Autonomic and cardiorespiratory responses to the active tilt test in individuals with Parkinson disease: cross-sectional study

Respostas autonômicas e cardiorrespiratórias ao teste ativo de inclinação em indivíduos com doença de Parkinson: estudo transversal

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Abstract

Background The Parkinson disease (PD) is frequently associated with autonomic dysfunctions. However, data regarding the influence of PD on the autonomic responses to postural changes is limited.

Objective To analyze and compare the autonomic responses, evaluated through linear and non-linear methods of heart rate variability, and cardiorespiratory parameters in two groups: Parkinson disease (PDG) and control (CG), at rest and during the active tilt test.

Methods A total of 48 participants were analyzed (PDG: $n = 25; 73.40 \pm 7.01$ years / CG: $n = 23; 70.17 \pm 8.20$ years). The autonomic modulation and cardiorespiratory parameters were evaluated at rest and during the active tilt test. To assess the autonomic modulation the linear indices, at the time (rMSSD, SDNN) and frequency (LF, HF, LF/HF) domains, and the non-linear indices, obtained through the Poincaré plot (SD1, SD2, SD1/SD2), were calculated. The cardiorespiratory parameters evaluated were heart rate (HR), systolic (SBP), and diastolic blood pressure (DBP), peripheral oxygen saturation (SpO_2), and respiratory rate.

Results At rest, the PDG presented significantly lower values of rMSSD, SDNN, LF, HF, SD1, SD2, and DBP, and higher values of SpO_2. During test, in the PD group, modifications were observed in HR, and SBP, besides a reduced parasympathetic response, and an increased global modulation. The qualitative analysis of the Poincaré

Keywords
► Arterial Pressure
► Autonomic Nervous System Diseases
► Heart Rate
► Parkinson Disease
► Respiratory Rate

plot showed that the PDG has a lower dispersion of the RR intervals during rest and the active tilt test.

Conclusion Individuals with PD present reduced global variability and parasympathetic modulation at rest, and reduced parasympathetic response and damage in HR regulation when performing the active tilt test, compared with controls.

Resumo

Antecedentes A doença de Parkinson (DP) está frequentemente associada a disfunções autonômicas. Porém, dados sobre a influência da DP nas respostas autonômicas às mudanças posturais são limitados.

Objetivos Analisar e comparar as respostas autonômicas, avaliadas por métodos lineares e não lineares de variabilidade da frequência cardíaca e parâmetros cardiorrespiratórios em dois grupos: DP (GDP) e controle (CG), em repouso e durante o tilt test ativo.

Métodos Foram analisados 48 participantes (GDP: $n = 25; 73,40 \pm 7,01$ anos/GC: $n = 23; 70,17 \pm 8,20$ anos). A modulação autonômica e os parâmetros cardiorrespiratórios foram avaliados em repouso e durante o tilt test ativo. Para avaliar a modulação autonômica foram calculados os índices lineares, nos domínios do tempo (rMSSD, SDNN) e frequência (LF, HF, LF/HF), e os índices não lineares, obtidos através do plot de Poincaré (SD1, SD2, SD1/SD2). Os parâmetros cardiorrespiratórios avaliados foram frequência cardíaca (FC), pressão arterial sistólica (PAS), diastólica (PAD), saturação periférica de oxigênio (SpO_2) e frequência respiratória.

Resultados Em repouso, o GDP apresentou valores menores de rMSSD, SDNN, LF, HF, SD1, SD2 e PAD, e maiores valores de SpO_2. No teste, foram observadas modificações na FC e na PAS, redução da resposta parassimpática e aumento da modulação global no GDP. A análise qualitativa do plot de Poincaré mostrou que o GDP apresentou menor dispersão dos intervalos RR no repouso e no tilt test ativo.

Conclusão Indivíduos com DP apresentam redução da variabilidade global e modulação parassimpática em repouso, redução da resposta parassimpática e prejuízo na regulação da FC ao realizar o tilt test ativo, em comparação aos controles.

Palavras-chave
► Pressão Arterial
► Doenças do Sistema Nervoso Autônomo
► Frequência Cardíaca
► Doença de Parkinson
► Taxa Respiratória

INTRODUCTION

The Parkinson disease (PD) is a neurodegenerative disorder, characterized by damage to the neurons from the substantia nigra pars compacta,[1] which affects approximately 1% of the population over 60-years-old.[2]

Besides motor symptoms, several non-motor dysfunctions have been reported in individuals with PD,[3] including impairments related to the autonomic nervous system (ANS) which are associated with lower survival rate, worse disease progression,[4] and reduced quality of life.[3]

The heart rate variability (HRV) is a method that allows the investigation of ANS efficiency through the description of the intervals between consecutive heartbeats.[5] HRV analysis combined with autonomic tests,[6] such as the active tilt test,[7] provides more complete ANS assessment.[6]

Reductions in HRV indices in the time and frequency domains have already been described in individuals with PD.[8,9] However, studies evaluating HRV during autonomic tests have considered only the passive tilt test,[10,11] which is not feasible in clinical settings. Thus, the active tilt test may represent a simple and economical alternative[12] for the evaluation of individuals with PD. Furthermore, active tilt test seems to promote more evident changes in musculoskeletal and cardiovascular responses when compared with passive tilt test.[7] However, to date, no studies have evaluated the HRV of individuals with PD during the active tilt test. Moreover, studies that have evaluated cardiorespiratory system in PD are incipient and did not evaluate parameters such as respiratory rate (RR) and peripheral oxygen saturation (SpO_2).

