MONITORING AUTONOMIC RESPONSES IN PARKINSON’S DISEASE INDIVIDUALS: NON-LINEAR AND CHAOTIC GLOBAL METRICS OF HEART RATE VARIABILITY

Heloisa Balotari Valente[a*], Natacha de Lima Gervazoni[a], Maria Júlia Lopez Laurino[a], Mileide Cristina Stoco-Oliveira[a], Felipe Ribeiro[a], Augusto Cesinando de Carvalho[a], Luiz Carlos Marques Vanderlei[a], David M. Garner[b]

[a]Universidade Estadual Paulista "Júlio de Mesquita Filho", Faculdade de Ciências e Tecnologia, Departamento de Fisioterapia, Presidente Prudente SP, Brazil.

[b]Cardiorespiratory Research Group, Department of Biological and Medical Sciences, Faculty of Health and Life Sciences, Oxford Brookes University, Headington Campus, Gipsy Lane, Oxford OX3 0BP, United Kingdom.

E-mails: helobalov@hotmail.com; natacha_gervazoni@hotmail.com; majulaurino@hotmail.com; cristina.mileide@gmail.com; ribeiro-felipe@outlook.com; augusto.cesinando@unesp.br; lcm.vanderlei@unesp.br; davidmgarner1@gmail.com.

*Corresponding Author: Heloisa Balotari Valente (e-mail: helobalov@hotmail.com).

ABSTRACT

Aim: To examine and contrast the autonomic responses, as assessed through the non-linear and chaotic global metrics of heart rate variability in two distinct cohorts: the Parkinson's Disease Group (PDG) and the Control Group (CG), both at rest and during an active tilt test. **Methods**: The study encompassed a total of 46 participants (PDG: n=23; 73.73±7.28 years old; CG: n=23; 70.17±8.20 years old). Initial data collection involved the acquisition of participant's physical, cognitive, and clinical characteristics. The autonomic modulation was estimated both at rest and during the active tilt test. For the assessment of autonomic modulation, we computed non-linear indices derived from five entropies (Approximate, Sample, Shannon, Renyi and Tsallis), Detrended Fluctuation Analysis (DFA) and the seven chaotic global metrics (*hs*CFP1 to *hs*CFP7). **Results:** At rest, the PDG exhibited significantly lower values of *hs*CFP3 (0.818±0.116 vs. 0.904±0.065; $p<0.05$) and Sample Entropy (0.720±0.149 vs. 0.799±0.171; $p<0.05$). During the active tilt test, the PDG demonstrated significantly lower values of ApEn, while the CG presented significantly lower values of SampEn, *hs*CFP1, *hs*CFP3, *hs*CFP7, and higher values of *hs*CFP5. An interaction effect was observed, indicating that *hs*CFP1 and *hs*CFP3 exhibit differential behavior for the CG and PDG in response to the active tilt table. **Conclusion:** subjects with PD exhibited reduced complexity of the RR interval series at rest, and a diminished autonomic response to the active tilt test when compared with the CG. The active tilt test, together with non-linear indices, may serve as a valuable tool for assessing the Autonomic Nervous System in individuals with PD in a clinical setting. However, the interpretation of these data should be approached with caution, given the possible influences of pharmacotherapies on autonomic regulation and the inclusion of diabetic participants in the study cohorts.

Keywords: Active Tilt Test; Autonomic Nervous System; Chaotic Global Metrics; Heart Rate Variability; Parkinson's Disease.

INTRODUCTION

Parkinson’s disease (PD) is a slow and progressive neurodegenerative condition [1,2], that is primarily characterized by the loss of neurons of the substantia nigra pars compacta [3,4], which leads to various fundamental motor manifestations, encompassing bradykinesia, muscle rigidity, resting tremor and impairment in both posture and gait [5].

In addition to the motor symptoms, PD is also associated with a spectrum of non-motor symptoms including cognitive decline, sleep disturbances, and dysautonomia [6]. Autonomic dysfunction is a pervasive issue in individuals with PD, and has been linked to both a decreased survival rate [7] and a diminished quality of life [8].

Autonomic dysregulation in PD can be assessed using heart rate variability (HRV) [9]. HRV serves as a simple, cost-effective, non-invasive and reliable measure that allows for the evaluation of the functional efficiency of the autonomic nervous system (ANS) by analyzing the RR intervals of successive heartbeats [9]. The ANS is instrumental in the regulation of various physiological processes, including those of the cardiovascular system [9]. Given the frequent occurrence of ANS dysfunction in PD, the assessment of autonomic function using HRV is particularly pertinent in this patient population.

The majority of research has predominantly focused on the application of linear HRV methodologies for assessing the autonomic modulation in individuals with PD [10,11]. Current evidence underscores the intricate and non-linear interactions involved in cardiovascular regulation [12]. Consequently, conventional HRV analytical techniques may not capture the complex dynamics of heartbeat generation [12]. Non-linear HRV methodologies, which take into account the intricate characteristics of the body’s control systems [12] have been shown to offer valuable insights into the ANS of individuals with PD. These insights can serve to augment the findings derived from linear analyses. Notably, the existing body of literature lacks studies employing ‘globally chaotic’ techniques. These techniques are recognized for their heightened sensitivity to variability in biodynamic systems, particularly when compared to linear methods in the time, frequency and geometric domains [13].

In addition to the assessment of the ANS under resting conditions, numerous studies have delved into the exploration of autonomic reactivity in response to specific autonomic tests in individuals with PD [14,15]. Among these, the tilt test has gained considerable recognition due to its ability to induce an increase in sympathetic activity and a decrease in parasympathetic activity in healthy individuals [16]. This test can be administered in either passive or active manner [17]. The active tilt test [17] in particular presents a straightforward and economically viable alternative for the assessment of individuals with PD. Compared to its passive counterpart, the active tilt test elicits more pronounced changes in both musculoskeletal and cardiovascular responses [17].

To date, a singular study has undertaken the task of evaluating the HRV of subjects with PD during the active tilt test [14]. This study primarily employed frequency domain and geometric analyses via Poincaré plots. However, no studies have ventured to apply chaotic global metrics [18], entropies [19] or Detrended Fluctuation Analysis (DFA) [20] to this context, underscoring the novelty of the present study. Chaotic global metrics are anticipated to exhibit superior performance when applied to short time-series [21] as is the case of the present study.

Understanding these characteristics could potentially provide innovative perspectives on the ANS responses of individuals with PD as they navigate postural changes, a common occurrence in daily lives. Such insights could significantly contribute to the enrichment of the scientific research literature, particularly in relation to the identification and development of optimal therapeutic interventions targeting postural changes in patients with PD.

The primary objective of this study was to meticulously examine and compare the autonomic modulation responses in individuals diagnosed with PD and their healthy counterparts, both under resting conditions and during the active tilt test. To achieve this, we employed non-linear HRV indices derived from five distinct entropies (Approximate, Sample, Shannon, Renyi and Tsallis), Detrended Fluctuation Analysis (DFA), and chaotic global HRV techniques (*hs*CFP1 to *hs*CFP7). Our working hypothesis posited that individuals with PD would exhibit a reduced autonomic modulation response both at rest and during active tilt test, when compared to healthy subjects.

METHODS

Study design

This study was a cross-sectional investigation conducted in São Paulo, Brazil, spanning from August 2017 to April 2018. The study received approval from the Institution’s Research Ethics Committee (CAEE:71395617.7.0000.5402). The research methodology was designed and executed in adherence to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines [22].

