Original Research

Analysis of Autonomic Modulation in Patients with Chronic Obstructive Pulmonary Disease

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Abstract: The aim of this study was to analyze autonomic modulation and factors that may be associated in patients with COPD. We carried out a cross-sectional, observational study of a quantitative nature, from the recruitment of 11 individuals with COPD, assisted by a specialized hospital in the state of Ceará. For data collection, the following were used: an evaluation form containing demographic and clinical data, prepared by the researchers; a cardiofrequency meter to measure the heart rate during and after the walk test; the *Duke Activity Status Index* (DASI) questionnaire to assess the capacity functional scale, the *London Chest Activity of Daily Living* (LCADL) scale to check the level of dyspnea and the *State-Trait Anxiety Inventory* (STAI) and *Beck Anxiety Inventory* (BAI) to analyze the level of anxiety. We identified the LCADL scale was significantly correlated with the BAI (r= 0.847; p=0.001). Also, we found that the DASI scale was negatively correlated with the BAI (r= -0.632; p=0.037), and it was verified that the lower the score, the greater the anxiety and the lower the performance in activities of daily living (ADLs). In this context, we observed that anxiety significantly impacts ADLs in the evaluated population.

Keywords: Chronic obstructive pulmonary disease; Heart rate; Autonomic modulation.

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1. Introduction

Chronic obstructive pulmonary disease (COPD) is defined as a treatable disease that persists, progresses, and can be prevented, characterized by chronic obstruction and limitation of airflow in response to significant exposure to noxious particles and gases, causing abnormal airways. Airlines [1]. COPD can be of two phenotypes, chronic bronchitis where the clinical picture is characterized by the chronic production of mucus, inflammation in the airways, metaplasia and hyperplasia of the mucous membranes and mucus connections [2], being associated with an accelerated loss of lung function and the increased frequency of COPD exacerbations [3]. A greater impairment of lung function, more intense airway inflammation, parenchymal destruction, and possibly more severe extrapulmonary disability are characteristic of patients with the pulmonary emphysema type [4].

According to epidemiological data from the state of Ceará, in 1997 non-communicable chronic diseases (NCDs) represented 32.7% of all deaths, in turn, in 2016 they reached almost half of all deaths (49.4%), representing an increase of 51.1% between 1997 and 2016, with COPD being one of the main causes with an increase of 63.6% [5]. Abajobir et al. [6] found that there was an increase in the death rate of 24.2% between the years 2005 and 2016, thus making COPD the second cause of mortality today. Contrary to previous

epidemiological studies that estimated that in 2030 COPD would be the third cause of death in the world [7-8].

In addition to dyspnea, other dysfunctions may manifest in patients with COPD, such as hypoxemia and hypercapnia, making gas exchange difficult; productive cough resulting from hypersecretion; pulmonary hypertension, due to hypoxic vasoconstriction of the pulmonary arteries and, therefore, right ventricular hypertrophy, which may lead to heart failure [1]. Therefore, this interferes with the prognosis of the disease, as the disease induces lesions in the lungs and affects cardiac function, culminating in the patient's death [10]. Among the consequences on cardiac function is the impairment of autonomic modulation, which is the variation in the intensity of heartbeats. Modulation can be analyzed both statically and dynamically. Regarding the various factors that interfere with heart rate (HR), those originating from the respiratory act stand out, as they express interference of autonomic modulation on the heart.

The Heart Rate Variability (HRV) is described by the oscillations caused by the heartbeat in the R-R intervals, sometimes influenced by the ANS [10]. A high HRV is a sign of efficient functioning of the ANS, whereas a low HRV means a change in this functioning. HRV is an indicator that precedes commitments related to the health of individuals, requiring additional investigations to find a specific diagnosis [10]. In this context, COPD, being considered a cardiorespiratory disorder, may cause changes in the ANS [11]. Studies show that patients with COPD have significant functional changes in autonomic modulation, such as increased heart rate at rest and reduced HRV. This is characterized by the ratio of increased sympathetic pathway function during rest, reduced parasympathetic pathway function, and reduced noradrenaline in blood and muscle caused by this dysfunction [12]. Patients with COPD, compared to healthy people, may have increased airway resistance, even in the absence of respiratory failure, causing the effort to breathe to increase, which may affect autonomic function.

There is a relationship between the RR and SGRQ intervals, indicating a close relationship between heart function and quality of life in patients with COPD. These patients have high levels of anxiety, which can cause an increase in heart rate, as seen by decreased RR intervals. All this translates into a decrease in the quality of life of these people. There is a relationship of changes in autonomic modulation with sustained hypoxemia, hypercapnia, increased peripheral chemoreceptors, muscle weakness, oxidative stress, stimulating metaboreceptors, pulmonary hyperinflation, bronchoconstriction, systemic inflammation, and loss of baroreflex sensitivity found in patients with COPD [12]. Therefore, the study of HRV is an essential procedure to detect physiological changes related to the ANS, as the reduction in HRV is closely related to the large number of morbidity and mortality in patients with COPD [11].