Understanding these aspects, it may provide a new perspective on the characteristics of the ANS of individuals with PD in the face of postural changes, which are frequently in the daily lives. Furthermore, this information may assist in the consolidation of the literature regarding the most appropriate therapeutic interventions concerning postural changes for this population.

Therefore, the aim of this study was to analyze and compare the response of autonomic modulation, through linear and non-linear HRV methods, and cardiorespiratory parameters at rest and during the active tilt test in individuals with and without PD. We hypothesized that individuals with PD would present a reduced response of autonomic modulation

and cardiorespiratory parameters at rest and in the active tilt test, when compared with individuals without the disease.

METHODS

Study design
Cross-sectional study developed in a city of west of São Paulo, Brazil, between August of 2017 and April of 2018, approved by the Institution's Research Ethics Committee (CAEE:71395617.7.0000.5402). The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines were followed to report this study.

The experimental procedure was conducted in two evaluation sessions with a minimal interval of 48 hours between them. Both sessions were performed in a climatized room, with temperature and humidity controlled and maintained between 21° and 23°C, and 40 and 60%,[13] respectively, between 8:00 and 12:00 AM to minimize the circadian variation.[14] In the first evaluation session, the population profile regarding the participants' physical, cognitive, and clinical characteristics were assessed. The second session was composed of the active tilt test and outcomes assessment.

Population
A total of 48 participants were evaluated and divided into two groups: PD (PDG) and control (CG). The PDG ($n = 25$) was composed of individuals with a medical diagnosis of PD, classified between stages 1 and 3 of the Hoehn and Yahr (HY) disability scale,[15] and who did not present cognitive deficits according to the Mini-Mental State Examination (MMSE).[16] The CP ($n = 23$) was composed of individuals without cognitive deficits and neurological diseases, paired by sex and age with the participants from the PDG.

All participants of the PDG were recruited at the neurology sector of the Center for Physical Therapy and Rehabilitation Studies and Treatment of the São Paulo State University's (UNESP) Faculty of Sciences and Technology, Presidente Prudente, Brazil, and the corresponding controls were recruited from health centers in the same city.

Current smokers, current heavy drinkers, individuals with active infections, as well as cardiovascular and respiratory diseases that could interfere with cardiac autonomic control were not included. Participants with >5% error in their HRV record were excluded.

The sample size was defined considering the rMSSD index. The magnitude of the significant difference assumed was 14 milliseconds[17] and a standard deviation of 12 milliseconds, with an α risk of 5% and a β risk of 80% was considered, which resulted in 21 participants.

Participants were previously informed about the objectives and procedures of the study and provided written informed consent.

Experimental procedure

First evaluation
The anthropometric measures, such as weight, height, body mass index (BMI),[18] and waist-hip ratio (WHR),[19] as well as the cognitive deficits, according to the MMSE,[16] were assessed in all participants. For the participants with PD, the HY disability scale,[15] and the revised version of the Unified Parkinson Disease Rating Scale (MDS-UPDRS)[20] were applied.

Second evaluation
In this session, the active tilt test was performed. Participants were instructed not to consume stimulating substances such as coffee, tea, and chocolate at least 12 hours before this session. For participants with PD, this evaluation was performed during the "on" period of their medication (approximately one hour after ingestion).[21]

To record the heart rate (HR) beat-to-beat, and to generate the RR intervals series used for the autonomic modulation evaluation, the Polar RS800CX (Polar Electro Oy, Kempele, Finland)[6] was utilized.

Each participant was instructed to remain lying at rest, without talking, and in spontaneous breathing for 30 minutes. Then, the participant was instructed to stand up, and to remain in a standing position for 10 minutes. Cardiorespiratory parameters were assessed during rest (CR1), immediately after the participant stood up (CR2), and after 10 minutes in a standing position (CR3).

