of the circles, and the right y-axis shows the scale. The x-axis shows the 64 words; the coding can be found in Fig. 2.

Dominant words in both groups with constant behavior were 000, 111, 222 and 333, representing low fluctuations in RR intervals. The word 000 was significantly different in all maneuvers between groups with significant participation in pathologic group, while the word 333 was significantly different only during active standing and controlled breathing, being more important in healthy condition. The dominant words 002, 022 and 200, have one variation and were able to differentiate healthy from pathologic condition only during controlled breathing statistically. Considering the dominant words' participation in the whole dynamic during the different maneuvers, the pathological volunteers showed a higher percentage of these words. In fact, in control stage, values close to 0.9 can be observed; suggesting a decreased HRV, and it can be observed in Fig. 4.

For the second analysis, dominants words that became non-dominant words between groups at the different maneuvers are shown in the row two of Fig. 5. The circles represent the dominants words in control cases that are non-dominant in the pathologic case. The squares represent dominants words in pathological volunteers that are non-dominant in a healthy situation. We can observe that the control volunteers have more of these dominant words than the pathological volunteers for all the maneuvers. These words participate at least 10% in the construction of the time series, and these are words that have variable patterns such as 011, 110, 223, 233, 322, and 332. These results show that the control volunteers present a larger complexity in the HRV than the pathologic ones, independently of the maneuver. Further, there are non-dominant words that showed significant differences at least in two maneuvers between control and pathological volunteers such as 110, 232 and 322, which showed a higher occurrence in control volunteers with respect to PD patients. These complement the dominant words to generate a rich pattern in HRV for control volunteers, even though these words have a limited participation, control volunteers showed more participation between maneuvers than PD patients. Additionally, the comparison versus control stage for each group showed that controlled breathing was the maneuver with more statistical differences. In contrast, the pathological volunteers did not show a different behavior against control stage, which suggests that controlled breathing is a maneuver able to assess the cardiovascular system's appropriate functioning. Finally, the Renyi entropy analysis of a sequence of symbols from original time series at different maneuvers, showed in Table 2, was significantly higher in the control group for all the maneuvers, which support the difference in the complexity of the sequence of symbols between groups. These results were obtained with q =0.25, which evidence the relevance of symbols with smaller occurrences. This situation could not be found throughout Shannon entropy.

3.2.1. *Multiscale symbolic entropy*

The results of Renyi entropy from multiscale analysis are shown in Fig. 6 for $a = 0.03$ and $a = 0.05$ (symbolic coding) with $q = 0.25$ (Renyi parameter). A significant decrease was observed in patients with PD with respect to control volunteers during active standing and post-hyperventilation maneuvers in most of the scales for both a values. The decrease of Renyi entropy in patients with PD is more evident in control with $a = 0.03$, while in the case of controlled breathing, better discrimination is showed with $a = 0.05$.

In supine resting with $a = 0.03$ is possible to observe how the complexity of the RR interval signal decreases as the scale is increased in both groups and it is also clearly observed that PD patients have a significant decrease in complexity with respect to control volunteers along the ten scales evaluated.

The values of Renyi entropy in the controlled breathing maneuver showed an increase in the complexity of the signals along the scales corresponding to the short-term variations (1 −5), followed by a decrease in large scales. This behavior is more evident for control volunteers using the factor $a = 0.05$, since this a value considers changes farther from the mean value, and it is the parameter that allows analyzing better the variations of this maneuver.

The significant differences of the maneuvers with respect to control of the values of Renyi entropy from the RR intervals are also displayed in Fig. 6. Renyi entropy values of active standing and post-hyperventilation maneuvers increased with respect to control stage in many scales, mainly in control volunteers. In the case of controlled breathing maneuver, control volunteers showed an increase with respect to control stage only with $a = 0.05$. Renyi entropy values of PD patients were significantly different from control stage only in small scales during post-hyperventilation maneuver with both a values, and in controlled breathing only for scales 3 and 4 for each value of a respectively.