Sample

The study sample comprised forty-six participants, who were equally divided and assessed (n=23 both groups): the Parkinson’s Disease group (PDG) and the control group (CG). The PDG consisted of subjects who had received a medical diagnosis of PD, classified at stages 1, 2 or 3 of the Hoehn and Yahr (HY) disability scale [23]. All participants of the PDG were recruited from the neurology section of the Center for Physical Therapy and Rehabilitation Studies and Treatment of the São Paulo State University’s (UNESP) Faculty of Sciences and Technology, located in Presidente Prudente, Brazil. The CG was composed of individuals without any neurological diseases. These individuals were matched by age and gender (according to biological characteristics) with the participants from the PDG and were recruited from health centers situated in the same municipality.

Participants presenting cognitive deficits, as determined by the Mini-Mental State Examination (MMSE), were excluded from the study [24]. Additionally, individuals who were smokers, heavy consumers of alcoholic beverages, or infected, as well as those with cardiovascular and respiratory conditions that could potentially interfere with cardiac autonomic control, were also excluded. Furthermore, any subjects whose HRV records displayed an error rate exceeding 5% were omitted from the study.

The sample size for this study was predetermined. The anticipated significant difference was assumed to be 14 milliseconds [11], with a standard deviation of 12 milliseconds. An alpha risk of 5% and a beta risk of 80% was factored into the calculations. These parameters indicated a requirement of no fewer than 21 subjects for the study. All participants were thoroughly briefed about the objectives and procedures of the study, following which they provided their confidential written informed consent.

Experimental procedure

The experimental procedures were conducted over the course of two distinct assessment periods. A minimum intermission of 2 days was ensured between these sessions.

During the initial assessment, comprehensive data pertaining to the physical, cognitive, and clinical characteristics of the groups were meticulously collected. The subsequent evaluation encompassed the active tilt test and an assessment of autonomic modulation. Participants were explicitly instructed to abstain from the consumption of any stimulating substances, such as caffeinated beverages and chocolate, for a minimum duration of 12 hours preceding the experimental session. For participants diagnosed with PD, this period was strategically scheduled to be approximately one hour post their medication intake [25].

Both sessions were conducted in a research laboratory, under strictly controlled environmental conditions. The ambient temperature was maintained between 21°C and 23°C, and relative humidity was kept within the range of 40% to 60%. To account for potential circadian variations, the timing for the sessions was standardized and scheduled between 8:00 AM and mid-day [26].

Characterization assessment

Anthropometric measurements, including mass, height, Body Mass Index (BMI), and Waist-Hip Ratio (WHR), were meticulously measured for all participants (refer to Tabel 1). Cognitive deficits were evaluated in accordance with the MMSE. For the subset of participants with PD, additional assessments were conducted using the HY disability scale and the revised version of the Unified Parkinson Disease Rating Scale (MDS-UPDRS) [27].

Active tilt test

Each participant was instructed to maintain a supine position at rest, refraining from speaking or sleeping, and to breathe spontaneously for 30 minutes (designated as the rest period). Subsequent to this, the participant was directed to assume a standing position and to maintain this posture for a span of 10 minutes (referred to as the active tilt test period). The assessment of autonomic modulation was conducted during both the rest period and active tilt test period.

Outcomes

Autonomic modulation

The estimation of autonomic modulation was conducted through the application of non-linear and chaotic global procedures to HRV. The HRV data was assessed from the RR intervals, which were recorded using a Polar RS800CX heart rate monitor (Polar Electro Oy, Kempele, Finland) [28]. The device operates with a sampling rate of 1000 Hz. Following the data collection, the RR intervals were exported to a computer system. This was achieved through the utilization of the pulse receptor's data transmission port, which communicated with the Polar Precision Performance software (Polar Electro Oy, Kempele, Finland), version 4.01.029. The transmission of data was facilitated using an infra-red signal interface.

The series of RR intervals underwent an initial digital filtration process, facilitated by the Polar Precision Performance software (Polar Electro Oy, Kempele, Finland). This software applied a moderate filter to the data. Subsequent to this, a manual filtering process was conducted using Microsoft Excel software (Microsoft Corp. Redmond, WA, United States of America). This stage of the process was crucial in eliminating ectopic beats and artifacts. Following the completion of both digital and manual filtering processes, a visual inspection of temporal series of the RR intervals was undertaken This inspection revealed an absence of artifacts that could potentially compromise the integrity of the HRV analysis.

The scope of the study was confined to series that exhibited more than 95% of sinus beats. Rigorous measures were taken to ensure that only traces that met the requisite quality standards were advanced for further analysis. The series of RR intervals were scrutinized during two distinct periods: at the rest period and the active tilt test period. From these periods, segments demonstrating the highest degree of signal stability were identified. Precisely 256 successive RR intervals were selected from these segments.

Complexity Measures

Five Entropies & DFA

In our study, we employed five distinct entropy measures to quantify the chaotic responses and irregularities inherent in the electrocardiographic RR-intervals. These measures included Approximate (ApEn) [29] Sample (SampEn) [30], Shannon [31], Tsallis with entropic index of 0.25 [32], and Renyi with entropic order of 0.25 [33]. A dataset with low entropy is characterized by high predictability, indicating a degree of regularity in the RR intervals. Conversely, a dataset with high entropy is indicative of greater imbalance, suggesting a higher degree of irregularity and complexity in the RR intervals. Furthermore, we observed that an increase in entropy and chaotic global metrics (*hs*CFP1 to *hs*CFP7) often epitomize an increase in heart rate dynamics, and vice versa.

In our analysis, we utilized both Approximate and Sample Entropy as computational tools to assess the irregularities present in the time-series data. Approximate Entropy, in particular, estimates the level of regularity within the time-series and conversely unpredictability of the time-series.

DFA [20] serves as a robust method for quantifying the levels of fractal correlation present in the successive heartbeats. This technique is particularly effective when applied to time-series data characterized by fluctuating means, variances and autocorrelations. It provides a measure of how the instabilities within a signal scale with the size of the sample of that signal. A high DFA value is indicative of poor biological and physiological status. It is noteworthy that the response of DFA is inversely related to that of entropy measures.

Three Chaotic Global metrics & Seven Permutations (*hs*CFP1 to *hs*CFP7)

High spectral Entropy (*hs*Entropy) is a function that quantifies the variability in both the frequency and amplitude of the power spectrum. This measure is derived by applying Shannon entropy [34] to the power spectrum obtained via Multi-Taper Method (MTM) [35]. the MTM power spectrum minimizes the unpredictability and the potential for errors arising from spectral leakage throughout the time-series. This reduction in spectral leakage is achieved in comparison with the Welch [36] power spectrum, which has been utilized in previous studies [37]. *High spectral* Detrended Fluctuation Analysis (*hs*DFA) is computed in a manner analogous to *hs*Entropy. However, in this case, DFA is applied to the MTM power spectrum as an alternative.

The parameters for the MTM were established as follows: (a) The sampling frequency was set at 1Hz for (b) The time bandwidth for the Discrete Prolate Spheroidal Sequences (DPSS), also referred to as Slepian sequences [38] was set at 3; (c) The FFT size was determined as the larger value between 256 and the next power of two that is greater than the length of the segment; (d) Thomson's '*adaptive*' nonlinear combination method was employed to combine individual spectral estimates. It should be noted that the DPSS was set at 3, as opposed to the value of 5 used by Garner and Ling [39,40]. This adjustment was made in consideration of the shorter length of the time-series under analysis.

The Spectral Multi-Taper Method (sMTM) quantifies the area enclosed between the MTM power spectrum and its baseline. In the context of a perfect sinusoidal signal, which is continuous in time and infinite in length, the MTM yields a power spectrum with no area beneath it [41]. In the case of entirely uniformly distributed random variables, the power spectrum manifests a flat and unresponsive entity, resulting in significantly reduced values. The introduction of broadband noise, however, elevates the peaks and overall tendency of the spectrum up and above the baseline. At that point, chaotic and irregular time-series are associated with higher sMTM values.