Outcomes

Cardiorespiratory parameters
Blood pressure (BP) was verified indirectly using a Tycos aneroid sphygmomanometer (WelchAllyn, Skaneateles Falls, NY, USA) and a Classic III Littman stethoscope (3M Company, Maplewood, MN, USA) on the participant's left arm.[22] HR was assessed by the Polar RS800CX heart monitor (Polar Electro Oy, Kempele, Finland) and SpO_2 was assessed through a digital pulse oximeter (ChoiceMMed finger oximeter, MD300C29, China). RR was assessed by counting the number of respiratory incursions performed by the participant during 60 seconds.[23]

Autonomic modulation
Autonomic modulation was evaluated by the HRV linear methods (time and frequency domains), and by the quantitative and qualitative analyzes of the Poincaré plot. HRV was assessed from the RR intervals obtained by a Polar RS800CX heart rate monitor (Polar Electro Oy, Kempele, Finland) with a sampling rate of 1000 Hz. Data on the RR intervals were sent to a microcomputer, by the pulse receptor's data transmission port to the Polar Precision Performance software (Polar Electro Oy, Kempele, Finland), version 4.01.029, using an infrared signal interface. Initially, the RR intervals series were digitally filtered by Polar Precision Performance software (Polar Electro Oy, Kempele, Finland),[24] using a moderate filter, and then, a manual filtering was performed using Microsoft Excel (Microsoft Corp. Redmond, WA, USA) software,[5,14] to eliminate the remaining ectopic beats and artifacts. Finally, a visual inspection of temporal series of the RR interval was performed in the computer monitor, which showed absence of artifacts that could interfere with the HRV analysis.

Only series with $> 95\%$ of sinus beats were analyzed,[25] this care was taken so that only traces of good quality were used in the analyzes. The RR intervals series were analyzed at rest period (TT1) and the active tilt test period (TT2). Two five-minute sections with at least 256 consecutive RR intervals were extracted from the period of greatest stability of the signal of these two periods (TT1 and TT2).

The HRV indices were calculated using the Kubios HRV (Kubios, Kuopio, Finland) software, version 54100230.[26] For the time domain were considered the indices: rMSSD (root mean square of the successive differences between adjacent normal RR intervals), and SDNN (the standard deviation of all normal RR intervals).[5] For the frequency domain, the fundamental oscillatory components of high frequency (HF/0.15 to 0.4 Hz), and low frequency (LF/0.04 to 0.15 Hz),[5] expressed in milliseconds squared (ms^2) and normalized units (nu), and the LF/HF ratio were considered. The Fast Fourier Transform was used as an algorithm for spectral analysis, with 50% overlap and window of 256 beats.

The qualitative analysis was performed through the evaluation of the figures generated by the Poincaré plot attractor[5]: 1) Figure in which an increase in the dispersion of RR intervals beat-to-beat can be verified; 2) Figure with a small dispersion of RR intervals, both in the short and long term.[5] The plot figure was drawn from the union of RR intervals of all participants in the study.

All procedures followed the recommendations described in the literature[14] and the normality values for HRV indices have been described by other authors.[27,28]

Data analysis

The normality of the data was tested by the Shapiro-Wilk test. For the sample characterization, the descriptive statistical method was used, and the results were presented as means and standard deviations (SD) 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, cardiorespiratory parameters, and HRV indices between groups, at rest, was made using the Student t-test or Mann-Whitney test. For the categorical data, the chi-square test was performed, considering the Yates continuity correction for 2×2 cross tables. The Cohen d effect size was calculated, and values over 0.2 and under 0.5 were considered as having small effect, between 0.5 and 0.8 a moderate effect, and higher than 0.8 a high effect.

To compare the effect of the active tilt test on the cardiorespiratory parameters and HRV indices, considering groups and moments, analysis of variance for repeated measures was used. Possible differences were identified by the Bonferroni post-hoc test. The effect size was calculated using Eta-squared (small effect: ≥ 0.01 to < 0.06; moderate effect: ≥ 0.06 to < 0.14; high effect: ≥ 0.14). The level of significance adopted was $< 5\%$ and the statistical software used was the Statistical Package Social Sciences (SPSS Inc., Chicago, IL, USA), version 15.0.
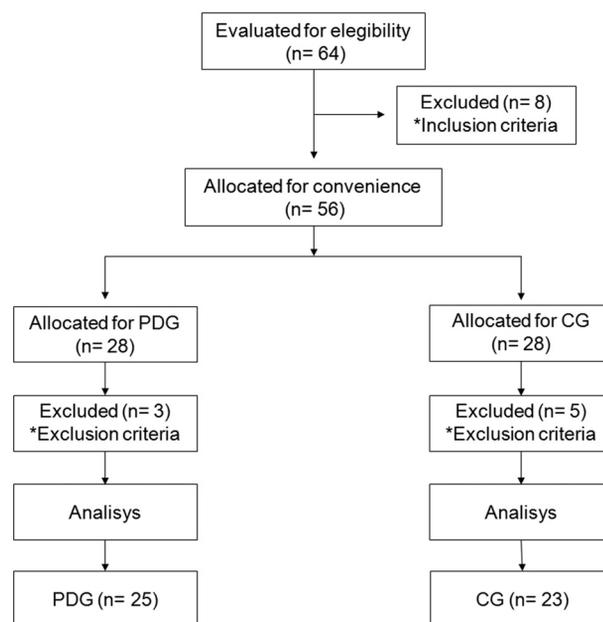
Figure 1 Sample loss flowchart. Representation of distribution and sample losses during study execution.

