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The exclusive presence of the chronic pulmonary disease could be more important in affecting autonomic cardiac modulation than the severity of airflow obstruction: Analysis using heart rate variability

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ABSTRACT

The autonomic nervous system regulates the caliber of the airways, blood flow, secretion production, modulates the inflammatory response and modulates airway responses to inflammation. Despite this, some intrinsic features could be more important in affecting autonomic modulation than the airflow severity. This study aimed to analyze the effects of chronic obstructive pulmonary disease (COPD) on autonomic modulation through heart rate variability (HRV) and its relationship with airflow severity. Outpatients with COPD (n = 30) and a control group (n = 26) were evaluated. The main outcome measures were anthropometry, spirometry and HRV. The presence of COPD had a large effect on autonomic modulation, demonstrated by a significant reduction in 6 out of 12 HRV indices according to the comparisons between the COPD groups (high and low severity) and the control group through HRV indices (rMSSD: 13.5 ± 7.3 vs. 10.4 ± 6.3 vs. 20.7 ± 7.1 ms; SDNN: 22.0 ± 11.2 vs. 17.1 ± 8.0 vs. 33.6 ± 13.8 ms; SD1: 9.6 ± 5.2 vs. 7.4 ± 4.5 vs. 14.6 ± 5.0 ms; SD2: 29.5 ± 15.2 vs. 22.9 ± 10.7 vs. 44.8 ± 20.0 ms). However, the severity of COPD presented no significant differences even when considering age, sex and body mass index (BMI). This study suggests that the presence of COPD could be more important in affecting HRV than the severity of airflow obstruction, independent of the sex, age or BMI.

1. Introduction

Chronic Obstructive Pulmonary Disease (COPD) is currently considered the fourth leading cause of death worldwide. The World Health Organization estimates that in 2030 it will be the third [1]. COPD is defined by persistent airflow limitation, the degree of which may have an impact on functional limitations and the prognosis of the disease [2,3]. The disease is progressive with partially reversible characteristics, and is associated with increased lung inflammatory responses arising from the inhalation of particles or toxic gases [4].

In addition to the pulmonary characteristics, COPD is associated with changes in autonomic behavior [5,6]. Autonomic behavior can be evaluated through the analysis of heart rate variability (HRV), a non-invasive assessment technique which describes the amount of variations of the intervals between consecutive heart beats [7].

Few studies [2,3] demonstrate the relationship between HRV and airflow severity in COPD and the existing studies do not present consensual results regarding the influence on autonomic modulation. In addition, even though the autonomic nervous system regulates the caliber of the airways, blood flow, secretion production and also modulates the inflammatory response and airway responses to inflammation [8], some intrinsic features of COPD,

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such as sex, age, and body mass index (BMI), and the exclusive influence of the disease could be more important in affecting HRV than the airflow severity. In this context, our hypothesis was that airflow severity would not influence autonomic modulation. Thus, this study aimed to analyze the effects of COPD on autonomic modulation and its relationship with airflow severity; considering age, sex and BMI.

2. Methods

2.1. Subjects

This is a cross-sectional study and included thirty outpatients that met the following inclusion criteria: a diagnosis of COPD and reported absence of associated diseases (cardiovascular, pulmonary and orthopedic). Forty-nine subjects participated in the initial evaluation. Of these, eight were excluded for failing to meet the inclusion criteria; and a further 11 who did not present 95% sinus beats in the temporal series of intervals between consecutive cardiac beats used to analyze HRV. Thus, the final sample consisted of 30 individuals. The control group included 26 volunteers who presented medical certificates of health. For the sample size calculation, we use the previous published studies as reference to select the RMSSD index [9,10]. Using this we ensured a test power over 90%, calculated through the standard deviation obtained from the RMSSD index for the high severity COPD group (7.3 ms), considering a detected difference of 7.2 ms between the control group, a significance level of 5% and a two-tailed hypothesis test.

All participants were informed about the study objectives and procedures and signed an informed consent form. In addition, the procedures were approved by the Ethics Committee of The Federal University of São Paulo (CAAE: 33726314.8.0000.5505) and were conducted according to the Helsinki Declaration.

Regarding the study design, the participants underwent the following procedures, performed by a physical therapist: anamnesis, anthropometry, spirometry and autonomic evaluation. These procedures were performed in two days, being anamnesis, anthropometry, spirometry in the first one and autonomic evaluation in the second day.