The enhancement of heart rate dynamics is typically characterized by an increase in *hs*Entropy, (1-*hs*DFA) and sMTM. These metrics serve as robust and efficient indicators, making them suitable for risk assessments for Parkinson's Disease subjects who are undergoing DBS, active tilt table manipulations and pharmacotherapies. In our study, we further extended our analysis to include seven non-trivial variants of the three aforementioned chaotic global metrics.

The three chaotic global metrics under consideration were originally defined by Garner and Ling [40]. Subsequent research led to the development of to their *high spectral* variants [39]. The computation of these metrics was originally based on the Welch power spectrum [36]. However, the methodology was later revised with the introduction of the *high spectral* variants, which are computed by using the MTM power spectrum throughout [42]. This computational approach yields the chaotic forward parameters denoted as *hs*CFP1 to *hs*CFP7. These parameters are derived from the algebraic equations provided below.

$$hsCFP1 = \left[norm\left(hsEntropy\right)^2 + norm\left(sMTM\right)^2 + \left(1 - \left[norm\left(hsDFA\right)\right]\right)^2 \right]^{\frac{1}{2}}$$

$$hsCFP2 = \left[norm\left(hsEntropy\right)^2 + \left(1 - \left[norm\left(hsDFA\right)\right]\right)^2 \right]^{\frac{1}{2}}$$

$$hsCFP3 = \left[norm\left(hsEntropy\right)^2 + norm\left(sMTM\right)^2 \right]^{\frac{1}{2}}$$

$$hsCFP4 = \left[norm\left(sMTM\right)^2 + \left(1 - \left[norm\left(hsDFA\right)\right]\right)^2 \right]^{\frac{1}{2}} .$$

$$hsCFP5 = \left[\left(1 - \left[norm\left(hsDFA\right)\right]\right)^2 \right]^{\frac{1}{2}}$$

$$hsCFP6 = \left[norm\left(sMTM\right)^2 \right]^{\frac{1}{2}}$$

$$hsCFP7 = \left[norm\left(hsEntropy\right)^2 \right]^{\frac{1}{2}}$$

Statistical analysis

The normality of the data was ascertained using the Shapiro-Wilk test. In order to characterize the sample, we employed descriptive statistical methods. The results were presented as means and standard deviations for parametric data, median and interquartile range for non-parametric data, and absolute numbers and frequency for categorical data. The comparison of the sample profile and HRV indices between groups in resting state was conducted using the Student t-test or Mann-Whitney test, depending on the nature of the data. For categorical data, we utilized the Chi-square test, taking into account the Yates continuity correction for 2-x-2 cross tables.

HRV Indexes: One-way analysis of variance & Kruskal-Wallis Tests

The datasets under consideration require a normal distribution for the execution of parametric statistics thereby positioning the mean as a central tendency indicator. In instances where data normalization is impracticable, means should not be compared. To ascertain the levels of normal distribution, we employed the Anderson-Darling [43] test. Thus, we computed both the parametric one-way analysis of variance (ANOVA1) [44] and the non-parametric Kruskal-Wallis [45] tests. During the mathematical analysis, we describe three effect sizes: Cohen's *ds*, Hedges' *gs* and Glass's Δ delta. Magnitudes of these effect sizes are classified as follows: 0.01 signifies a very small effect; 0.20 indicates a small effect; 0.50 represents a medium effect; 0.80 denotes a large effect; 1.20 designates a very large effect. These classifications are predicted on the benchmarks established by Cohen and Fritz *et al* [46,47]. For the Partial Eta squared effect size, the extents are nominated as follows: 0.01 signifies a small effect size; 0.06 represents a medium effect size and 0.14 indicates a large effect size. The computation was performed using the Statistical Package for the Social Sciences (IBM SPSS Inc., Chicago, IL, United States of America), version 27.0.

RESULTS

In our study, we conducted an analysis on a total of forty-six subjects, who were evenly divided into two distinct groups: the Parkinson’s Disease Group (PDG) and the Control Group (CG), each comprising 23 individuals. The demographic and clinical characteristics of the participants in both groups are presented in Table 1. It is noteworthy that a significant majority of the participants in both groups, 82.6% (n = 19), male > Upon statistical analysis, we observed significant differences between the two groups on terms of BMI and MMSE scores, with p-value less than0.001.

#Insert Table 1#

Table 2 provides a comprehensive overview of the medication regimen followed by participants in both the PGD and CG. Upon analysis, we observed significant differences in the usage of several medications, specifically for Levodopa, Dopamine agonist, Amantadine Hydrochloride, Monoamine Oxidase Inhibitors, and Antipsychotics.

#Insert Table 2#

Table 3 delineates the disparity between the groups (CG & PDG) in terms of HRV indices at rest. A noteworthy observation from our analysis was the significant differences in the values of *hs*CFP3 and Sample Entropy between the two groups. For *hs*CFP3, both the ANOVA1 and the Kruskal-Wallis tests revealed negative effect sizes ranging from -0.895 to -1.314). In the case of Sample Entropy, only the Kruskal-Wallis test was applied, revealing negative effect sizes ranging from -0.460 to -0.490).

#Insert Table 3#

Table 4 elucidates the disparities between two distinct moments - Rest & Active Tilt Table - for HRV indices in Control subjects. A significant divergence is observed in the values of *hs*CFP1, *hs*CFP3, *hs*CFP5, *hs*CFP7 and Sample Entropy. The effect sizes for *hs*CFP1 exhibit a negative trend, ranging from -0.738 to -0.992. Similarly, *hs*CFP3 also shows a negative trend in effect sizes, varying from -1.456 to -1.938). Conversely, *hs*CFP5 presents a positive trend in effect sizes, with values ranging from 0.815 to 0.843). *hs*CFP7 follows a negative trend similar to *hs*CFP1 and *hs*CFP3, with effect sizes ranging from -0.765 to -0.786. Lastly, Sample Entropy also exhibits a negative trend in effect sizes varying from -0.794 to -0.843. During the active orthostatic test, lower values were recorded for *hs*CFP1, *hs*CFP3, *hs*CFP7, and Sample Entropy, while *hs*CFP5 recorded higher values, when compared to the resting state.

#Insert Table 4#

Table 5 delineates the variation between the moments of rest Active Tilt Table for HRV indices in subjects with Parkinson's disease. A significant difference was observed in the values of Approximate Entropy, as determined solely by the Kruskal-Wallis test. The effect sizes for Approximate Entropy exhibited a negative trend, ranging from -0.624 to -0.868. during the active orthostatic test, lower values were recorded for Approximate Entropy when compared to the resting state.

#Insert Table 5#

In order to compare the impact of the active tilt test on the HRV indices, a balanced two-way 'between-groups' analysis of variance (ANOVA2) was employed. This analysis was conducted based on two distinct pathological states: (a) normal and (b) Parkinson's disease patients. These states were examined under two positional modes: (a) at rest and (b) active tilt table. The dependent variables in this analysis were *hs*CFP1 to *hs*CFP7. The study incorporated two independent variables. The first variable was 'position', which had two levels: at rest and active tilt table. The second independent variable is the 'condition', which also had two levels: normal or Parkinson's disease.

#Insert Table 6#

#Insert Table 7#

The application of the two-way Analysis of Variance (ANOVA2) test is predicted on two assumptions. The first assumption pertains to statistical normality, while the second assumption concerns the equality of variances, as determined by Levene's test [48]. These assumptions were satisfied by the majority of the chaotic global combinations implemented in this study. However, an exception was observed in the case of *hs*CFP3, where the p-value was marginally significant (p=0.007). This statistic suggests that the reliability of the ANOVA2 results for *hs*CFP3 may be compromised. In the absence of an alternative for the two-way (between-groups) analysis of variance when Levene's test is not satisfied, we have opted to adjust the significance threshold for *hs*CFP3. Specifically, we have tightened the significance level from p<0.05 (5%) to p<0.01 (1%) to mitigate the potential unreliability of the results for *hs*CFP3.

