



Complexity of autonomic nervous system function in individuals with COPD

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Submitted: 16 March 2017.

Accepted: 21 July 2017.

Study carried out under the auspices of the Programa de Pós-Graduação, Curso de Fisioterapia, Faculdade de Ciências e Tecnologia, Universidade Estadual Paulista – FCT/UNESP – Presidente Prudente (SP) Brasil.

INTRODUCTION

COPD, which is characterized by chronic airflow obstruction or limitation that is not fully reversible,⁽¹⁾ affects three million individuals worldwide,⁽²⁾ ranks fourth among the leading causes of death globally,⁽³⁾ and is associated with numerous complications, chief among which are changes in the autonomic nervous system (ANS).^(4,5)

The ANS is an example of a system with nonlinear dynamics⁽⁶⁾ that has an influence on heart rate and blood pressure to ensure the proper functioning of bodily organs so that their actual needs are met. This system can be evaluated via heart rate variability (HRV) and reflects the ability of the heart to respond to autonomic changes over time.⁽⁷⁾

Studies evaluating the ANS in COPD via HRV primarily use linear indices in the time and frequency domains for this analysis and report that COPD patients show a decrease in these indices at rest when compared with controls of the same age group.⁽⁸⁾ The few studies that have used nonlinear methods in this population find a reduction in

ABSTRACT

Objective: To evaluate autonomic modulation in individuals with COPD, compared with healthy controls, via recurrence plots (RPs) and linear heart rate variability (HRV) indices.

Methods: We analyzed data on 74 volunteers, who were divided into two groups: COPD (n = 43) and control (n = 31). For calculation of HRV indices, heart rate was measured beat-by-beat during 30 min of supine rest using a heart-rate meter. We analyzed linear indices in the time and frequency domains, as well as indices derived from the RPs.

Results: In comparison with the control group, the COPD group showed significant increases in the indices derived from the RPs, as well as significant reductions in the linear indices in the time and frequency domains. No significant differences were observed in the linear indices in the frequency domains expressed in normalized units or in the low frequency/high frequency ratio. **Conclusions:** Individuals with COPD show a reduction in both sympathetic and parasympathetic activity, associated with decreased complexity of autonomic nervous system function, as identified by RPs, which provide important complementary information in the detection of autonomic changes in this population.

Keywords: Pulmonary disease, chronic obstructive; Autonomic nervous system; Nonlinear dynamics; Recurrence; Heart rate; Sympathetic nervous system.

short-term heart rate fractal correlation properties⁽⁹⁾ and a reduction in beat-by-beat RR interval dispersion on electrocardiogram, as determined by analysis of Poincaré plots,⁽⁴⁾ indicating lower HRV in individuals with COPD.

Analysis of HRV by nonlinear methods have garnered increasing interest, since there is evidence that the mechanisms involving cardiovascular regulation are likely to interact with each other nonlinearly.⁽¹⁰⁾ One of the methods used for this purpose is the recurrence plot (RP), which was originally developed by Eckmann et al.⁽¹¹⁾ as a graphical tool for revealing hidden fluctuations and periodicities in the temporal evolution that go undetected by other methods⁽¹²⁾; the RP allows one to obtain measures that are primarily based on diagonally oriented lines in the plot, such as recurrence rate (REC), determinism (DET), and entropy.^(12,13)

Traditional nonlinear methods are limited to long stationary signals, a condition that is rarely seen in biology,⁽¹⁴⁾ whereas the RP was developed to locate non-stationary, structural changes⁽¹¹⁾ and may be a more sensitive tool for detecting physiological changes⁽¹⁵⁾

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Financial support: Laís Manata Vanzella received financial support from the Brazilian Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq, National Council for Scientific and Technological Development) Institutional Program for Young Investigator Grants.

and contribute to the surveillance and monitoring of individuals with COPD.

In view of these facts, the present study is intended to evaluate autonomic modulation in individuals with and without COPD, by analyzing RP indices as well as HRV indices in the time and frequency domains. We hypothesize that individuals with COPD will show a reduction in autonomic modulation and that the RP will be found to be a sensitive tool for identifying this condition.

METHODS

Study population

This was a prospective case-control study. For the purposes of the present study, we recruited 74 volunteers, who were divided into two groups: COPD ($n = 43$), as defined by the Global Initiative for Chronic Obstructive Lung Disease (GOLD) criteria⁽⁴⁾; and control ($n = 31$).

