ORIGINAL RESEARCH

Fractal correlation property of heart rate variability in chronic obstructive pulmonary disease

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Background: It was reported that autonomic nervous system function is altered in subjects with chronic obstructive pulmonary disease (COPD). We evaluated short- and long-term fractal exponents of heart rate variability (HRV) in COPD subjects.

Patients and methods: We analyzed data from 30 volunteers, who were divided into two groups according to spirometric values: COPD (n = 15) and control (n = 15). For analysis of HRV indices, HRV was recorded beat by beat with the volunteers in the supine position for 30 minutes. We analyzed the linear indices in the time (SDNN [standard deviation of normal to normal] and RMSSD [root-mean square of differences]) and frequency domains (low frequency [LF], high frequency [HF], and LF/HF), and the short- and long-term fractal exponents were obtained by detrended fluctuation analysis. We considered $P < 0.05$ to be a significant difference.

Results: COPD patients presented reduced levels of all linear exponents and decreased short-term fractal exponent (alpha-1: 0.899 ± 0.18 versus 1.025 ± 0.09, $P = 0.026$). There was no significant difference between COPD and control groups in alpha-2 and alpha-1/alpha-2 ratio.

Conclusion: COPD subjects present reduced short-term fractal correlation properties of HRV, which indicates that this index can be used for risk stratification, assessment of systemic disease manifestations, and therapeutic procedures to monitor those patients.

Keywords: pulmonary disease, chronic obstructive, heart rate, nervous system, cardiology

Introduction

Chronic obstructive pulmonary disease (COPD) is characterized by chronic airflow obstruction, which is not fully reversible,[1,2] and significant systemic manifestations such as nutritional depletion, structural and functional changes of respiratory and peripheral muscles, and arrhythmias.[3] Autonomic nervous system (ANS) dysfunction is also reported in COPD patients.[4–6] This may represent an important negative factor, as the ANS regulates internal functions of the body.

One method to evaluate the ANS function is the analysis of heart rate variability (HRV), the conventionally accepted term to describe the fluctuations in the intervals between consecutive heartbeats (RR intervals), which are indicated to influence the sinusal node.[7] Previous studies indicate that COPD subjects present decreased HRV at rest compared with control subjects at the same age.[8–10] Those studies regard specific changes of autonomic function in COPD-assessed HRV through linear methods in the time and frequency domains. However, to the best of our knowledge, no previous investigation has employed nonlinear methods to evaluate HRV in COPD patients.

HRV analysis using nonlinear methods has been receiving attention. There is evidence that mechanisms involved in cardiovascular regulation likely interact between each other in a nonlinear fashion.[11–13] One method used for this purpose is detrended fluctuation analysis (DFA), which quantifies the presence or absence of fractal correlation properties of the RR intervals.[11] According to Tulppo et al[14,15] fractal indices are able to detect slight changes in the dynamics of RR intervals better than conventional spectral analyses. Moreover, impairment of fractal correlation properties of short- and long-term dynamics of HRV helps clinical professionals to detect autonomic dysfunction and avoid disease development.

Based on the above considerations, we hypothesized that COPD patients would present altered heart rate dynamics. Therefore, this investigation was undertaken to evaluate short- and long-term fractal exponents of HRV in COPD subjects.

Methods
Population
We selected 15 patients (10 male) with a medical diagnosis of COPD, confirmed through spirometric test according to the Global Initiative for Chronic Obstructive Pulmonary Disease (GOLD),[1] who were under treatment at the Centro de Estudos e Atendimento em Fisioterapia e Reabilitação da Faculdade de Ciências e Tecnologia, Universidade Estadual Paulista (Presidente Prudente, Brazil). When unhealthy conditions were reported, except for hypertension, the subject was not included in the sample. Furthermore, we excluded current smokers, individuals who were taking medication that influences the cardiac autonomic modulation, patients who presented COPD exacerbation in the last 2 months prior to the experimental protocol, and those who presented a restrictive pattern or no reproducible curves during the spirometric tests. The control group consisted of 15 healthy subjects (8 male), without diagnosis of COPD and who presented normal spirometric values. Group profiles are presented in Table 1.

All volunteers were informed about the procedures and objectives of the study, and on agreement they signed a consent letter. All work procedures were approved by the Ethics Committee in Research of our university (protocol number 246/08) and followed Resolution 196/96 of the National Health Council of October 10, 1996.