RESULTS

We analyzed 48 participants. The distribution and sample losses are described in ►**Figure 1**.

The characteristics of the groups are shown in ►**Table 1**. In both groups there was a male predominance (PDG: 84%, $n = 21$; CG: 82.6%, $n = 19$), and significant differences were found to BMI and MMSE ($p < 0.001$). Regarding the use of medication, significant differences were found for Levodopa and Dopamine agonist (►**Table 2**).

►**Table 3** shows the comparison between groups for cardiorespiratory parameters and HRV indices at rest. Lower values of SDNN, rMSSD, LFms^2 HFms^2 SD1, and SD2 ($p < 0.05$) were observed for PDG compared with CG. Regarding cardiorespiratory parameters, significant differences were observed for DBP and SpO$_2$ ($p < 0.05$). Higher SpO$_2$ values were found in the PDG.

►**Table 4** shows the comparison between groups for HRV indices evaluated in TT1 and TT2. Differences between groups were observed for the SDNN, rMSSD, LFms^2 HFms^2 SD1, and SD2 ($p < 0.05$). Differences within moments were observed for rMSSD, HFms^2 and SD1 ($p < 0.05$), with lower values in the active tilt test period, when compared with rest in both groups, and for SDNN, LFun, LF/HF, and SD1/SD2 ($p < 0.05$) indices, however with higher values in the active tilt test when compared with rest. Furthermore, an interaction between groups and moments was observed for rMSSD, HFms^2 and SD1 indices ($p < 0.05$).

►**Table 5** shows the values of the cardiorespiratory parameters in CR1, CR2, and CR3. Differences between groups were found for DBP and SpO$_2$ ($p < 0.05$). Differences within moments were observed for SBP and HR ($p < 0.05$). For PDG, SBP values were higher in CR3 compared with CR2. For HR, the values were higher in CR2 and CR3 compared

Table 1 Sample characteristics and comparison between groups

Variable	PDG (n = 25)	CG (n = 23)	p-value
Age (years)[a]	73.40 ± 7.01	70.17 ± 8.20	0.15
Weight (kg)[a]	71.94 ± 13.03	77.79 ± 10.77	0.10
Heigth (m)[a]	1.64 ± 0.09	1.63 ± 0.07	0.80
BMI (kg/m^2)[a]	26.80 ± 3.84	29.34 ± 4.11	**0.03**
WHR[a]	0.93 ± 0.10	0.94 ± 0.07	0.69
MEMS[b]	25.00 [7.00]	28.00 [3.00]	**0.02**
HY scale	2.32 ± 0.63	—	—
MDS-UPDRS T	64.20 ± 23.46	—	—
MDS-UPDRS I	13.04 ± 4.96	—	—
MDS-UPDRS II	14.60 ± 6.31	—	—
MDS-UPDRS III	32.68 ± 14.44	—	—
MDS-UPDRS IV	3.88 ± 3.55	—	—

Abbreviations: BMI, body mass index; CG, control group; HY, Hoehn and Yahr; MDS-UPDRS I, result from the part I of the Unified Parkinson Disease Rating Scale; 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; MDS-UPDRS T, total result of the revised version of the MDS-UPDRS; MEMS, mini-exam of mental state; PDG, Parkinson disease group; WHR, waist-hip ratio.
Notes: [a]Unpaired Student t-test: data presented as mean ± standard deviation. [b]Mann Whitney test: data presented as median (interquartile range).

Table 2 Medication in use by participants of control (CG) and Parkinson disease (PDG) group

Medication	PDG (n = 25)	CG (n = 23)	p-value
Neurological Action			
Levodopa	20 (80)	0 (0)	**0.00**
Antidepressant	11 (44)	6 (26.09)	0.32
Dopamine agonist	7 (28)	0 (0)	**0.01**
Amantadine hydrochloride	5 (20)	0 (0)	0.05
Monoamine oxidase inhibitors	5 (20)	0 (0)	0.05
Antipsychotics	5 (20)	0 (0)	0.05
Others	8 (32)	4 (17.39)	0.40
Cardiovascular Action			
Adrenergic blockers	10 (40)	5 (21.74)	0.29
Angiotensin II antagonists	10 (40)	9 (39.13)	1.00
Hypoglycemic	4 (16)	4 (17.39)	1.00
Antiplatelet	6 (24)	8 (34.78)	0.62
Statins	5 (20)	7 (30.43)	0.62
Diuretics	4 (16)	7 (30.43)	0.40
Vasodilators	3 (12)	6 (26.09)	0.28
Others	6 (24)	2 (8.70)	0.25
Other Medication	17 (68)	13 (56.52)	0.60

Abbreviations: CG, control group; PDG, Parkinson disease group, n (percentage).

with CR1 in both groups, and lower in CR3 compared with CR2 in the CG.

▶Figures 2 and 3 correspond to the visual representation of the Poincaré Plot pattern of PDG and CG, at rest (2A and 2B) and during the active tilt test (3A and 3B), respectively. These representations required the RR intervals of all subjects examined in the study to plot the chart.