The COPD group included former smokers who had a physician diagnosis of COPD, which was confirmed by an obstructive pattern on pulmonary function testing and by reproducible curves, and who had not had a COPD exacerbation in the last two months. The control group included nonsmokers of the same age group who did not have a diagnosis of COPD, which was confirmed by a normal pattern on pulmonary function testing and by reproducible curves.

Neither group included individuals who had at least one of the following characteristics: being an alcoholic; being on medications that could affect autonomic modulation; and having cardiac and/or metabolic diseases.

The study procedures were approved by the Research Ethics Committee of the São Paulo State University School of Science and Technology (CAAE no. 15922813.9.0000.5402-306.419), located in the city of Presidente Prudente, Brazil, and all volunteers were fully informed about the procedures and purposes of the study. Upon agreement to participate in the study, subjects signed a written informed consent form.

Experimental protocol

The experimental protocol involved two steps. The first consisted of an initial evaluation to collect participant's identification data, perform anthropometric measurements, and assess pulmonary function. In the second step, conducted 24 h later, each participant's heart rate was measured beat-by-beat during 30 min using a heart-rate meter (Polar S810i; Polar Electro, Kempele, Finland) for subsequent calculation of HRV indices.

Initial evaluation

Participants were identified by name, age, and medication use; underwent anthropometric measurements (body mass and height); and were assessed for pulmonary function. Body mass was measured with an electronic digital scale (Lumina

MEA-02550; Plenna, São Paulo, Brazil), and height was measured with a stadiometer (Personal Caprice; Sanny, São Bernardo do Campo, Brazil) with subjects being barefoot and standing erect. From the data obtained, we calculated the body mass index (BMI) using the following formula: $BMI = \text{weight}/\text{height}^2$ (kg/m^2).⁽¹⁶⁾

For pulmonary function assessment, participants underwent spirometry with a Spirobank spirometer (MIR, Rome, Italy).^(17,18) Three acceptable and two reproducible curves were obtained, after a maximum of eight attempts. Obstructive lung disease was defined according to GOLD guidelines.⁽¹⁾

Assessment of autonomic modulation

Autonomic modulation was assessed 24 h after completion of the first step. For this assessment, participants were instructed not to consume alcohol or any drinks that could stimulate the ANS, such as coffee, tea, soft drinks, and chocolate milk, and not to perform any vigorous exercise in the 24 h preceding the test.

For the assessment of autonomic modulation, heart rate was measured beat-by-beat, in the morning (from 8:00 to 11:00), in a quiet environment with a room temperature between 21°C and 24°C and a relative humidity between 40% and 60%.

Heart rate was measured with a chest strap, which was placed on the distal third of the sternum, and a heart-rate meter (Polar Electro), which was worn on the wrist; this equipment has been previously validated for measuring heart rate beat-by-beat and for use in the calculation of HRV indices.⁽¹⁰⁾ Participants were instructed to remain silent, awake, and at rest and to breathe spontaneously for 30 min in the supine position on a stretcher. After this assessment, participants were released.

For calculation of HRV indices, we used 1,000 RR intervals obtained from the most stable part of the tracing. The series of RR intervals initially underwent filtering, using the standard filter in the Polar ProTrainer 5 (version 5.41.002) software (Polar Electro),⁽¹⁹⁾ using a moderate filter (median protection zone of six heartbeats), and, subsequently, a visual inspection of the temporal series of RR intervals on the computer screen was performed, which showed no artifacts that could affect HRV analysis. Only series showing more than 95% of sinus beats were included in the study.⁽¹⁰⁾

HRV indices in the time and frequency domains were calculated using Kubios HRV version 2.0 software (Kubios Oy; Kuopio, Finland), whereas RP indices were calculated using Visual Recurrence Analysis version 4.9 software (Eugene Kononov, Springfield, MA, USA).

In the time domain, we calculated the following indices: the standard deviation of the NN interval (SDNN), representing all normal RR intervals; and the root mean square of successive differences (RMSSD), which corresponds to the square root of the mean squared differences between successive RR intervals over a given time period.⁽¹⁰⁾

In the frequency domain, we used low-frequency (LF; 0.04-0.15 Hz) and high-frequency (HF; 0.15-0.40 Hz) spectral components, in ms^2 and in normalized units (nu), as well as the ratio of these two components (LF/HF). Spectral analysis was performed using the fast Fourier transform algorithm.⁽¹⁰⁾

RPs were analyzed qualitatively and quantitatively. Qualitative analysis was based on visualization of plots, and quantitative analysis was based on the following indices: REC; DET; Shannon entropy (SE); laminarity (LAM); trapping time (TT); and maximum line length (MaxLine). The parameters used in creating the RPs were as follows: embedding dimension = 10; time delay = 1; radius = 70; line length = $2^{(20)}$; and color scheme in gray.