A notable discrepancy was observed in mean *hs*CFP3 for Position (*hs*CFP3, Position F (1,88) = 5.300 p<0.024; <2.4% with Partial Eta squared of 0.057. However, the Levene's Test of Equality of Error Variances indicated a lack of reliability for *hs*CFP3. Consequently, this result must be dismissed as non-significant due to its p-value exceeding the adjusted threshold (p>0.01 or >1%).

A substantial alteration was observed in the mean *hs*CFP1 for Interaction (*hs*CFP1, Interaction F (1,88) = 4.303 p<0.041, <4.1% and Partial Eta squared of 0.047. Furthermore, a more pronounced variation was noted between the mean *hs*CFP3 for Interaction (*hs*CFP3, Interaction F (1,88) = 15.327 p<0.001, <1%, with a Partial Eta squared of 0.148. Given this level of significance, we can affirm the validity of *hs*CFP3 as per Levene's Test of Equality of Error Variances.

The interaction observed in the two-way Analysis of Variance (ANOVA2) indicates a differential effect of the active tilt table is different on the CG and the PDG. Specifically, the response of the PDG, as measured by*hs*CFP1 (with a Partial Eta Squared is 0.047) and *hs*CFP3 (with a Partial Eta Squared is 0.148) exhibits a distinct pattern compared to CG. This differential response suggests that the active tilt table test, in conjunction with the measurements of *hs*CFP1 and *hs*CFP3, could serve as an effective screening tool for identifying subjects with Parkinson's Disease.

DISCUSSION

The main finds of this study suggest that individuals with PD exhibited a compromised autonomic modulation at rest This impairment was characterized by diminished values of *hs*CFP3 and Sample Entropy. In response to the active tilt test, both the CG and the PDG demonstrated autonomic responses that were characterized by increased linearity and reduced complexity of the series. However, this response was less noticeable in the PDG.

In the analysis of HRV, it was observed that, at rest, the values of *hs*CFP3 and Sample Entropy, which are indicative of global modulation, were diminished in the PDG as compared to the CG. This observation suggests a reduced complexity of the RR intervals series in the PDG. This finding may be partially attributed to the decreased parasympathetic modulation observed in individuals with PD at rest, which tends to the increase the predictability of the system. It is postulated that the vagal component plays a significant role in maintaining higher variability and complexity [49]. Furthermore, the observation of reduced parasympathetic modulation at rest in individuals with PD has been corroborated by several studies, including those by Stoco-Oliveira *et al.* [10] and Valente *et al.* [14].

In the Control Group (CG), a transition from a resting state to an active tilt table state resulted in a decrease in Sample Entropy, *hs*CFP1, *hs*CFP3, and *hs*CFP7, whereas *hs*CFP5 exhibited an increase. In contrast, for the Parkinson's Disease Group, a similar transition from rest to the active tilt table led to a decrease in ApEn, as determined solely by ANOVA1. In healthy individuals, the ANS response to the active tilt test is characterized by an activation of the sympathetic nervous system and a reduction in parasympathetic modulation [16]. This sympathetic predominance reduces the variation between consecutive RR intervals, favoring linearity and reducing the complexity of the series. This is evidenced by the decrease in Sample Entropy, hsCFP1, hsCFP3, and hsCFP7 in the CG. These findings suggest an abnormal adaptation of the ANS of individuals with PD in response to postural changes.

It is crucial to underscore that orthostatic hypotension, a non-motor symptom, is frequently manifested in individuals with PD [50]. Therefore, the observed reduction of ApEn within the PD group may be attributed to a compensatory elevation in heart rate in response to a decline in blood pressure.

Dysautonomia in PD is associated with the degeneration of autonomic neurons [51]. This denervation, affection both the sympathetic and parasympathetic branches of the autonomic system, may underlie the observed differences HRV indices between individuals with PD and their healthy counterparts [51]. Findings from a recent longitudinal study provide compelling evidence of the pervasiveness of autonomic disfunction in PD, with 100% of individuals with PD exhibiting signs of autonomic dysfunction after a three-year follow-up period [52]. This underscores the critical importance of comprehensive autonomic assessment in this population.

Typically, *hs*CFP1 is recognized as the most statistically robust metric, while *hs*CFP3 is often the most statistically significant. This holds true across various analyses, with the exception of Parkinson’s subjects transitioning from rest to the active tilt table (refer to Table 5). *hs*CFP3 is a function of *hs*Entropy, which in turn is a measure of the disorder and irregularity within the power spectrum. The sMTM serves as an indicator of the levels of broadband noise present in the signal, thereby reflecting the degree of chaotic responses and their irregularity. The MTM has been validated as the optimal power spectrum for the subsequent analysis. This was confirmed in a study of T1DM [53], and malnourished children [54], where it was found that six other power spectra - Welch, Periodogram, Yule-Walker, Burg, and Covariance - were all inferior to MTM. DFA, Shannon, Renyi and Tsallis Entropies were all found to be insignificant across all comparisons. However, additional non-linear measures, such as Multiscale Multifractal Analysis (MMA) [55], could be considered as could fractal dimensions, such as Katz's [56] and the correlation dimension [57]. The measures could potentially offer beneficial insights in a manner comparable to the aforementioned metrics.

For ApEn and SampEn, a systematic investigation that compares the influence of embedding dimensions (m) and tolerances (r) on their respective outcomes could provide valuable insights into the precise locations of the most significant results. This type of analysis has already been conducted for COPD [58], T1DM [59] and malnourished children [60] for ApEn. However, it is important to note that the process of determining the optimal values of m and r can be both time-consuming and unpredictable.

The Renyi entropy (with an entropic order of $\alpha=0.25$) and the Tsallis entropy (with an entropic index of $q=0.25$) exhibited insignificant responses throughout the analysis. However, this observation could potentially be further scrutinized by conducting a systematic investigation into the effects of varying their respective appropriate entropic order and index.

Among the strengths of our study is the examination of the autonomic modulation in individuals with PD in response to the active tilt test. This test, which assess autonomic function, offers greater reproducibility in clinical practice compared to the passive tilt test. Furthermore, our study employed nonlinear HRV methods. These methods offer a more comprehensive understanding of the ANS behavior and serve to complement the insights obtained from linear indices.

CONCLUSION

Our findings indicate that individuals with Parkinson's Disease exhibit alterations in autonomic modulation at rest, characterized by the reduction in the non-linear dynamics of HR.

Furthermore, these individuals demonstrated a diminished autonomic response during the active tilt test compared to healthy controls. This suggests the potential utility of the active tilt table as a screening mechanism for autonomic dysfunction in this population. These observations underscore the importance of incorporating the non-linear indices in the evaluation autonomic function in individuals with PD. The active tilt table, given its reproducibility and ease of use in clinical practice, may serve as an effective screening tool for autonomic dysfunction in individuals with PD. However, it is important to interpret these findings with caution, given the potential influence of pharmacotherapies on autonomic regulation. The participants in our study continued their routine pharmacotherapies during the data collection period (as detailed in Table 2). Our study design did not enable the assessment of the influence of specific pharmacotherapies, such as Levodopa and Dopamine agonists, on the autonomic modulation of PD participants. Finally, our study included diabetic participants in both groups, albeit in minor proportions (PDG: 13.04%, n=3; CG: 17.39%, n=4). No significant differences were observed in hypoglycemic values between the groups (as shown in Table 2).