Initial evaluation
Before beginning the experimental procedure, we collected the following information: age, gender, height, weight, body

Table 1 Anthropometric and spirometric profile, baseline heart rate, and blood pressure of the COPD and control groups

Variable	COPD[a]	Control[a]	P
Age (years)	73.93 ± 6.61 [70.28–77.59]	68.73 ± 7.27 [64.70–72.76]	0.050
Weight (kg)	65.46 ± 9.05 [60.45–70.47]	69.30 ± 12.9 [62.13–76.41]	0.358
Height (cm)	1.63 ± 0.09 [1.51–1.75]	1.58 ± 0.09 [1.44–1.74]	0.112
BMI (kg/m²)	24.47 ± 2.85 [22.89–26.05]	27.73 ± 4.88 [25.03–30.43]	0.036
FVC (%)	81.59 ± 18.60 [58.0–109.3]	97.18 ± 14.62 [73.4–131.6]	0.0164
FEV$_1$ (%)	51.69 ± 16.32 [31–88]	97.18 ± 14.62 [73.4–131.60]	<0.0001
FEV$_1$/FVC	47.42 ± 10.8 (47.0) [41.43–53.40]	79.36 ± 11.4 (80.0) [73.06–85.66]	<0.0001
PEF (L/s)	3.36 ± 1.5 (3.53) [2.56–4.17]	6.38 ± 2.16 (6.17) [5.18–7.57]	0.0003
HR (bpm)	70.73 ± 10.9 [64.6–76.8]	65.93 ± 7.6 [61.71–70.15]	0.092
SBP (mm Hg)	127.8 ± 18.7 (130) [90–160]	132.8 ± 11.13 (130) [118–160]	0.5328
DBP (mm Hg)	74.0 ± 12.07 (70) [58–100]	81.73 ± 9.96 (80) [76.2–87.2]	0.0766

Note: [a]Mean ± standard deviation (median) [confidence interval 95%].
Abbreviations: COPD, chronic obstructive pulmonary disease; BMI, body mass index; FVC, forced vital capacity; FEV$_1$, forced expiratory volume at the first second; PEF, peak expiratory flow; HR, heart rate; SBP, systolic blood pressure; DBP, diastolic blood pressure.

mass index (BMI), heart rate (HR), systolic blood pressure (SBP), and diastolic blood pressure (DBP). Anthropometric measurements were obtained following the standard recommendations proposed by Lohman et al.[16] BMI was calculated using the following formula: weight (kg)/height (m²).

Experimental protocol
Data were collected under controlled temperature (21°C–24°C) and humidity (50%–60%), and volunteers were instructed to avoid consuming alcohol and caffeine for 24 hours before evaluation. Data were collected between 8 a.m. and 11 a.m. in order to minimize the interference of circadian rhythm. All procedures necessary for the data collection were explained to the individuals, and the subjects were instructed to remain at rest and to avoid talking during the data collection.

After the initial evaluation the heart monitor strap was placed on each subject's thorax over the distal third of the sternum. The HR receiver (Polar S810i monitor, Polar Electro OY, Kempele, Finland) was placed on the wrist. This equipment has been previously validated for

beat-by-beat measurements and for HRV analysis.[17–20] The subjects were placed in the dorsal decubitus position on a cushion and remained at rest with spontaneous breathing for 30 minutes.

After the experimental procedures, we performed spirometric tests to identify and stratify the degree of bronchial obstruction. We used the Spirobank spirometer and a computer equipped with WinspiroPRO 1.1.6 software (Medical International Research, Rome, Italy). Data analysis was done according to the criteria described by the Guidelines for Pulmonary Function Tests.[21]

Linear index of HRV evaluation

HRV was recorded beat by beat through the monitoring process at a sampling rate of 1000 Hz. During the period of higher signal stability, an interval of 5 minutes was selected, and series with more than 256 RR intervals were used for analysis,[7] following digital filtering complemented with manual filtering for the elimination of premature ectopic beats and artifacts. Only series with more than 95% sinus rhythm were included in the study.[13]

To analyze HRV in the frequency domain, the low frequency (LF) (0.04–0.15 Hz) spectral component, which indicates both sympathetic and parasympathetic activity,[7,20] and high frequency (HF) (0.15–0.40 Hz) spectral component, which indicates parasympathetic activity,[7,20] were used,[2] as well as the ratio between these components (LF/HF). The spectral analysis was calculated using the Fast Fourier Transform algorithm.[7,20] Analysis in the time domain was performed by means of SDNN (standard deviation of normal-to-normal RR intervals) and RMSSD (root-mean square of differences between adjacent normal RR intervals in a time interval). For analysis of linear indexes in the time and frequency domains, we used the software HRV analysis.[22]