RPs visualize the behavior of trajectories in phase space and show the times at which a dynamic system repeats itself.⁽¹¹⁾ RPs are defined as a symmetric matrix consisting of ones and zeros, and $RP(i,j)$ is 1 if the vector ξ_i on the trajectory is closed for the vector ξ_j .⁽²¹⁾

$$PR(i, j) = \begin{cases} 1 & \text{se } d(\xi_i - \xi_j) < r, \\ 0 & \text{se cc,} \end{cases}$$

where $d(\xi_i - \xi_j)$ is the Euclidean distance, r is a fixed threshold, and *o/w* stands for "otherwise".

Based on this matrix, vectors are calculated by reconstruction of the space, and the sum of these vectors enables the determination of Euclidean distance values. The Euclidean distance values are compared with the r value, and this enables the construction of a plot. If the distance between the vectors ξ_i and ξ_j on the reconstructed trajectory is smaller than r , a black dot is placed at location (i,j) in the matrix; otherwise, the location is left blank (white).⁽²²⁾

REC is the probability of similar states occurring within a given system.⁽²³⁾ DET is the proportion of recurrent points that form diagonal lines through which systems with similar or equal phase spaces remain in the same regions over a given time period.⁽²³⁾ LAM is represented by the radius between recurrent points that form vertical lines, determining the occurrence of laminar states in the system.⁽²⁴⁾ The number and length of vertical lines are defined as TT.⁽²⁴⁾ MaxLine is defined as the length of the longest diagonal line in the RP.⁽²⁵⁾ And, finally, we calculate entropy, defined on the basis of the frequency distribution of the diagonal line lengths.⁽¹⁵⁾ The term entropy refers to the SE of the probability $p(l) = P(l)/N_l$ to find diagonal lines corresponding to given line lengths l ($N_l = \sum_{l \geq l_{\min}} P(l)$), where l is the number of diagonal lines, N_l is the total number of diagonal lines, and P is probability.

Data analysis

The sample was characterized with descriptive statistics, and the results are expressed as mean, median, and minimum-maximum value. For comparison of anthropometric variables, age, spirometric values, and HRV indices between groups, data were tested for normality by using the Shapiro-Wilk test; for data

showing a normal distribution (age, weight, height, FVC, FEV_1/FVC , REC, TT, SE, SDNN, LF/HF), the Student's *t*-test for unpaired data was used, whereas for data with a non-normal distribution (BMI, FEV_1 , DET, LAM, MaxLine, RMSSD, LF [ms^2], HF [ms^2], LF [un], and HF [un]), the Mann-Whitney test was used. Statistically significant differences were defined as those with p values > 0.05 .

RESULTS

Table 1 presents the characteristics of the volunteers in the two groups studied. Significant differences were observed between the groups for height, FVC, FEV_1 , and FEV_1/FVC .

The linear HRV indices analyzed in the time and frequency domains are presented in Table 2. Lower values for SDNN, RMSSD, LF (ms^2), and HF (ms^2) were observed in the COPD group as compared with the control group ($p < 0.05$). No statistically significant differences were found between the groups for LF (un), HF (un), or the LF/HF ratio.

Table 3 presents the indices derived from the RCs of the groups studied. Increases in all indices derived from the RCs were observed for the COPD group ($p < 0.05$).

Figure 1 shows a representative example of the visual analysis of RPs. The presence of more points in a given configuration state (black dots) is observed in the COPD group as compared with the control group.

DISCUSSION

The results of the present study suggest that individuals with COPD exhibit decreased complexity of ANS function, associated with reductions in both sympathetic and parasympathetic activity. In addition, there were increases in all indices derived from RPs in the COPD group as compared with the control group.

REC and DET were associated with the complexity of cardiac autonomic modulation.⁽²¹⁾ According to Webber et al.,⁽¹⁵⁾ periodic systems show high REC values as compared with nonperiodic systems, and structured deterministic systems show high DET values. Because structured periodic systems are less complex, high REC and DET values indicate lower complexity of autonomic modulation, which can be observed in the COPD patients analyzed in the present study.