DISCUSSION

The main findings of this study suggest that, when at rest, individuals with PD have reduced global and parasympathetic modulation, lower DBP, and higher SpO$_2$ when compared with healthy individuals. The autonomic responses to the active tilt test were characterized by reduced parasympathetic and

Table 3 Comparison between groups for the HRV indexes and cardiorespiratory parameters assessed at rest

Variables	PDG	CG	*p*-value	Effect size
Hear rate variability				
SDNN[a]	21.46 ± 9.93	32.47 ± 13,0	**0.002**	**-0.96**
rMSSD[a]	14.82 ± 6.36	23.47 ± 9,60	**0.001**	**-1.07**
LFms^2[b]	76.0 [65.5]	206.0 [361.0]	**0.001**	**-0.93**
LFnu[a]	57.48 ± 16.97	59.03 ± 20.17	0.77	**-0.08**
HFms^2[b]	56.0 [71.0]	151.0 [211.0]	**0.004**	**-0.83**
HFnu[a]	42.42 ± 16.91	40.89 ± 20.09	0.78	**0.08**
LF/HF[b]	1.36 [1.41]	1.74 [1.51]	0.52	**-0.13**
SD1[a]	10.49 ± 4.5	16.65 ± 6.84	**0.001**	**-1.90**
SD2[b]	29.5 [20.0]	37.3 [22.0]	**0.008**	**-0.78**
SD1/SD2[b]	2.91 [1.48]	2.55 [1.15]	0.45	**0.23**
Cardiorespiratory				
SBP (mmHg)[b]	130.0 [10.0]	130.0 [20.0]	0.14	**-0.51**
DBP (mmHg)[b]	80.0 [20.0]	80.0 [10.0]	**0.02**	**-0.76**
HR (bpm)[b]	64.0 [15.0]	63.0 [12.0]	0.73	**0.02**
SpO$_2$ (%)[b]	98.0 [2.0]	96.0 [1.0]	**0.00**	**0.23**
RR (rpm)[b]	16.0 [6.0]	18.0 [5.0]	0.47	**-0.30**

Abbreviations: bpm, beats per minute; CG, control group; DBP, diastolic blood pressure; HF, high frequency component; HR, heart rate; mmHg, millimeters of mercury; HRV, heart rate variability; LF, low frequency component; nu, normalized units; PDG, Parkinson disease group; rMSSD, root mean square of the successive differences between adjacent normal RR intervals, expressed in ms; rpm, respiration per minute; RR, respiratory rate; SBP, systolic blood pressure; SD1, standard deviation of the variability of RR intervals in the short term; SD2, standard deviation of RR intervals in the long term; SDNN, the standard deviation of all normal RR intervals (recorded in a time interval, expressed in ms); SpO$_2$, peripheral oxygen saturation.
Notes: [a] Unpaired Student *t*-test: data presented as mean ± standard deviation. [b] Mann-Whitney test: data presented as median (interquartile range).

increased global modulation in both groups; however, the PDG presented a lower parasympathetic response to the test, when compared with the CG. The cardiorespiratory responses were characterized by increased HR and reduced SBP in both groups. Furthermore, the qualitative analysis of the Poincaré plot showed the PDG presents a lower dot dispersion at rest and in the active tilt test, when compared with the CG.

In the HRV analysis, at rest, the SDNN, LFms^2 and SD2 indices, which represent a global modulation,[5] were decreased in the PDG compared with the CG. These results, together with the reduction observed in the rMSSD, HFms^2 and SD1, might indicate that individuals with PD present increased sympathetic and reduced parasympathetic modulation, suggesting a reduction in the complexity of the RR intervals series of the PDG. Similar results have been found by Rocha et al.,[8] Stoco-Oliveira et al.,[29] and Harnold et al.[30]

Cardiovascular autonomic dysregulation in PD has been attributed to involvement of both the central as well as the peripheral postganglionic autonomic nervous system.[31] Solla et al.[32] have suggested that the autonomic dysfunction present in PD is associated with significant increase in morbidity and mortality. Moreover, it is important to highlight that individuals with PD with impaired autonomic function may present impaired functional performance more quickly,[33] which highlights the importance of the autonomic assessment.

In response to the active tilt test, reduced rMSSD, HFms^2 and SD1 were observed in both groups, but the magnitude of the reduction was smaller for the PDG. These results are in accordance with Barbic et al.,[34] demonstrating the impaired ANS adjustments in individuals with PD and indicating a diminished response of the parasympathetic modulation[5] of these individuals in comparison to the CG. The impairment of ANS autonomic adjustments is harmful to the organism because it reveals its inability to provide adequate adaptive responses to stress, which removes the organism from homeostasis.[5]

Regarding the indices which represent the global modulation, our results show that individuals with PD presented increased SDNN, LFms^2, and SD2 with the execution of the test. This increase is likely due to the SNA adaptation to the test. Alterations in HR are promoted by adjustments that occur in the sympathetic and parasympathetic SNA components. These alterations induce increased RR interval variations, justifying the increased global variability.