In the active standing maneuver, a decrease with respect to the control is observed in Renyi entropy, in scale 1 in control volunteers and PD patients with $a = 0.03$. In contrast, in larger scales, a significant increase was found with respect to control stage, only in control volunteers, which suggests that in the long term the complexity recovers,

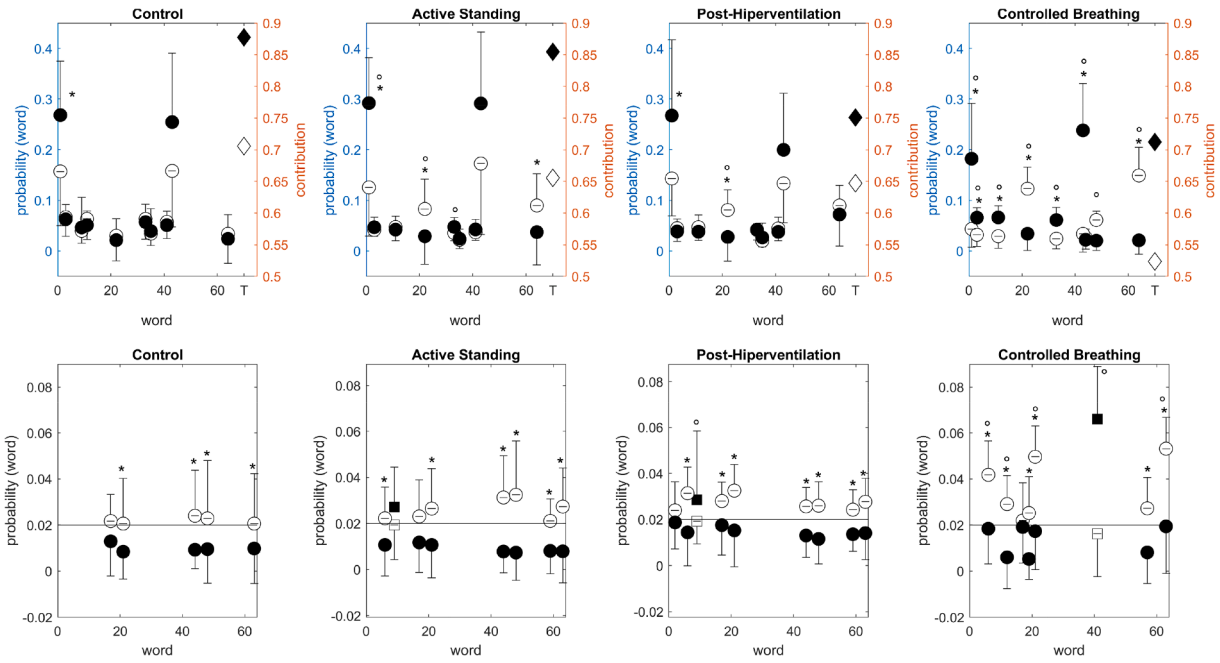

Fig. 5. Mean and standard deviation of the words probability. First row illustrates dominant words in both groups (probability >2%) with black circles as PD patients and white circles as control volunteers. T means the total occurrence of the dominant words, indicated by diamonds. The second row displays dominants words that became in non-dominant words between groups. The squares represent dominants words in pathological volunteers that are non-dominant in control ones. * Significant differences between control volunteers and PD patients. ∘ Significant differences vs Control ($p < 0.05$).