According to Javorka et al.,⁽⁶⁾ lower TT and LAM values translate to higher complexity of a dynamic system. In our study, we observed that COPD patients showed an increase in TT and LAM values as compared with controls, again suggesting lower complexity in the former.

Regarding SE, low values appear to be associated with stochasticity, whereas high values are associated with a more deterministic behavior.⁽²¹⁾ In the present study, we observed that the individuals in the COPD group showed higher SE values, which indicates a more

Table 1. Characteristics of the study volunteers in the control and COPD groups.^a

Variable	Group		p
	Control (n = 31)	COPD (n = 43)	
Age, years	63.25 ± 7.13 (63.00) [52.00-79.00]	66.37 ± 8.27 (66.00) [48.00-83.00]	0.080
Weight, kg	68.83 ± 16.26 (65.00) [46.00-113.00]	69.74 ± 13.88 (71.00) [35.30-106.50]	0.802
Height, cm	155.45 ± 7.52 (155.00) [140.00-173.00]	161.84 ± 8.76 (162.00) [144.00-176.00]	0.001
BMI, kg/m ²	29.83 ± 9.49 (29.00) [19.00-67.00]	26.41 ± 4.67 (26.00) [18.00-38.72]	0.071
FVC, L	2.95 ± 0.62 (2.79) [2.00-4.24]	2.52 ± 0.85 (2.27) [1.03-4.38]	0.015
FVC, % of predicted	104.70 ± 18.03 [72.00-146.00]	82.41 ± 23.93 [36.00-137.00]	< 0.001
FEV ₁ , L	2.36 ± 0.47 (2.30) [1.63-3.50]	1.31 ± 0.52 (1.10) [0.54-2.45]	< 0.001
FEV ₁ , % of predicted	105.03 ± 16.90 [75.00-145.00]	54.79 ± 21.04 [21.00-106.00]	< 0.001
FEV ₁ /FVC, %	80.35 ± 5.28 (79.00) [72.00-93.00]	51.70 ± 11.74 (51.60) [29.00-71.00]	< 0.001

BMI: body mass index. ^aValues expressed as mean ± SD (median) [minimum – maximum].

Table 2. Linear heart rate variability indices in each group.^a

Index	Group		p
	Control	COPD	
SDNN	34.48 ± 12.51 (32.50) [17.30-58.60]	28.04 ± 12.18 (26.60) [8.20-63.00]	0.031
RMSSD	21.71 ± 11.60 (19.90) [8.70-60.70]	13.80 ± 7.19 (12.90) [3.10-30.70]	0.001
LF, ms ²	339.25 ± 299.40 (213.00) [72.00-1.138.00]	205.93 ± 219.79 (141.00) [7.00-1.193.00]	0.013
HF, ms ²	161.19 ± 145.38 (115.00) [24.00-606.00]	74.02 ± 74.92 (42.00) [1.00-282.00]	0.001
LF, nu	67.72 ± 10.93 (69.00) [38.60-83.20]	72.43 ± 18.165 (75.70) [28.30-97.20]	0.061
HF, nu	32.25 ± 10.92 (31.00) [16.80-61.40]	27.56 ± 18.165 (24.30) [2.80-71.70]	0.061
LF/HF	2.44 ± 1.16 (2.22) [0.62-4.97]	5.72 ± 6.94 (3.11) [0.39-34.22]	0.062

SDNN: standard deviation of the NN interval (i.e., standard deviation of all normal RR intervals), expressed in milliseconds; RMSSD: root mean square of successive differences between adjacent normal RR intervals, expressed in milliseconds; LF: low frequency; HF: high frequency; and nu: normalized units. ^aValues expressed as mean ± SD (median) [minimum – maximum].

deterministic system and, therefore, lower complexity of ANS function in these individuals.

Finally, we observed that the individuals with COPD showed higher MaxLine values as compared with controls. MaxLine is the longest diagonal line in the RP⁽²⁵⁾ and is known to correspond to the persistence of the state over a given time interval⁽²²⁾; therefore, higher MaxLine values translate to less chaotic systems,⁽²⁶⁾ which again indicates lower complexity of autonomic modulation in the COPD group.