FUNDING

The present study was supported by the Programa Institucional de Bolsas de Iniciação Científica - PIBIC/Reitoria/CNPq/UNESP.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

DATA STATEMENT

Data and Matlab code enforced in the study remain confidential for commercial reasons.

REFERENCES

[1] B.R. Bloem, M.S. Okun, C. Klein, Parkinson's disease, Lancet 397(2021) 2284-2303. https://doi.org/10.1016/S0140-6736(21)00218-X

[2] S. K. Yadav, S. N. Rai, S.P. Singh. Mucuna pruriens reduces inducible nitric oxide synthase expression in Parkinsonian mice model, J Chem Neuroanat. 80 (2017) 1-10. doi: 10.1016/j.jchemneu.2016.11.009.

[3] D.J. Surmeier, J.N. Guzman, J. Sanchez-Padilla, P.T. Schumacker, The role of calcium and mitochondrial oxidant stress in the loss of substantia nigra pars compacta dopaminergic neurons in Parkinson's disease, Neuroscience 198 (2011) 221-231. https://doi.org/10.1016/j.neuroscience.2011.08.045.

[4] J. Prakash, S. Chouhan, S. K. Yadav, S. Westfall, S. N. Rai, S. P. Singh. Withania somnifera alleviates parkinsonian phenotypes by inhibiting apoptotic pathways in dopaminergic neurons. Neurochem Res. 39 (2014):2527-36. doi: 10.1007/s11064-014-1443-7.

[5] L.V. Kalia, A.E. Lang, Parkinson’s disease, Lancet 2015 386 (2015) 896–912. https://doi.org/10.1016/S0140-6736(14)61393-3.

[6] K. Ramakrishna, L. V. Nalla, D. Naresh, K. Venkateswarlu, M. K. Viswanadh, B. N. Nalluri, G. Chakravarthy, S. Duguluri, P. Singh, S. N. Rai, A. Kumar, V. Singh, S. K. Singh. WNT-β catenin signaling as a potential therapeutic target for neurodegenerative diseases: current status and future perspective, Diseases. 11 (2023):89. doi: 10.3390/diseases11030089.

[7] E. Pablo-Fernandez, C. Tur, T. Revesz, A.J. Lees, J.L. Holton, T.T. Warner, Association of autonomic dysfunction with disease progression and survival in Parkinson disease, JAMA Neurol. 74 (2017)970-976. https://doi.org/10.1001/jamaneurol.2017.1125.

[8] W. Poewe, K. Seppi, C. Tanner, G. Halliday, P. Brundin, J. Volkmann, A-E. Schrag, A.E. Lang, Parkinson disease, Nat Rev Dis Primers 23 (2017) 17013. https://doi.org/ 10.1038/nrdp.2017.13.

[9] L.C.M. Vanderlei, C.M. Pastre, R.A. Hoshi, T.D. Carvalho, M.F. Godoy, Basic notions of heart rate variability and its clinical applicability, Rev Bras Cir Cardiovasc. 24 (2009) 205-217. https://doi.org/10.1590/s0102-76382009000200018.

[10] M.C. Stoco-Oliveira, A.L. Ricci-Vitor, L.M. Vanzella, H.B. Valente, V.E.S. Silva, L.B. André, A.C. Carvalho, D.M. Garner, L.C.M. Vanderlei, Parkinson's disease effect on autonomic modulation: an analysis using geometric indices, Arq Neuropsiquiatr. 79 (2021) 114-121. https://doi.org/10.1590/0004-282X-anp-2020-0088.

[11] D. Brisinda, A.R. Sorbo, R. Di Giacopo, A. Venuti, A.R. Bentivoglio, R. Fenici, Cardiovascular autonomic nervous system evaluation in Parkinson disease and multiple system atrophy, J Neurol Sci. 336 (2014) 197-202. https://doi.org/10.1016/j.jns.2013.10.039.

[12] M.F. Godoy, Nonlinear analysis of heart rate variability: a comprehensive review, Journal of Cardiol Ther. 3 (2016) 528–533. https://doi.org/10.17554/j.issn.2309-6861.2016.03.101-4.

[13] N.M. Souza, LC.M. Vanderlei, D.M. Garner, Risk evaluation of diabetes mellitus by relation of chaotic globals to HRV, Complexity, 20 (2015) 84-92. https://doi.org/10.1002/cplx.21508

[14] H.B. Valente, N.L. Gervazoni, M.J.L. Laurino, L.M. Vanzella, M.C. Stoco-Oliveira, M.V. Rodrigues, L.B. André, F. Ribeiro, A.C. Carvalho, L.C.M. Vanderlei, Autonomic and cardiorespiratory responses to the active tilt test in individuals with Parkinson disease: cross-sectional study, Arq Neuropsiquiatr. 80 (2022) 689-698. https://doi.org/10.1055/s-0042-1755225.

[15] F. Barbic, F. Perego, M. Canesi, M. Gianni, S. Biagiotti, G. Costantino, G. Pezzoli, A. Porta, A. Malliani, R. Furlan, Early abnormalities of vascular and cardiac autonomic control in Parkinson’s disease without orthostatic hypotension, Hypertension 49 (2007) 120–126. https://doi.org/10.1161/01.HYP.0000250939.71343.7c.

[16] B. Aysin, J. Colombo, E. Aysin, Comparison of HRV analysis methods during orthostatic challenge: HRV with respiration or without? Conf Proc IEEE Eng Med Biol Soc. 2007 (2007) 5047-5050. https://doi.org/10.1109/IEMBS.2007.4353474.

[17] P.K. Jones, C.H. Gibbons, Autonomic function testing: an important diagnostic test for patients with syncope. Pract Neurol. 15 (2015) 346–351. https://doi.org/10.1136/practneurol-2015-001102.

[18] M. Alves, D.M. Garner, A.M. Fontes, L.V.A. Sousa, V.E. Valenti, Linear and complex measures of heart rate variability during exposure to traffic noise in healthy women, Complexity, 2018 (2018). https://doi.org/10.1155/2018/2158391

[19] F. Vanderlei, L.C.M. Vanderlei, L.C. Abreu, D.M. Garner, Entropic analysis of HRV in obese children, International Archives of Medicine, 8 (2015) 1-9. https://doi.org/10.3823/1799

[20] C.K. Peng, S. Havlin, H.E. Stanley, A.L. Goldberger, Quantification of scaling exponents and crossover phenomena in nonstationary heartbeat time series, Chaos 5 (1995) 82-7. https://doi.org/10.1063/1.166141.

[21] D.M. Garner, F.M. Vanderlei, V.E. Valenti, L.C.M. Vanderlei, Non-linear regulation of cardiac autonomic modulation in obese youths: interpolation of ultra-short time series, Cardiol Young 29 (2019) 1196-1201. https://doi.org/10.1017/S1047951119001951.

[22] A.A. Ghaferi, T.A. Schwartz, T.M. Pawlik, STROBE reporting guidelines for observational studies, JAMA surgery 156 (2021) 577-578. https://doi.org/10.1001/jamasurg.2021.0528.

[23] M.M. Hoehn, M.D. Yahr, Parkinsonism: onset, progression and mortality, Neurology 17 (1967) 427–442. https://doi.org/10.1212/wnl.17.5.427.

[24] P.H.F. Bertolucci, S.M.D Brucki, S.R. Campacci, Y. Juliano, O Mini- Exame do Estado Mental em uma população geral: impacto da escolaridade, Arq Neuropsiquiatr. 52 (1994) 1–7. https://doi.org/10.1590/S0004-282X1994000100001.

[25] M. Carpenter, J. Allum, F. Honegger, A. Adkin, B. Bloem, Postural abnormalities to multidirectional stance perturbations in Parkinson’s disease, J Neurol Neurosurg Psychiatry 75 (2004) 1245-1254. https://doi.org/10.1136/jnnp.2003.021147.