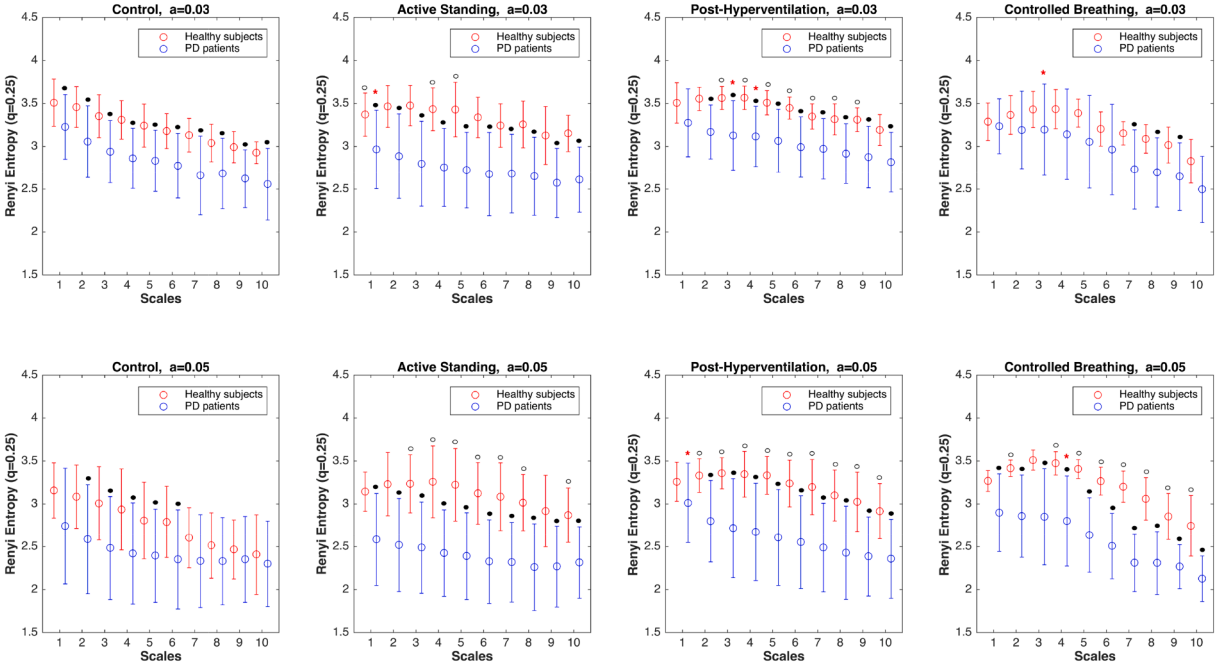

Fig. 6. Mean and standard deviation of the values of Renyi Entropy of the RR intervals in both groups during Control, AS, PH y CB maneuvers with $a = 0.03$ y $a = 0.05$. • Significant differences between control volunteers and PD patients. ∘ Significant differences vs Control stage in healthy volunteers. * Significant differences vs Control stage in PD patients ($p < 0.05$).

whereas this behavior does not occur in PD patients.

3.3. Classification

Table 3 shows the classification results to discern between PD patients and control volunteers automatically. Note that all the performance metrics achieve more than 90% in the cardio-respiratory reflex tests, which means a good separation between classes. In addition, we can observe that each maneuver uses different type and number of features. For example, in the controlled breathing just one entropy feature is needed to fully separate PD and control volunteers. The control stage used only entropy features, and active standing and post-hyperventilation needed from all types of features to achieve a good performance. The control stage had the lowest performance metrics with

Table 3
Mean performance values of the SVM classifier (PD vs control). Values are expressed in percentages.

Maneuver	Features	Accuracy (%)	Specificity (%)	Sensitivity (%)
Control	RE6, RE8, RE	83.3 ± 38.1	75 ± 45.2	91.7 ± 28.9
Active Standing	RE, VLF, Mean	95.8 ± 20.4	100 ± 0	91.7 ± 28.9
Controlled Breathing	RE5	100 ± 0	100 ± 0	100 ± 0
Post-Hyperventilation	RE2, RE5, LF/HF, RMSSD, VLF, Mean	95.8 ± 20.4	100 ± 0	91.7 ± 28.9

REx: Renyi entropy in 'x' scale.
RE: Renyi entropy for maneuvers.

an accuracy of 83.3%. Fig. 7 shows the features distribution, the support vectors and the hyperplane for control, active standing and controlled breathing.

4. Discussion

This paper explores the behavior of RR intervals through classic indices of time and frequency domain and nonlinear characteristics. Particularly, nonlinear characteristics were assessed by means of symbolic dynamics and a mutiscale analysis based on entropy. Although HRV has been studied in PD to our knowledge there is no report about the complexity study based on multiscale entropy considering different cardiovascular and cardiorespiratory stress tests. The performed analyses showed that PD patients had blunted cardiovascular response, but symbolic dynamics and multiscale symbolic entropy expose in a better way this behavior in PD patients.