Thus, due to the high prevalence of COPD and associated cardiovascular disorders, as well as the verification of scientific evidence that points to autonomic modulation as an important outcome related to these patients, we sought to analyze autonomic modulation and factors that may be associated in patients with COPD.

2. Material and methods

2.1 Patients

A cross-sectional, observational, quantitative study was carried out in the Pulmonary Rehabilitation service of Hospital de Messejana Dr. Carlos Alberto Studart Gomes, located in the city of Fortaleza - Ceará, from March to May 2019. The study population consisted of individuals with COPD assisted in this service and the sample consisted of 11 participants, based on the study by Goulart, 2016. The study included patients with a clinical diagnosis of COPD, regardless of severity, of both genders, aged between 40 and 80 years, clinically stable (absence of exacerbation in the last 3 months prior to the survey) and who agreed to participate in the survey by through the signing of the Informed Consent Form.

Participants who had other associated chronic respiratory diseases were excluded from the study; physical or cognitive limitations that prevented the implementation of the proposed protocol and those who dropped out of the research during the methodological course of data collection. The sample consisted of patients selected for convenience and all study participants were evaluated regarding sociodemographic and clinical data, autonomic modulation, physical capacity, momentary anxiety, and activities of daily living (ADLs).

Initially, the participants were evaluated using an evaluation form previously prepared by the researchers, which contained the following sociodemographic data: age, biological sex, marital status, occupation, comorbidities, disease duration, smoking history, use of continuous supplemental oxygen, practice of physical activity, data from functional measures such as: spirometric variables (forced expiratory volume in one second (FEV1), forced vital capacity (FVC)) measures taken from the spirometry test and distance covered in the 6-minute walk test (6MWT) , which was recorded after follow-up with the house professional, stress level, medication used and use of caffeine.

Users were informally contacted and, during this conversation, the subject of the research was explained, as well as the objectives of the investigation and the ethical aspects that involve research with human beings, such as the guarantee of confidentiality, anonymity, employment of the information only for the purposes foreseen in the research and the return of the benefits obtained through this study. Signing the Informed Consent Form was an essential condition for the individual to take part in the study.

2.2 Autonomic modulation

Autonomic modulation was evaluated by analyzing Heart Rate Variability (HRV) using a Polar V800® heart rate monitor that was positioned on the participant's sternal region, with a watch attached to the right arm, for analysis of R-R intervals. corresponding to the cardiac cycle, for 1 minute and the following variables were recorded: low frequency (0.04-0.15 Hz), high frequency (0.15-0.40 Hz) [13].

It is noteworthy that the HRV analysis occurred at rest, right after the patient's break and after 5 minutes of the end of an exercise test. For this purpose, the six-minute walk test (6MWT) was performed, in accordance with the recommendations established in the guidelines of the European Respiratory Society and American Thoracic Society. The patient was encouraged to walk the maximum distance possible in a 30-meter-long corridor with a flat surface for a period of six minutes. At the end of the test, the examiner recorded the distance covered [14].

2.3 Duke Activity Status Index (DASI)

The Duke Activity Status Index (DASI) was developed and validated at Duke University, in Durham, NC, USA, in 1989. It is a questionnaire that is simple to apply and has the purpose of predicting oxygen consumption (VO_2), without the the need for maximal cardiorespiratory testing. The DASI is a short and quick questionnaire that can be applied to patients with physical limitations, being previously validated with physiological measurements, such as VO_2 [15].

Despite having been created to assess patients with heart disease, the DASI also proved to be valid and adequate to assess functional capacity in patients with moderate to severe COPD [16]. The DASI consists of 12 items involving personal care, walking, housework, sexual activity, and recreational activity. Each item presents a score proportionally based on the metabolic expenditure of each activity, measured in metabolic equivalent. For each affirmative answer, points are added, resulting in a total DASI score. The sum of the affirmative answers produces a score from zero (worst result) to 58.2 (best result). VO_2 (mL • kg−1 • min−1) is estimated using the following multiple linear regression equation: $VO_2 = 0.43 \times DASI + 9.6$, aimed at healthy individuals. The VO_2 value is estimated according to the level of physical activity described by the patient when

answering the questionnaire. Lower values indicate greater limitation in Activities of Daily Living (ADL) [15].

2.4 London Chest Activity of Daily Living (LCADL)

Garrod et al. [17] developed an instrument, the *London Chest Activity of Daily Living* (LCADL) scale, which has four domains (personal care, domestic activities, physical activities and leisure activities), with the purpose of evaluating the ADL limitation in patients with COPD. The LCADL scale has proven to be a reliable, valid, and sensitive instrument for assessing the response to a pulmonary rehabilitation program. This scale was translated and validated for Brazil by Pitta et al. [18]. The Brazilian version of the LCADL scale is a reliable and valid instrument to assess dyspnea during ADL in patients with severe COPD [19].

The LCADL scale has 15 questions covered in four domains: personal care, domestic activities, physical activities and leisure activities. Each domain item receives a score, indicated by the patient, ranging from 0 to 5, with the highest value representing the maximum inability to perform ADL. The total score can vary from 0 to 75 points, and the higher it is, the greater the limitation of ADL [17]. This scale has great applicability to assess ADL limitation in more severe patients, in whom dyspnea is a disabling symptom even for the most common day-to-day activities [20].