[26] A.M. Catai, C.M. Pastre, M.F. Godoy, E. Silva, A.C.M. Takahashi, L.C.M. Vanderlei, Heart rate variability: are you using it properly? Standardisation checklist of procedures, Braz J Phys Ther. 24 (2020) 91-102. https://doi.org/10.1016/j.bjpt.2019.02.006.

[27] C.G. Goetz, B.C. Tilley, S.R. Shaftman, G.T. Stebbins, S. Fahn, P. Martinez-Martin, W. Poewe, C. Sampaio, M.B. Stern, R. Dodel, B. Dubois, R. Holloway, J. Jankovic, J. Kulisevsky, A.E. Lang, A. Lees, S. Leurgans, P.A. LeWitt, D. Nyenhuis, C.W. Olanow, O. Rascol, A. Schrag, J.A. Teresi, J.J. van Hilten, N. LaPelle, Movement Disorder Society UPDRS Revision Task Force, Movement Disorder Society-sponsored revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS): scale presentation and clinimetric testing results, Mov Disord. 23 (2008) 2129-2170. https://doi.org/10.1002/mds.22340.

[28] T.R. Giacon, F.M. Vanderlei, D.G. Christofaro, L.C.M. Vanderlei, Impact of diabetes type 1 in children on autonomic modulation at rest and in response to the active orthostatic test, PLoS One 11 (2016) e0164375. https://doi.org/10.1371/journal.pone.0164375.

[29] S.M. Pincus, Approximate entropy as a measure of system complexity, Proc Natl Acad Sci USA. 88 (1991) 2297-2301. https://doi.org/10.1073/pnas.88.6.2297.

[30] J.S. Richman, D.E. Lake, J.R. Moorman, Sample entropy, Methods Enzymol. 384 (2004) 172-184. https://doi.org/10.1016/S0076-6879(04)84011-4.

[31] C.E. Shannon, A mathematical theory of communication, Bell Syst. tech. j. 27 (1948) 379-423. https://doi.org/10.1002/j.1538-7305.1948.tb01338.x

[32] R.J. Santos, Generalization of Shannon’s theorem for Tsallis entropy, J. Math. Phys. 38 (1997) 4104. https://doi.org/10.1063/1.532107.

[33] A.M. Mariz, On the irreversible nature of the Tsallis and Renyi entropies, Phys. Lett. A 165 (1992) 409-411. https://doi.org/10.1016/0375-9601(92)90339-N.

[34] C.E. Shannon, A mathematical theory of communication, ACM SIGMOBILE Mobile Computing and Communications Review 5 (2001) 3-55. https://doi.org/10.1145/584091.584093.

[35] M. Ghil, The SSA-MTM Toolkit: applications to analysis and prediction of time series, Proc SPIE, 3165 (1997) 216-230. https://doi.org/10.1117/12.279594

[36] A. Alkan, M.K. Kiymik, Comparison of AR and Welch methods in epileptic seizure detection, J Med Syst. 30 (2006) 413-419. https://doi.org/10.1007/s10916-005-9001-0.

[37] N.M. Souza, L.C.M. Vanderlei, D.M. Garner, Risk evaluation of diabetes mellitus by relation of chaotic globals to HRV, Complexity 20 (2015) 84-92. https://doi.org/10.1002/cplx.21508.

[38] B.P. Day, A. Evers, D.E. Hack, Multipath Suppression for Continuous Wave Radar via Slepian Sequences, IEEE Trans. Signal Process 68 (2020) 548-557. https://doi.org/10.1109/TSP.2020.2964199.

[39] D.M. Garner, B.W.K. Ling, Measuring and locating zones of chaos and irregularity by application of high spectral chaotic global variants, Int. J. Bifurc. Chaos Appl. Sci. Eng. 31 (2021) 2150236. https://doi.org/10.1142/S0218127421502369.

[40] D.M. Garner, B.W.K. Ling, Measuring and locating zones of chaos and irregularity, J Syst Sci Complex. 27 (2014) 494-506. https://doi.org/10.1007/s11424-014-2197-7.

[41] P. Dirac, New notation for quantum mechanics, Math. Proc. Camb. Philos. Soc. 35 (1939) 416-418. https://doi.org/10.1017/S0305004100021162.

[42] R. Wajnsztejn, T.D. Carvalho, D.M. Garner, L.C.M. Vanderlei, M.F. Godoy, R.D. Raimundo, C. Ferreira, V.E. Valenti, Abreu L.C., Heart rate variability analysis by chaotic

global techniques in children with attention deficit hyperactivity disorder, Complexity 21 (2016) 412-419. https://doi.org/10.1002/cplx.21700.

[43] N.M. Razali, Y.B. Wah, Power comparisons of Shapiro-Wilk, Kolmogorov-Smirnov, Lilliefors and Anderson-Darling tests, JOSMA 2 (2011) 21-33.

[44] J.C. Hsu, Multiple Comparisons: Theory and Methods. Boca Raton, Florida: CRC Press, 1996. https://doi.org/10.1201/b15074.

[45] P.E. McKight, J. Najab, Kruskal-wallis test, The corsini encyclopedia of psychology, 1 (2010) 1-10. https://doi.org/10.1002/9780470479216.corpsy0491.

[46] J. Cohen, Statistical power analysis for the behavioral sciences, Routledge, 2013.

[47] C.O. Fritz, P.E. Morris, J.J. Richler, Effect size estimates: current use, calculations, and interpretation, J Exp Psychol Gen. 141 (2012) 2-18. https://doi.org/10.1037/a0024338.

[48] J.L. Gastwirth, Y.R. Gel, W. Miao, The impact of Levene's test of equality of variances on statistical theory and practice, Statist. Sci. 24 (2009) 343-360. https://doi.org/10.1214/09-STS301.

[49] J.P. Higgins, Nonlinear systems in medicine, Yale J Biol Med., 75 (2002) 247-260.

[50] A. Fanciulli, F. Leys, C. Falup-Pecurariu, R. Thijs, G.K. Wenning. Management of orthostatic hypotension in Parkinson's disease, J Parkinsons Dis. 10(2020):S57-S64. doi: 10.3233/JPD-202036.

[51] Z. Chen, G. Li, J. Liu, Autonomic dysfunction in Parkinson's disease: implications for pathophysiology, diagnosis, and treatment, Neurobiol Dis. 134 (2020) 104700. https://doi.org/10.1016/j.nbd.2019.104700.

[52] I. Stanković, I. Petrović, T. Pekmezović, V. Marković, T. Stojković, N. Dragašević-Mišković, M. Svetel, V. Kostić, Longitudinal assessment of autonomic dysfunction in early Parkinson's disease, Parkinsonism Relat Disord. 66 (2019) 74-79. https://doi.org/10.1016/j.parkreldis.2019.07.008.

[53] D.M. Garner, N.M. Souza, L.C.M. Vanderlei, Risk assessment of diabetes mellitus by chaotic globals to heart rate variability via six power spectra, Rom J Diabetes Nutr Metab Dis. 24 (2017) 227-236. https://doi.org/10.1515/rjdnmd-2017-0028.

[54] D.M. Garner, F.M. Vanderlei, L.C.M. Vanderlei , V.E. Valenti, C.J.R. Benjamim, G.S. Barreto, Chaotic global metric analysis of heart rate variability following six power spectral manipulations in malnourished children, Series Endo Diab Met. 4 (2022) 44-58. https://doi.org/10.54178/jsedmv4i2002.

[55] J. Gieraltowski, D. Hoyer, F. Tetschke, S. Nowack, U. Schneider, J. Zebrowski, Development of multiscale complexity and multifractality of fetal heart rate variability, Auton Neurosci. 178 (2013) 29-36. https://doi.org/10.1016/j.autneu.2013.01.009.