The visual (qualitative) analysis of the Poincaré plot (►Figures 2 and 3) shows a lower dispersion of the beat-to-beat intervals in the PDG, at rest and during the test, which can be noted by the shape of the plots, indicating impaired autonomic modulation at rest and reduced response capacity in the active tilt test. To our knowledge, this is the first study to assess autonomic test responses of individuals with PD using the qualitative and quantitative

Table 4 Repeated measured ANOVA for a two-factor scheme: linear and non-linear indexes of HRV

	Variables	PDG	CG			
		Mean ± SD		Effect	p-value	Eta-Squared
SDNN				Group	**0.003**	0.172
	TT1	21.46 ± 9.93	32.47 ± 13.0	Moments	**0.048**	0.082
	TT2	26.76 ± 12.15*	37.36 ± 22.14	Group x Moments	0.94	0.0
RMSSD				Group	**0.003**	0.18
	TT1	14.82 ± 6.36	23.47 ± 9.6	Moments	**0.0**	0.358
	TT2	12.83 ± 6.25*	16.32 ± 6.7*	Group x Moments	**0.006**	0.151
LFms^2				Group	**0.005**	0.16
	TT1	97.88 ± 100.49	348.0 ± 373.36	Moments	0.84	0.001
	TT2	182.68 ± 220.81	280.17 ± 234.01	Group x Moments	0.07	0.069
LFun				Group	0.85	0.001
	TT1	57.48 ± 16.97	59.03 ± 20.17	Moments	**0.0**	0.292
	TT2	70.6 ± 17.05*	70.77 ± 18.92*	Group x Moments	0.81	0.001
HFms^2				Group	**0.004**	0.169
	TT1	79.32 ± 78.93	196.91 ± 188.51	Moments	**0.0**	0.248
	TT2	47.76 ± 38.21*	94.61 ± 84.27*	Group x Moments	**0.045**	0.084
HFun				Group	0.85	0.001
	TT1	42.42 ± 16.91	40.89 ± 20.09	Moments	**0.0**	0.294
	TT2	29.24 ± 17.0*	29.11 ± 18.87*	Group x Moments	0.81	0.001
LF/HF				Group	0.69	0.003
	TT1	1.93 ± 1.76	2.17 ± 1.81	Moments	**0.01**	0.132
	TT2	5.14 ± 8.33	4.13 ± 3.63*	Group x Moments	0.53	0.009
SD1				Group	**0.003**	0.18
	TT1	10.49 ± 4.5	16.65 ± 6.84	Moments	**0.0**	0.357
	TT2	9.08 ± 4.43*	11.55 ± 4.75*	Group x Moments	**0.006**	0.152
SD2				Group	**0.04**	0.087
	TT1	30.23 ± 14.25	42.68 ± 17.51	Moments	0.07	0.069
	TT2	37.6 ± 17.81	44.64 ± 23.05	Group x Moments	0.29	0.024
SD1/SD2				Group	0.33	0.021
	TT1	2.93 ± 1.45	2.69 ± 0.74	Moments	**0.0**	0.338
	TT2	4.49 ± 2.26*	4.05 ± 1.41*	Group x Moments	0.74	0.002

Abbreviations: CG, control group; SD: standard deviation; HF, high frequency component; HRV, heart rate variability; LF, low frequency component; ms^2: milliseconds squared; nu, normalized units; PDG, Parkinson disease group; rMSSD, root mean square of the successive differences between adjacent normal RR intervals (expressed in ms); SD1, standard deviation of the variability of RR intervals in the short term; SD2, standard deviation of RR intervals in the long term; SDNN, the standard deviation of all normal RR intervals, recorded in a time interval (expressed in ms); TT1, rest period; TT2, active tilt test period.
Notes: *Different from TT1.

analysis of the Poincaré plot, which can assist the interpretation and analysis of the results, since in biological systems, non-linear behavior prevails.[5]

Regarding cardiorespiratory parameters, lower DBP values and higher SpO$_2$ values for PDG were observed, at rest. Despite the difference found between PDG and controls, this result corresponds to normal values of DBP,[22] suggesting individuals with PD do not have impairment in the PA regulation when at rest. This is the first study to consider the SpO$_2$, and our results, when analyzed together with the information that none of the participants reported to have

respiratory diseases, suggest the respiratory system of individuals with PD is not impaired. Furthermore, our findings are in accordance with previous studies, which have found normal results on respiratory spirometry assessments in individuals diagnosed with PD.[35]

Both groups showed increase HR immediately after the active tilt test and, after 10 minutes, the participants had not returned to the initial condition yet. However, in the CG the HR value after 10 minutes was significantly lower than the HR value obtained after participants stood up, which did not occur in the PDG, suggesting a delay in HR recovery in

Table 5 Repeated measured ANOVA for a two-factor scheme: cardiorespiratory parameters