Temporal and frequency indices were able to identify statistical differences between control volunteers and PD patients with a Hoehn-Yahr scale 1 and 2. The indices RMSSD, LF and HF were lower in PD patients, suggesting that control of the ANS is affected by the disease. The frequency domain results are consistent with previous studies in the supine position during 5 to 10 min in rest and in the early stage of the disease [11,12,18]. However, other authors have not reported significant differences in frequency domain indices between PD patients and healthy age matched volunteers in the same condition [10,14,26]. Considering active standing, Vianna et al. [14] also found differences in LF and HF between healthy volunteers and PD patients with orthostatic hypotension but not with PD patients without orthostatic hypotension. In our study, the presence of orthostatic hypotension was not assessed. However, it is essential to consider this aspect since orthostatic hypotension is the result of defective sympathetic outflow and a failure to increase peripheral resistance when standing [41] and PD patients with orthostatic hypotension have showed lower baroreflex sensitivity than in those without orthostatic hypotension [20]. Delgado et al. [15] also explored the PD patient's response to active standing founding decreases in total power, LF and HF. However, the comparison was against healthy volunteers younger than patients (∼ 38 years). Regarding deep breathing maneuver, it was possible to differentiate control volunteers from PD patients based on RMSSD, VLF, LF and HF indices. Other authors have performed the same cardiorespiratory test [12,13,15,18], but only Maetzler et al. [13] and Delgado et al. [15] have reported a decrease in some frequency domain indices. In addition to these studies, we found that PD patients were not able to adapt their cardiovascular system in response to the cardiovascular autonomic reflex tests, as it was observed in control volunteers employing LF% and HF% indices in comparison with the control stage. Furthermore, it is worth noting that controlled breathing to 0.1 Hz showed significant differences in LF and LF% compared to the control in both groups. However, this increase is due to the 0.1 Hz breathing and does not suggest an increase in the sympathetic pathway.

On the other hand, symbolic dynamics showed that pathological volunteers have a higher number of dominant words than control volunteers. This imply that HRV is depressed in PD patients during the four maneuvers. Renyi entropy was able to show a minor complexity of the sequence of symbols in PD patients in each autonomic stress test including the resting stage. It is important to note that symbolic analysis

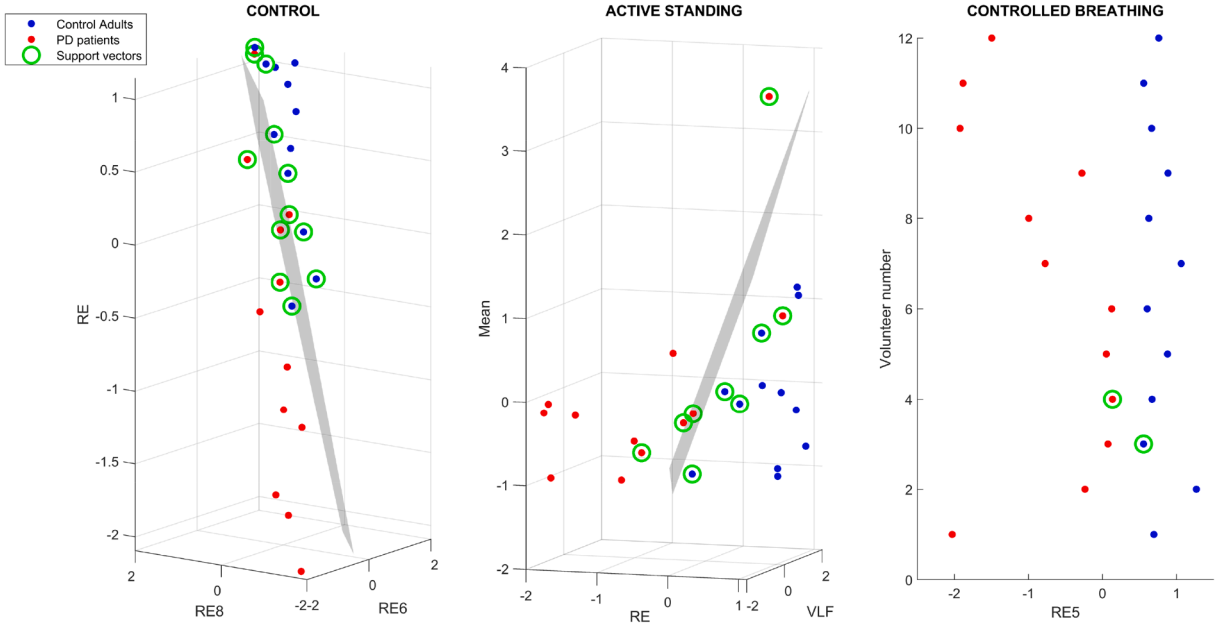

Fig. 7. Features distribution of control adults and PD patients of control, active standing and controlled breathing maneuvers. The support vectors and the hyperplane are also displayed. RE: Renyi entropy.