[56] D.M. Garner, N.M. Souza, L.C.M. Vanderlei, Heart rate variability analysis: Higuchi and Katz's fractal dimensions in subjects with type 1 diabetes mellitus, Rom J Diabetes Nutr Metab Dis. 25 (2018) 289-295. https://doi.org/10.2478/rjdnmd-2018-0034.

[57] J.E. Skinner, C. Carpeggiani, C.E. Landisman, K.W. Fulton, Correlation dimension of heartbeat intervals is reduced in conscious pigs by myocardial ischemia, Circ.Res. 68 (1991) 966-976. https://doi.org/10.1161/01.res.68.4.966.

[58] D.M. Garner, A.F.B. Bernardo, L.C.M. Vanderlei, HRV Analysis: unpredictability of approximate entropy in chronic obstructive pulmonary disease, Series Cardiol Res. 3 (2021) 1-10. https://doi.org/10.54178/2768-5985.2021a1.

[59] D.M. Garner, N.M. Souza, L.C.M. Vanderlei, Unreliability of approximate entropy to locate optimal complexity in diabetes mellitus via heart rate variability, Series Endo Diab Met. 2 (2020) 32-40. https://doi.org/10.54178/jsedmv2i2003

[60] D.M. Garner, G.S. Barreto, V.E. Valenti, F.M. Vanderlei, A.A. Porto, L.C.M. Vanderlei, HRV analysis: undependability of approximate entropy at locating optimum complexity in

malnourished children, Cardiol Young 32 (2021) 425-430. https://doi.org/10.1017/S1047951121002316.

Table 1. Sample characteristics and comparison between groups.

Characteristic	PDG (n=23)	CG (n=23)	p-value
Age (years)[a]	73.74 ± 7.28	70.17 ± 8.20	0.13
Mass (kg)[a]	71.17 ± 13.03	77.79 ± 10.77	0.07
Height (m)[a]	1.63 ± 0.09	1.63 ± 0.07	0.86
BMI (kg/m^2)[a]	26.54 ± 3.61	29.34 ± 4.11	**0.02**
WHR[a]	0.93 ± 0.11	0.94 ± 0.07	0.63
MEMS[b]	25.00 [8.00]	28.00 [3.00]	**0.02**
HY scale	2.00 [1.00]	----	----
MDS-UPDRS T	66.26 ± 23.32	----	----
MDS-UPDRS I	12.00 [7.00]	----	----
MDS-UPDRS II	14.70 ± 6.57	----	----
MDS-UPDRS III	32.00 [14.00]	----	----
MDS-UPDRS IV	3.00 [6.00]	----	----

Legend: [a]Unpaired Student t-test: data presented as mean ± standard deviation; [b]Mann Whitney test: data presented as median [interquartile range]; PDG: Parkinson disease group; CG: control group; BMI: body mass index; WHR: waist-hip ratio; MEMS: Mini-exam of mental state; HY: Hoehn and Yahr; MDS-UPDRS T: total result of the revised version of the Unified Parkinson's Disease Rating Scale; MDS-UPDRS I: result from the part I of the MDS-UPDRS; MDS-UPDRS II: result from the part II of the MDS-UPDRS; MDS-UPDRS III: result from the part III of the MDS-UPDRS; MDS-UPDRS IV: result from the part IV of the MDS-UPDRS; Kg: kilogram; m: meter; Kg/m^2: kilogram/squared meter.

Table 2. Pharmacotherapies for participants of control (CG) and Parkinson disease (PDG) group.

Pharmacotherapies	**PDG (n=23)**	**CG (n=23)**	**p-value**
Neurological Action			
Levodopa	19 (82.61)	0 (0)	**<0.001**
Antidepressant	11 (47.83)	6 (26.09)	0.22
Dopamine Agonist	6 (26.09)	0 (0)	**0.02**
Amantadine Hydrochloride	5 (21.74)	0 (0)	**<0.05**
Monoamine Oxidase Inhibitors	5 (21.74)	0 (0)	**<0.05**
Antipsychotics	5 (21.74)	0 (0)	**<0.05**
Others	6 (26.09)	4 (17.39)	0.72
Cardiovascular Action			
Adrenergic Blockers	**7** (30.43)	5 (21.74)	0.74
Angiotensin II Antagonists	9 (39.13)	9 (39.13)	1.00
Hypoglycaemics	3 (13.04)	4 (17.39)	1.00
Antiplatelet	5 (21.74)	8 (34.78)	0.51
Statins	6 (26.09)	7 (30.43)	1.00
Diuretics	3 (13.04)	7 (30.43)	0.28
Vasodilators	2 (8.70)	6 (26.09)	0.24
Others	5 (21.74)	2 (8.70)	0.24
Other Medications	16 (69.57)	13 (56.52)	0.54

Legend: CG = control group; PDG = Parkinson disease group; n (percentage).

Table 3. Between groups comparison for the HRV indexes assessed at rest.

HRV Indexes	**CG Mean**	**CG ± SD**	**PD Mean**	**PD ± SD**	**ANOVA 1**	**KW**	**Glass's Delta Δ**	**Hedge's g_s**	**Cohen's d_s**
ApEn	0.854	0.103	0.857	0.121	0.941	0.826	0.024	0.022	0.022
SampEn	0.799	0.171	0.720	0.149	0.104	0.048	-0.460	-0.481	-0.490
DFA	0.280	0.211	0.378	0.253	0.159	0.119	0.466	0.415	0.423
Shannon	0.811	0.090	0.759	0.130	0.124	0.166	-0.576	-0.455	-0.463
Renyi	0.994	0.003	0.991	0.005	0.092	0.166	-0.673	-0.500	-0.509
Tsallis	0.832	0.081	0.784	0.118	0.118	0.166	-0.589	-0.462	-0.470
***hs*CFP1**	0.956	0.074	0.915	0.123	0.178	0.067	-0.551	-0.397	-0.404
***hs*CFP2**	0.631	0.118	0.637	0.139	0.868	0.965	0.054	0.049	0.049
***hs*CFP3**	0.904	0.065	0.818	0.116	0.003	0.023	-1.314	-0.895	-0.911
***hs*CFP4**	0.760	0.175	0.734	0.249	0.680	0.750	-0.151	-0.120	-0.122
***hs*CFP5**	0.285	0.136	0.366	0.195	0.108	0.091	0.598	0.475	0.484
***hs*CFP6**	0.700	0.137	0.628	0.187	0.141	0.153	-0.528	-0.434	-0.442
***hs*CFP7**	0.524	0.200	0.430	0.270	0.186	0.091	-0.471	-0.389	-0.396

Mean values and standard deviation (Mean ± S.D. both n=23) for Approximate (ApEn), Sample (SampEn), Shannon, Renyi (entropic order, α=0.25) and Tsallis (entropic index, q=0.25) Entropies, Detrended Fluctuation Analysis (DFA) and the seven *high spectral* Chaotic Forward Parameters', *hs*CFP1 to *hs*CFP7 for the the two groups with time-series of exactly 256 RR-intervals. One way analsysis of variance (ANOVA1) and Kruskal-Wallis (KW) tests of significance are calculated. Additionally, three effect sizes Cohen's d_s, Hedges'g_s and Glass's Delta Δ were calculated. Significant negative effect sizes indicate a *decrease* in heart rate dynamics from normal to the Parkinson's disease cohort.

Table 4. Between groups comparison for the HRV indexes assessed for Control.