Fractal analysis of HRV

For the analysis of the fractal properties of the HR, DFA was applied to a time series of the RR intervals. This method is a modification of mean square root analysis of a random walk and is based on the analysis of fluctuations in the data following the removal of trends in the integrated time series,[23] which allows the detection of intrinsic self-similarity embedded in the nonstationary time series.[24] We calculated the short-term fractal exponent (alpha-1), which corresponds to a period of 4–11 beats; long-term fractal exponent (alpha-2), which represents periods longer than 11 beats;[25] and the alpha-1/alpha-2 ratio.

A software program available at PhysioNet (http://www.physionet.org) – an online forum that fuses records of biomedical signals and software programs for the analysis of these signals – was used for the DFA.[26]

Statistical analysis

A Shapiro–Wilk test was used to evaluate the normality of the data. The nonpaired Student's t-test was applied to verify differences between parametric variables (age, weight, height, BMI, forced vital capacity [FVC], HR, SBP, DBP, $HFms^2$, RMSSD, SDNN, alpha-1, alpha-2, and alpha-1/alpha-2). The Mann–Whitney test was used to verify differences between nonparametric variables ($LFms^2$, LF/HF, forced expiratory volume in the first second [FEV_1], FEV_1/FVC, and peak expiratory flow [PEF]). Differences were considered significant when the probability of a Type I error was lower than 5% ($P < 0.05$).

The calculation of the study power (StatMate GraphPad Software version 2.00 for Windows, GraphPad Software, San Diego, CA, USA) with the number of subjects analyzed and significance level of 5% (two-tailed test) confirmed a power higher than 80% to detect differences between the variables.

Results

Table 1 presents anthropometric measurements, spirometric values, HR, SBP, and DBP at rest in COPD and control groups. We observed that BMI, FVC, FEV_1, FEV_1/FVC, and PEF were significantly lower in COPD subjects compared with the control group. There was no significant difference between the groups regarding HR, SBP, and DBP at rest.

Table 2 shows the values of alpha-1, alpha-2, and the ratio alpha-1/alpha-2 in COPD and control groups. We noted that the COPD group presented lower values of alpha-1 compared with the control group. However, we did not report differences between the COPD and control groups with respect to alpha-2 and the ratio alpha-1/alpha-2 values.

Table 2 Values of alpha-1, alpha-2, and alpha-1/alpha-2 ratio in the COPD and control groups

Variable	COPD[a]	Control[a]	P
Alpha-1	0.9 ± 0.18 [0.79–1.00]	1.02 ± 0.09 [0.97–1.07]	0.026
Alpha-2	0.92 ± 0.11 [0.86–0.98]	0.91 ± 0.12 [0.85–0.98]	0.853
Alpha-1/alpha-2	0.99 ± 0.27 [0.84–1.14]	1.13 ± 0.13 [1.05–1.20]	0.069

Note: [a]Mean ± standard deviation [confidence interval 95%].
Abbreviation: COPD, chronic obstructive pulmonary disease.

Table 3 displays the values of the LF and HF indices in normalized units and ms^2 as well as the LF/HF ratio in COPD and control groups. There was reduction of all indices in COPD patients compared with control subjects.

Discussion

The results of the present study suggest that there is a loss or disarrangement of the properties of short-term fractal correlations of HRV associated with a reduction in both sympathetic and parasympathetic activity in COPD subjects.

According to Tulppo et al[15] and Acharya et al,[24] in relation to exponents obtained by the DFA, values close to 1 are indicative of a fractal system, whereas values close to 0.5 are associated with random signal, where there is no correlation between the values. Therefore, our results indicate that COPD patients exhibit dynamic changes in HR toward a more dynamic random profile, which indicates a condition of loss of chaos.