in PD patients has not been extensively applied, Vianna et al. [14] used symbolic dynamics considering patterns with 0, 1, and 2 variations, they found significant differences between control volunteers and PD patients only with patterns with 2 variations. The expected enhancement in cardiac sympathetic modulation and parasympathetic withdrawal following active standing was reported in healthy volunteers and PD patients without orthostatic hypotension, while PD patients with orthostatic hypotension showed a different and unexpected behavior. Porta et al. [27] also analyzed PD patients without orthostatic hypotension using different symbolization strategies, they found an increase in 2UV patterns in heart period and systolic arterial pressure (SAP) in PD patients compared to healthy controls. In addition, Baumert et al. [26] also explored patterns with 0, 1, and 2 variations, finding no differences between PD patients and healthy volunteers. However, they found differences using joint symbolic analysis of cardio-respiratory dynamics in PD patients, indicating a loss of cardio-respiratory coordination. Therefore, according to the Baumert common symbolic findings, our results are more straightforward in alphabet construction and analysis methods.

One main finding is that during supine resting and maneuvers, significant differences are found between control volunteers and PD patients using multiscale symbolic entropy of RR intervals. Besides, the Renyi entropy value of the multiscale symbolic series showed a significant decrease in PD patients with respect to control volunteers along the ten scales, suggesting a reduced HRV complexity. Multiscale Symbolic Entropy results during active standing in comparison with control showed a significant decrease in the first scale in both groups, and this suggests that the word distributions present a subset of patterns more likely, while others are missing or infrequent. Although both groups have a decreased complexity during active standing in scale one, the complexity was minor in PD patients, as also was observed during control. This result reflects the reduced adaptive capacity in the patients, result of a possible autonomic imbalance.

The complexity increase in higher scales (>4) for control volunteers during active standing suggests that long-term cardiac response could be blunted in PD patients, mainly affecting sympathetic-mediated components of HRV, leading to a structure less complex than control volunteers. One phenomenon that can have an influence around scales > 4 is the baroreflex, since to adjust systemic vascular resistance, the arterial baroreflex buffers blood pressure, showing a resonance behavior, where the resonance period is around 10 s (Mayer waves) [42]. The complexity decrease in scale one and a further complexity increase in scales above four was also observed in healthy young volunteers [43], where the complexity in small scales was associated with a decrease in respiratory sinus arrhythmia contribution due to parasympathetic inhibition during standing.

The behavior of a diminished complexity in PD patients was preserved in respiratory maneuvers. However, in the case of controlled breathing, the differences were observed with the parameter of symbolic dynamics $a = 0.05$, since this maneuver causes changes farther from the mean value in the RR intervals, and a higher value allows characterizing the phenomenon in a better way. Regarding the changes in respiratory maneuvers with respect to control, in post-hyperventilation and controlled breathing, an increase in complexity of RR intervals was found above scale 2 in control volunteers, with $a = 0.05$. However, in PD patients, the increase was present only during scales 1 and 4 in post-hyperventilation and controlled breathing, respectively, supporting the finding that long-term cardiac modulation is affected in PD patients.

Regarding the cardiovascular autonomic reflex tests, active standing and controlled breathing showed a better separation between groups. The hemodynamic and autonomic adjustments carried out after an upright posture can be summarized as a reduction in stroke volume, heart rate increases secondary to vagal withdrawal and sympathetic stimulation, and an increase in total peripheral resistance [44,17]. In this context, PD patients showed an impairment in the hemodynamic and autonomic adjustments, evidenced by symbolic dynamics and multiscale symbolic entropy analyses. On the other hand, controlled breathing at 0.1 Hz reduces the chemoreflex response to both hypoxia and hypercapnia and increases baroreflex sensitivity [45]. Besides, the HRV during controlled breathing increases [46,47]. However, the increase in complexity through the multiscale symbolic entropy analysis was evident only in the control group with $a = 0.05$.