	Variables	PDG	CG			
		Mean ± SD		Effect	p-value	Eta-Squared
SBP (mmHg)	CR1	126.4 ± 12.21	130.87 ± 13.46	Group	0.36	0.018
	CR2	123.2 ± 18.65	128.70 ± 14.56	Moments	**0.006**	0.107
	CR3	131.6 ± 14.63$^{\#}$	132.17 ± 15.65	Group x Moments	0.36	0.022
DBP (mmHg)	CR1	79.2 ± 10.38	86.52 ± 8.85	Group	**0.03**	0.104
	CR2	77.2 ± 11.73	88.26 ± 12.67	Moments	0.83	0.003
	CR3	82.8 ± 10.61	84.78 ± 21.51	Group x Moments	0.11	0.048
SpO$_2$ (%)	CR1	97.8 ± 0.96	96.17 ± 1.99	Group	**0.003**	0.172
	CR2	97.88 ± 0.97	96.7 ± 1.77	Moments	0.25	0.03
	CR3	97.68 ± 1.15	96.52 ± 2.54	Group x Moments	0.34	0.023
HR (bpm)	CR1	65.16 ± 9.21	62.57 ± 13.2	Group	0.79	0.002
	CR2	71.12 ± 9.85*	72.78 ± 15.37*	Moments	**0.0**	0.406
	CR3	68.96 ± 9.83*	67.26 ± 14.21*#	Group x Moments	0.09	0.05
RR (rpm)	CR1	17.52 ± 3.96	20.0 ± 11.27	Group	0.37	0.018
	CR2	18.2 ± 4.23	20.43 ± 12.31	Moments	0.26	0.029
	CR3	18.0 ± 3.54	20.17 ± 12.75	Group x Moments	0.89	0.002

Abbreviations: CG, control group; CR1, rest moment; CR2, immediately after the participant stood up; CR3, after 10 minutes in a standing position; DBP, diastolic blood pressure; HR, heart rate, bpm, beats per minute; mmHg, millimeters of mercury; PDG, Parkinson disease group; rpm, respiration per minute; RR, respiratory rate; SBP, systolic blood pressure; SD, standard deviation; SpO$_2$, peripheral oxygen saturation.
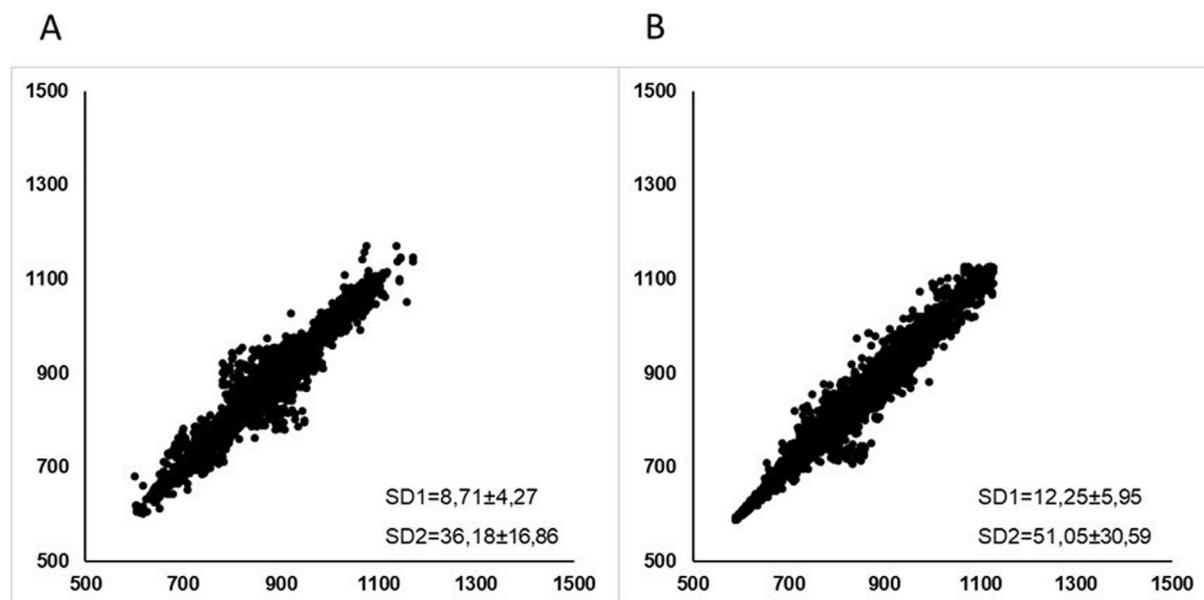**Notes:** *Different from CR1. #Different from CR2.
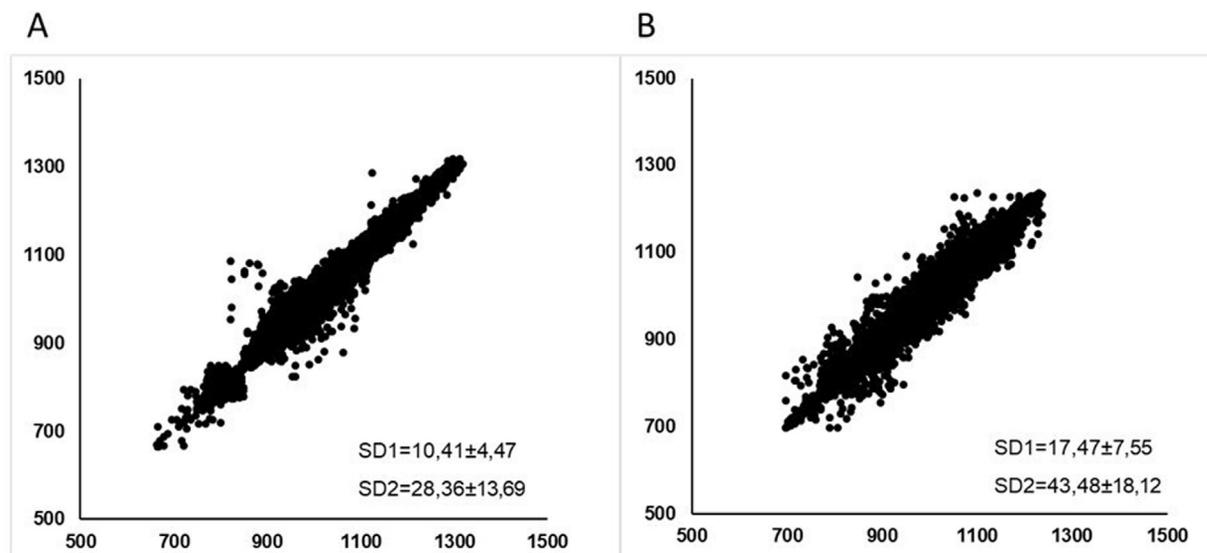
Figure 2 Visual representation of the Poincaré plot. Scatter plot that represents the qualitative analysis of Poincare plot in PDG (A) and CG (B) during rest.