Qualitative analysis based on visualization of RPs also demonstrates that individuals with COPD exhibit lower complexity of ANS function as compared with healthy individuals. In individuals with COPD, the presence of more points in a given configuration state (black dots)

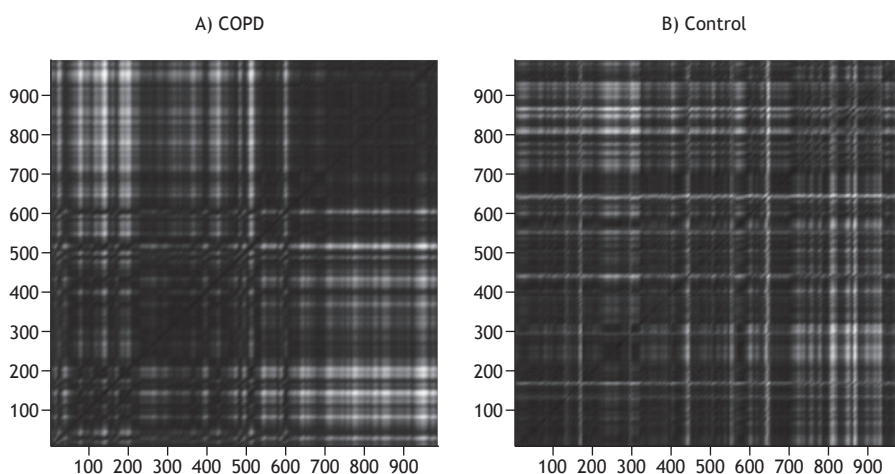
is noted, unlike what is found in individuals without COPD, in whom the presence of a greater number of points in different configuration states (white dots) can be observed.

Analysis of the diagonal, horizontal, and vertical lines in the RP enables rapid visual interpretation of the changes in autonomic modulation in individuals with pathological conditions.⁽²¹⁾ According to Assmann et al.,⁽²²⁾ diagonal lines indicate similar evolution of different parts of the trajectory, whereas horizontal and vertical lines show that the system does not change for some time. As reported by Ferreira,⁽²¹⁾ for time series of healthy subjects, the RP has a diagonal line and fewer apparent squares, which indicates higher HRV. Therefore, we can observe that Figure 1A shows a higher proportion of recurrent points as compared

Table 3. Recurrence plot indices for analysis of heart rate variability, by group studied.

Index	Group		p
	Control	COPD	
REC, %	28.87 ± 5.33 (28.67) [18.74-39.14]	33.20 ± 5.47 (34.20) [15.96-42.23]	0.001
DET, %	98.54 ± 0.81 (98.67) [96.65-99.51]	98.85 ± 0.97 (99.14) [94.95-99.825]	0.017
LAM, %	96.28 ± 3.03 (96.94) [87.25-99.46]	97.09 ± 4.62 (98.38) [71.76-99.89]	0.016
TT	9.99 ± 4.01 (8.82) [4.39-19.65]	12.52 ± 5.17 (12.41) [2.42-23.41]	0.021
SE, bits/s	-4.63 ± 0.43 (4.58) [3.76-5.46]	-4.91 ± 0.41 (4.96) [3.82-5.65]	0.008
MaxLine	377.45 ± 279.31 (282.00) [103.00-990.00]	589.11 ± 279.94 (600.00) [106.00-990.00]	0.001

REC: recurrence rate; DET: determinism; LAM: laminarity; TT: trapping time; SE: Shannon entropy; and MaxLine: length of the longest diagonal line in the recurrence plot. ^aValues expressed as mean ± SD (median) [minimum – maximum].


Figure 1. Recurrence plots. In A, a subject in the COPD group (REC = 32.98 and DET = 98.76), and, in B, a subject in the control group (REC = 28.67 and DET = 98.52). REC: recurrence rate; and DET: determinism.

with Figure 1B, indicating a more recurrent and less dynamic system in the COPD group and lower complexity of autonomic modulation in this population.

Detection of autonomic changes by using linear HRV indices has received increasing attention in the literature because of evidence indicating that the mechanisms involved in cardiovascular regulation interact with each other nonlinearly,⁽¹⁰⁾ enabling a better understanding of the complex and dynamic systems of the human body,⁽²⁷⁾ which provides additional information related to physiological interpretation and prognosis.⁽²⁸⁾ Carvalho et al.⁽⁹⁾ studied the fractal dynamics of heart rate in subjects with and without COPD by measuring short- and long-term fractal exponents and reported a decrease in the short-term fractal correlation properties of heart rate in the COPD group, indicating a reduction in autonomic complexity in these individuals, as was also observed in our study via application of RPs.