Under conditions where the action of sympathetic and parasympathetic components of the ANS on HR is organized in a reciprocal behavior, ie, an increased activity of a system is accompanied by a decrease of another, there is a strong short-term fractal correlation expressed by increasing the value of alpha-1.[14,27] Notwithstanding conditions in which there is increased activity of both ANS components (sympathetic and parasympathetic), loss of short-term HR fractal organization was noted, which decreased the value of alpha-1.[15,28,29] According to our study, the analysis of linear indices in the time and frequency domains in ms^2, as well as the ratio between these two components (LF/HF), in COPD patients showed reduction of both parasympathetic and sympathetic components of the ANS compared with the control group. Furthermore, reduced activity of sympathetic and para-

sympathetic components of the ANS in elderly patients with COPD compared with control subjects at similar age at rest and supine position was observed previously.[4–6] Taken together, our findings and previous investigations suggest that the reduction of alpha-1 reflects a decrease in both ANS component activities.

The loss of short-term fractal correlation property that we found in COPD subjects is related to the occurrence of several adverse clinical events such as heart failure[23,25] and acute myocardial infarction.[30] In addition, reduction of alpha-1 was observed before spontaneous onset of atrial fibrillation in patients without structural heart disease[27] associated with vulnerability to ventricular tachycardia[23,30] and ventricular fibrillation.[31] Exponent values lower than 0.85 were observed in patients with cardiovascular disease associated with increased mortality rate.[28–30] These values are close to those found in our study (alpha-1 = 0.899) in COPD patients.

Our investigation suggests that COPD subjects present autonomic dysfunction, characterized by loss of short-term fractal correlation of HRV and reductions of sympathetic and parasympathetic activity. It corroborates the importance of the use of nonlinear dynamics analysis in the prognostic assessment of morbid states, due to its ability to evaluate the degree of loss of the patient's homeostatic behavior, considering the whole and not only the severity of the diseases alone.

Nonlinear methods of HRV analysis describe complex fluctuations in heart rhythm and are able to separate structures with nonlinear behavior in heartbeat time series more adequately than linear methods.[12] They enable a better discrimination between individuals with normal and altered physiology,[13] as well as a better understanding of the nature of the complex dynamic systems that occur in the human body in both health and sickness.[32]

In relation to long-term exponents (alpha-2) and alpha-1/alpha-2 ratio, there was no difference between the COPD and control groups. Our findings suggest that COPD patients present autonomic dysfunction characterized by loss of short-term fractal correlation of HRV associated with sympathetic and parasympathetic activity reduction. Thus, interventions that may restore fractal dynamic properties of HR and increase HRV may have important clinical implications, and the performance of physical exercise programs should be emphasized. In a study that evaluated the effect of resistance training in healthy adults, Heffernan et al[33] found improvement of fractal dynamic properties of HR, whereas Borghi-Silva et al[4] investigated the effects of aerobic training

Table 3 Linear index values of heart rate variability (frequency and time domains) in the COPD and control groups

Variable	COPD[a]	Control[a]	P
LFms^2	28.80 ± 24.48 (20.0) [15.24–42.36]	130.00 ± 131.51 (88.0) [57.17–202.83]	0.0007
HFms^2	18.93 ± 9.89 [13.46–24.41]	52.5 ± 38.3 [31.33–73.74]	0.005
RMSSD	11.23 ± 3.48 [9.30–13.16]	18.93 ± 7.48 [14.78–23.07]	0.002
SDNN	14.13 ± 5.03 [6–24]	25.4 ± 9.5 [11–49]	0.0004

Note: [a]Mean ± standard deviation (median) [confidence interval 95%].
Abbreviations: COPD, chronic obstructive pulmonary disease; LF, low frequency; HF, high frequency; ms, miliseconds; RMSSD, root-mean square of differences between adjacent normal RR intervals in a time interval; SDNN, standard deviation of normal-to-normal RR intervals.

on autonomic cardiac regulation in COPD subjects and also found changes reflected by improvement of HRV indices in the time and frequency domains.

Our research presents a couple of points that should be addressed. First, both groups presented hypertensive patients; however, basal HR, SBP, and DBP were not significantly different between the groups. Second, COPD subjects presented different degrees of obstruction. Nevertheless, Camillo et al[5] have shown that COPD severity is not significantly related to HRV indices.

To the best of our knowledge, our findings are the first to evidence reduced alpha-1, the short-term fractal exponent, in COPD subjects. Our findings are relevant, as they indicate that these indices, obtained by a noninvasive and inexpensive method, may be useful both for clinical manifestations of systemic disease and for risk stratification and monitoring of therapeutic procedures performed with these patients.

In conclusion, COPD subjects present reduced short-term fractal correlation of HRV, indicating sympathetic and parasympathetic activity reduction.

Disclosure

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