individuals with PD. According to Roberson et al.,[36] individuals with PD have impaired capacity to regulate HR during the recovery period. Our results corroborate with this statement and may be related to impairments in autonomic modulation caused by autonomic dysfunction, as evidenced by HRV results found in our study.

Both groups presented non-significant, reduced SBP values in the test. However, 10 minutes after the postural change, the PDG showed increased SBP. These results represent normal physiological changes of individuals with PD in the test, since the reduction of PA in the baroreceptors promotes an immediate reflex, which results in increased sympathetic activity and in increased PA.[37] Furthermore, greater SpO$_2$ values were found in the PDG, and no significant changes were observed in both groups for RR, which represents a normal response, and it demonstrates the integrity of the participants' respiratory system.

Figure 3 Visual representation of the Poincaré plot. Scatter plot that represents the qualitative analysis of Poincare plot in PDG (A) and CG (B) during the active tilt test.

Some strengths of our study include the analysis of the autonomic modulation of individuals with PD in response to the active tilt test, an autonomic test that is more reproducible in clinical practice than the passive tilt test. Moreover, we measured respiratory parameters and utilized the qualitative and quantitative analysis of the Poincaré plot to assess autonomic modulation.

However, our study has some limitations. Due to the possible medication influence on autonomic regulation, the data should be interpreted with caution, since the participants used their habitual medication during the data collection (►Table 2). Furthermore, our study has not enabled the assessment of the influence of levodopa and dopamine agonists on the autonomic modulation of PD participants. Finally, diabetic participants were included in both groups. However, the number of diabetic participants was the same in both groups ($n = 4$), and significant differences for hypoglycemic values between groups were not observed (►Table 2).

The changes observed in the autonomic modulation and cardiorespiratory parameters in individuals with PD highlight the relevance of monitoring and evaluating the autonomic modulation in PD, which can be done by the active tilt test, as demonstrated in our study. Our results may help consolidate the active tilt test as a screening method, which can assist the choice of interventional therapies that require less postural changes. Studies comparing the autonomic modulation in response to the active tilt test and the passive tilt test can be also interesting in clinical practice.

In summary, our findings suggest that individuals with PD show reduced global variability and parasympathetic modulation when at rest, and reduced parasympathetic response and damage in HR regulation during the active tilt test, when compared with healthy individuals.

Authors' Contributions
All authors contributed significantly to this manuscript. HBV, NLG, MJLL, LMV, MCSO, ACC, LCMV: conceptualization; LCMV: project administration; HBV: funding acquisition; ACC: resources; MCSO, HBV, LBA, MVR: investigation; MCSO, HBV, LMV, LCMV: methodology; HBV, LCMV: supervision; MVR, FR: data curation; HBV, LMV: formal analysis; HBV, NLG, MJLL, LBA, MVR: writing-original draft; HBV, NLG, MJLL, LMV, FR, ACC, LCMV: writing-review & editing.

Conflict of Interest
The authors have no conflict of interests to declare.

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