Analysis of fractal dynamics differs in some aspects from RP analysis. Fractal dynamics was developed to characterize scale fluctuations, that is, short- and

long-term time series,⁽²⁰⁾ whereas the RP was developed to locate nonstationary structural changes,⁽¹¹⁾ thus enabling the identification of hidden fluctuations and periodicities in the temporal evolution.⁽¹²⁾ Therefore, the use of RPs as a tool for analyzing HRV can provide important complementary information in the detection of autonomic changes in individuals with COPD.

The state of being healthy is characterized by a certain degree of chaos in the ANS, and abnormalities in ANS function cause a decrease in cardiac chaos.^(21,29) Changes in autonomic modulation can lead to a marked reduction in the complexity of the dynamics of heart rate fluctuations, making the heart period less adaptable and making the heart less able to cope with a frequently changing environment.^(25,30)

Taken together, these data suggest that COPD patients exhibit decreased complexity of autonomic modulation and are consequently subject to poor health status. Decreased complexity of cardiac autonomic modulation is associated with adverse clinical events, such as coronary artery disease with stenosis ≥ 50%,⁽³¹⁾ type

I diabetes mellitus,⁽⁶⁾ and schizophrenia,⁽³²⁾ as well as with the aging process.⁽³³⁾

In addition to decreased complexity of ANS function, our findings show a reduction in LF and HF in ms^2 , as well as in SDNN and RMSSD, which suggests a decrease in overall variability and in sympathetic and parasympathetic activity.

Carvalho et al.⁽⁹⁾ also found reductions in LF and HF in ms^2 , as well as in SDNN and RMSSD, when comparing elderly subjects with COPD and controls of the same age group. Geometric indices have also indicated a decrease in vagal activity (standard deviation 1) and overall variability (standard deviation 2; triangular interpolation of NN interval histogram; and triangular index) in COPD patients.⁽⁴⁾ Several other studies have corroborated these findings, which indicate a change in cardiac autonomic modulation, demonstrating impairment of this activity in individuals with COPD.⁽³⁴⁻³⁸⁾

In addition, Mazzuco et al.⁽³⁹⁾ found that greater pulmonary function impairment translates to decreased heart rate dynamics in individuals with COPD, as shown by linear and nonlinear HRV indices. Also according to the same authors, there is in these individuals a negative relationship between DLCO and RR intervals during parasympathetic stimulation (respiratory sinus arrhythmia), which may be related to greater sympathetic stimulation that changes pulmonary capillary tone.

The mechanism by which autonomic modulation is altered in COPD has yet to be well established. Hypotheses are considered relative to predominant

tone in such cases, since the hyperinflation that is characteristic of COPD could generate altered vagal impulses.⁽⁴⁰⁾ Therefore, linear HRV indices indicate that individuals with COPD exhibit a reduction in both sympathetic and parasympathetic activity, and RP analyses show decreased complexity of ANS function, indicating poorer health status in this population. In addition, our findings contribute new information to the literature with regard to a new effective method that can detect changes related to the ANS in individuals with COPD by locating nonstationary structural changes.

One limitation of the present study is the heterogeneity in the degree of obstruction in the patients included in the COPD group. The COPD group comprised 3 patients classified as GOLD I ($\text{FEV}_1 \geq 80\%$ of predicted), 18 patients classified as GOLD II ($50\% < \text{FEV}_1 < 80\%$ of predicted), 17 classified as GOLD III ($30\% < \text{FEV}_1 < 50\%$ of predicted), and 5 patients classified as GOLD IV ($\text{FEV}_1 < 30\%$ of predicted). Although this is a heterogeneous group in terms of the degree of disease severity, Camilo et al.⁽⁵⁾ found that this aspect does not significantly affect HRV analysis. Another limitation is the use of bronchodilator medication. However, in our study, subjects were not under the daily effect of this medication during the period of data collection, and, as mentioned previously, none had had a recent COPD exacerbation, a fact that can overcome this limitation.

We therefore conclude that individuals with COPD exhibit decreased complexity of ANS function, as demonstrated by the indices derived from the RPs, associated with a reduction in both sympathetic and parasympathetic activity, as shown by the linear HRV indices.

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