HRV Indexes	**Rest Mean**	**Rest ± SD**	**TT Mean**	**TT ± SD**	**ANOVA 1**	**KW**	**Glass's Delta Δ**	**Hedge's g_s**	**Cohen's d_s**
ApEn	0.854	0.103	0.861	0.128	0.835	0.345	0.070	0.061	0.062
SampEn	0.799	0.171	0.663	0.150	0.006	0.007	-0.794	-0.829	-0.843
DFA	0.280	0.211	0.330	0.198	0.409	0.135	0.238	0.242	0.246
Shannon	0.811	0.090	0.776	0.101	0.215	0.292	-0.394	-0.364	-0.371
Renyi	0.994	0.003	0.992	0.004	0.185	0.282	-0.435	-0.390	-0.397
Tsallis	0.832	0.081	0.800	0.091	0.214	0.323	-0.395	-0.365	-0.371
***hs*CFP1**	0.956	0.074	0.882	0.117	0.014	0.003	-0.992	-0.738	-0.751
***hs*CFP2**	0.631	0.118	0.583	0.099	0.145	0.083	-0.405	-0.430	-0.437
***hs*CFP3**	0.904	0.065	0.777	0.102	<0.001	<0.001	-1.938	-1.456	-1.481
***hs*CFP4**	0.760	0.175	0.765	0.191	0.928	0.852	0.028	0.026	0.027
***hs*CFP5**	0.285	0.136	0.399	0.140	0.007	0.007	0.843	0.815	0.829
***hs*CFP6**	0.700	0.137	0.649	0.148	0.230	0.302	-0.373	-0.353	-0.359
***hs*CFP7**	0.524	0.200	0.371	0.189	0.011	0.006	-0.765	-0.773	-0.786

Mean values and standard deviation (Mean ± S.D. both n=23) for Approximate (ApEn), Sample (SampEn), Shannon, Renyi (entropic order, α=0.25) and Tsallis (entropic index, q=0.25) Entropies, Detrended Fluctuation Analysis (DFA) and the seven *high spectral* Chaotic Forward Parameters', *hs*CFP1 to *hs*CFP7 for the the two groups with time-series of exactly 256 RR-intervals.

Table 5. Between groups comparison for the HRV indexes assessed for Parkinson's disease subjects.

HRV Indexes	**Rest Mean**	**Rest ± SD**	**TT Mean**	**TT ± SD**	**ANOVA 1**	**KW**	**Glass's Delta Δ**	**Hedge's g_s**	**Cohen's d_s**
ApEn	0.857	0.121	0.752	0.200	0.037	0.065	-0.868	-0.624	-0.635
SampEn	0.720	0.149	0.639	0.203	0.131	0.180	-0.540	-0.446	-0.453
DFA	0.378	0.253	0.380	0.212	0.983	0.660	0.006	0.006	0.006
Shannon	0.759	0.130	0.800	0.114	0.270	0.272	0.309	0.324	0.329
Renyi	0.991	0.005	0.993	0.004	0.250	0.282	0.316	0.338	0.344
Tsallis	0.784	0.118	0.821	0.102	0.261	0.263	0.314	0.330	0.335
***hs*CFP1**	0.915	0.123	0.935	0.113	0.564	0.575	0.165	0.168	0.171
***hs*CFP2**	0.637	0.139	0.612	0.124	0.517	0.334	-0.183	-0.189	-0.193
***hs*CFP3**	0.818	0.116	0.851	0.100	0.310	0.073	0.283	0.298	0.303
***hs*CFP4**	0.734	0.249	0.779	0.217	0.515	0.531	0.182	0.190	0.194
***hs*CFP5**	0.366	0.195	0.358	0.163	0.887	0.709	-0.039	-0.041	-0.042
***hs*CFP6**	0.628	0.187	0.686	0.169	0.273	0.244	0.312	0.322	0.327
***hs*CFP7**	0.430	0.270	0.430	0.230	1.000	0.709	<0.001	<0.001	<0.001

Mean values and standard deviation (Mean ± S.D. both n=23) for Approximate (ApEn), Sample (SampEn), Shannon, Renyi (entropic order, α=0.25) and Tsallis (entropic index, q=0.25) Entropies, Detrended Fluctuation Analysis (DFA) and the seven *high spectral* Chaotic Forward Parameters', *hs*CFP1 to *hs*CFP7 for the the two groups with time-series of exactly 256 RR-intervals.

Table 6: Levene's Test of Equality of Error Variances: F-value and significances of *hs*CFP1 to *hs*CFP7. This tests the null hypothesis that the error variances of the dependant variable is equal across groups. Degrees of freedom, df_1=3 and df_2=88.

***hs*CFPx Metric**	**Levene's Statistic**	**Sig.**
***hs*CFP1**	1.692	0.174
***hs*CFP2**	1.353	0.263
***hs*CFP3**	4.342	0.007
***hs*CFP4**	1.409	0.246
***hs*CFP5**	1.849	0.144
***hs*CFP6**	1.038	0.380
***hs*CFP7**	1.678	0.178

Table 7: The table below exemplifies the results of a balanced two-way ‘between-groups’ analysis of variance for two conditions two-way analysis of variance (ANOVA2) based on a pathological state (a) normal and (b) Parkinson’s disease patients in two modes of position (a) at rest and (b) active tilt table. There are seven dependent variables (*high spectral* Chaotic Forward Parameter’s: *hs*CFP1 to *hs*CFP7). The independent variables are based on pathological state or the active tilt table position. Type III SSq. referes to the Type III Sum of Squares**,** *df* refers to the number of degrees of freedom, Sig. is the *p-value* for the test of statistical significance and Partial Eta-Squared is the chosen effect size to be enforced.

Source	**Dependent Variable**	**Type III SSq.**	***df***	**Mean Square**	**F**	**Sig.**	**Partial Eta Square *d***
POSITION (Mode)	***hs*CFP1**	0.017	1	0.017	1.396	0.241	0.016
	***hs*CFP2**	0.031	1	0.031	2.098	0.151	0.023
	***hs*CFP3**	0.051	1	0.051	5.300	0.024	0.057
	***hs*CFP4**	0.014	1	0.014	0.329	0.568	0.004
	***hs*CFP5**	0.065	1	0.065	2.553	0.114	0.028
	***hs*CFP6**	<0.001	1	<0.001	0.011	0.917	<0.001
	***hs*CFP7**	0.134	1	0.134	2.670	0.106	0.029
PARKINSON’S (Condition)	***hs*CFP1**	0.001	1	0.001	0.070	0.792	0.001
	***hs*CFP2**	0.007	1	0.007	0.483	0.489	0.005
	***hs*CFP3**	0.001	1	0.001	0.090	0.764	0.001
	***hs*CFP4**	0.001	1	0.001	0.020	0.889	<0.001
	***hs*CFP5**	0.009	1	0.009	0.367	0.546	0.004
	***hs*CFP6**	0.007	1	0.007	0.275	0.601	0.003
	***hs*CFP7**	0.007	1	0.007	0.142	0.707	0.002
POSITION * PARKINSON’S (Interaction)	***hs*CFP1**	0.051	1	0.051	4.303	0.041	0.047
	***hs*CFP2**	0.003	1	0.003	0.196	0.659	0.002
	***hs*CFP3**	0.146	1	0.146	15.327	<0.001	0.148
	***hs*CFP4**	0.009	1	0.009	0.213	0.646	0.002
	***hs*CFP5**	0.085	1	0.085	3.328	0.072	0.036
	***hs*CFP6**	0.069	1	0.069	2.649	0.107	0.029
	***hs*CFP7**	0.135	1	0.135	2.672	0.106	0.029
Error	***hs*CFP1**	1.041	88	0.012			
	***hs*CFP2**	1.284	88	0.015			
	***hs*CFP3**	0.841	88	0.010			
	***hs*CFP4**	3.868	88	0.044			
	***hs*CFP5**	2.255	88	0.026			
	***hs*CFP6**	2.288	88	0.026			
	***hs*CFP7**	4.431	88	0.050			