Multiscale symbolic entropy provides essential features to the classification process. However, multiscale entropy has two important shortcomings: 1) the course of the entropy-based complexity as a function of the time scale is partially linked to the reduction of variation inherent to the procedure for the elimination of the fast temporal scales and 2) the procedure for the elimination of the fast temporal scales exploits a filter with a frequency response that cannot prevent aliasing, thus being suboptimal especially in the presence of fast oscillations. Refined multiscale entropy proposed by Valencia el al. [48] deals with these two shortcomings. However, the refinement of multiscale entropy needs to be studied in detail, since just a few differences are reported between multiscale entropy and refined multiscale entropy in different experimental conditions. But it would be interesting to explore refined multiscale entropy to confirm the differences found between groups and to evidence a different behavior in longer time scales.

Finally, the classification process was satisfactory, in fact, it is possible to observe that only a few features were needed to achieve good separability. It is also essential to mention that the kernel in SVM was the linear one, meaning that the selected features have a high discrimination between groups. Furthermore, the proposal features, specifically Renyi entropy and its multiscale version can be found as selected features in all cases, and the exploration of these features for this task was never used. In addition, linear indices as mean value, RMSSD, and some frequency indices were selected as relevant features to accomplish the classification between groups, which reveals the importance of considering linear indices in the classification process. Thus, linear indices provide complementary information to nonlinear ones, as previous works have showed that linear indices are useful to differentiate control volunteers and PD patients [11,18,24]. Obviously, other classifiers can be used since the groups showed a linear separability but the advantage of SVM is the location of the decision boundary based on closer samples of each class, which implies major generalization in the classification process. In addition, it is important to mention that the major PD classification efforts have been oriented to classify between healthy and pathologic volunteers using movement or voice data [49,50]. Our proposed method is able to give additional information about the cardiorespiratoy system. Consequently, a possible clinical impact of this set of tools is to help the clinician to have a better cardiac diagnostics directly related to a possible dysautonomia in a simple way and in a possible real time version, for example, by applying controlled breathing, which is a test that could be done almost in any place.

One of the main limitations of this study is that the range of age between study groups is not the same, but both groups belong to elderly people. In the literature studies showed that cardiac function changed between young and elderly people [51,52]. For this reason, it could be interesting to explore groups matched by age. On the other hand, our results are according to a study where a group of patients with Parkinson's disease was matched by age with a healthy group. The symbolic indices from the heart period showed differences between groups and between rest and head-up tilt maneuver [27]. This could imply that elderly people present a similar cardiac function.

Another significant limitation is the analysis of the only HRV to characterize autonomic control of the PD group. The analysis of arterial blood pressure by the SAP signal gives additional information about the cardiovascular control in PD, such as baroreflex and feedforward mechanical pathway considering causal relationships. Therefore, it would be advisable to include the SAP signal analysis to extract essential features to evaluate a different feature space to classify between groups. In addition, regarding vascular control, SAP variability may increase without modification of heart period complexity in PD patients without

orthostatic hypotension as stated in [16].

5. Conclusion

This study was performed in order to assess the response of the ANS of PD patients through HRV and to classify between PD patients and healthy control volunteers. This assessment was carried out by applying different cardiovascular autonomic reflex tests such as active standing, post-hyperventilation and controlled breathing. The results of spectral and symbolic dynamics indices showed that autonomic nervous system of PD patients was not able to adapt to the applied maneuvers, which can be observed by the HRV low complexity evidenced by the proposed symbolic dynamics analysis, specifically this was assessed by the increase in the dominant words as well as a lower entropy. Therefore, the symbolic dynamics joint with the multiscale analysis could be useful as a complement index in the methodology of assessment of PD for diagnosis and treatment follow up of the disease. The found features showed a high discriminatory capacity, since we were able to have good separability between PD patients and control volunteers using anyone of the maneuvers. This suggests that clinical expert could choose one of the maneuvers to support the medical decision based on the classification.

CRediT authorship contribution statement

Guadalupe Dorantes-Méndez: Conceptualization, Methodology, Software, Formal analysis, Writing - original draft. **Martin O. Mendez:** Software, Formal analysis, Writing - original draft. **Laura E. Méndez-Magdaleno:** Software, Formal analysis. **Brenda G. MuñozMata:** Software. **Ildefonso Rodríguez-Leyva:** Writing - review & editing. **Aldo R. Mejía-Rodríguez:** Writing - review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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