2.2. Anamnesis

The anamnesis was performed through a questionnaire to identify the participants, confirm they met the inclusion criteria (diagnosis of COPD, full health certificate and no reported severe associated diseases) and investigate the clinical status (presence of acute inflammatory processes and presence of smoking habit) [5].

2.3. Anthropometry

Anthropometry was used to characterize the population and establish the predicted values regarding spirometry (sex and age were also considered). Body weight was measured in kilograms using a digital scale (Welmy, R/I 200, Brazil) and height was measured in meters using a stadiometer (Sanny, Brazil) with the participants barefoot and wearing light clothes. After this, BMI was calculated by dividing weight by height squared [5].

2.4. Spirometry

Spirometry was performed to verify the diagnosis in a clinical context by confirming a persistent obstruction. This was demonstrated through the ratio between forced expiratory volume in one second (FEV1) and forced vital capacity (FVC), with a result below 0.70 after bronchodilator administration. The airflow severity was classified as follows: mild FEV1 $\geq$ 80%; moderate 50% $\leq$ FEV1 < 80%; severe 30% $\leq$ FEV1 < 50% and very severe FEV 1 < 30% of predicted FEV1[11–13]. The examination was performed on a portable spirometer (MIR, Spirobank version 3.6, Italy) coupled to a microcomputer and analysis was carried out using Ocean and WinSpiro software for Windows, version 1.04[a].

2.5. Autonomic evaluation

The autonomic evaluation was performed through HRV. Prior to the evaluation, the participants were instructed to avoid stimulating drinks such as coffee, tea, soft drinks and chocolate drinks and suspend bronchodilator and mucolytic medication for 12 h [5].

During the evaluation, volunteers were placed individually in a room with a temperature between 21 and 23 °C and humidity between 40 and 60%, in the morning, between 8 and 12 h, to minimize interference from circadian rhythm. Participants were instructed to remain silent, breathing spontaneously for 20 min and then 10 min were recorded, in the supine position and avoid moving around. In sequence, an electrode was positioned on the chest of the volunteers next to the xiphoid process, using an elastic strap. A heart rate receiver was positioned on the wrist (Polar Electro S810i model, Finland) [14,15].This equipment has been previously validated for recording heart rate beat to beat and data analysis for HRV [14,15].

Analysis of the HRV indices, was performed using 256 intervals between consecutive heart beats which were selected from the most stable part of the recording, submitted to digital filtering, complemented by manual filtering to eliminate ectopic beats and artifacts and only series with 95% sinus beats were included in the study. The RRi were selected after 5 min of the recording at rest in supine position. The analysis was processed using Kubios software which calculate indices using non-detrended the selected RR interval series (Biosignal Analysis and medical Image Group, Department of Physics, University of Kuopio, Finland) [16].

In the time domain, the following indices were selected: rMSSD [root mean square of the successive differences in the intervals between consecutive heart beats in a time interval expressed in milliseconds (ms)], SDNN (standard deviation of all normal intervals between consecutive heart beats in a time interval expressed in ms) [17]; the triangular index (RRtri) and TINN (triangular interpolation of all normal intervals between consecutive heart beats histogram), calculated through the construction of a density histogram of normal intervals, which shows all possible values of RR intervals on the horizontal axis and the frequency in which each one occurred on the vertical axis. The union of the points in the histogram columns forms a figure similar to a triangle, from which the indices are extracted [18].

The triangular index consists of the integral of the histogram (i.e., the total number of intervals between consecutive cardiac beats) divided by the maximum density distribution (modal frequency of intervals between consecutive cardiac beats), measured on a discrete scale with 7.8125 ms boxes (1/128 s). The TINN consists of the baseline width of the distribution measured as the base of the triangle, approximating the distribution of all intervals between consecutive cardiac beats, being the differences of least squares used to determine the triangle [17].

In the Poincaré plot, the length of an interval between consecutive cardiac beats (iRRN) is represented on the “x” axis; and the following interval (iRRN + 1), on the “y” axis, so each point on the graph (iRRN, iRRN + 1) corresponds to two successive heartbeats. For the quantitative analysis of the plot, the following indices were calculated: SD1 (standard deviation of the instantaneous beat to beat variability) and SD2 (standard deviation of the long-term continuous intervals between consecutive cardiac beats) [19].

In the frequency domain, the low [LF: 0.004 – 0.15 Hertz (Hz)] and high frequency (HF: 0.15 – 0.40 Hz) spectral components were