2.5 Assess Patient's Anxiety

To assess patients' anxiety, the Brazilian versions of two questionnaires were applied: the *State-Trait Anxiety Inventory* (STAI) and *the Beck Anxiety Inventory* (BAI). These instruments were applied before and after the 6MWT. The State-Trait Anxiety Inventory (STAI) was translated and validated for Brazil by Biaggio et al. [21], the STAI evaluates the individual's momentary anxiety and is composed of two different scales to measure two different concepts of anxiety.

State anxiety (A-state) is a transient and momentary state of anxiety related to an adversity situation and trait anxiety (A-trait) refers to a relatively stable individual tendency to anxiety, as a personal characteristic. The STAI trait anxiety scale consists of 20 statements in which the patient should mark the one that best describes how he was feeling at that moment. For each statement, the subject should mark one of the four alternatives, indicating how he/she feels: not; a little; quite; and very much (on the A-state scale); almost never; sometimes; often; almost always (on the A-trait scale) [21].

According to Cunha et al. [22], BAI is considered the gold standard for determining the sensitivity and specificity of the Anxiety Scale and its intensity. The BAI Inventory consists of a list of 21 symptoms with four alternatives each, in ascending order of the level of anxiety. The alternatives are not; lightly, it doesn't bother me much; moderately, it was very unpleasant, but I could bear it; grievously, I could hardly bear it.

The symptoms evaluated are: (1) Numbness or tingling; (2) Sensation of heat (regardless of temperature); (3) Tremors in the legs; (4) Unable to relax; (5) Fear of the worst happening; (6) Stunned or dizzy; (7) Palpitation or Acceleration of the heart; (8) No balance; (9) Terrified; (10) Nervous; (11) Feeling of Suffocation; (12) Tremors in the hands; (13) Trembling; (14) Fear of losing control; (15) Difficulty breathing; (16) Fear of dying; (17) Frightened; (18) Indigestion or discomfort in the abdomen; (19) Feeling faint; (20) flushed face; (21) Sweat (not due to heat). The Brazilian classification proposes as results the levels of 0 to 9 as minimum, from 10 to 16 as mild, from 18 to 29 points moderate, and 30 points or more severe, with a maximum score of 63 points [23].

2.6 Statistical analysis

Data were analyzed using the statistical program Statistical Package for the Social Sciences IBM® version 20.0. Data distribution was analyzed using the Kolmogorov-Smirnov test. For descriptive analysis, mean, standard deviation (for parametric data),

median and interquartile range (for non-parametric data), relative frequency and absolute frequency were used. For data comparison, the ANOVA test for repeated measures was used with the Bonferroni post hoc test. To assess the association between the variables, the Pearson/Spearman correlation test was used. P<0.05 was considered statistically significant.

3. Results

The data shown below are preliminary data performed with 11 patients diagnosed with COPD, 8 females (72.7%), with a mean age of 66.91 ± 9.39 years, with comorbidities such as Hypertension, Diabetes Mellitus, Obesity, Cardiopathies, Hepatopathy and Chronic Kidney Disease (CKD) shown in Table 1, 10 were former smokers (90.9%), with time of use from 16 to 50 years, spirometric data are also present after the use of Bronchodilator (Post-BD). Other clinical and sociodemographic information is shown in Table 1.

Table 1. Sociodemographic and preliminary clinical characterization of 11 patients with COPD participating in the research.

Variables	Parameters
Age (years) (mean±SD)	66,91 ± 9,39
Height (cm) (mean±SD)	150,10 ± 8,49
Weight (kg) (mean±SD)	60,86 ± 10,10
Gender	
Male (n/%)	3 / 27,3
Female (n/%)	8 / 72,7
Time of Illness (years) (mean±SD)	3,57 ± 3,98
Smoking time (years) (mean±SD)	37,64 ± 9,58
Smoking Load (un/day) (mean±SD)	22,36 ± 17,13
Physical activity	
Frequency (week)(n/%)	0,82 ± 1,83
Comorbidities	
Hypertension (n/%)	9 / 81,8
Diabetes Mellitus (n/%)	6 / 54,5
Cardiopathies (n/%)	2 / 18,2
Obesity (n/%)	1 / 9,1
Liver disease (n/%)	2 / 18,2
DRC (n/%)	1 / 9,1
Oxygen supplementation (n/%)	0 / 0
R: VEF^1/CVF (%) (mean±SD)	54,74 ± 18,05
VEF^1 (L) (mean±SD)	1,33 ± 0,47
VEF^1 PREDITO PÓS-BD (%) (mean±SD)	70,55 ± 29,49
CVF (L) (mean±SD)	2,46 ± 0,47
CVF PREDITO PÓS-BD (%) (mean±SD)	98,17 ±16,41

Legend. n=number of individuals; %=percentage; SD = standard deviation; Kg= kilogram; un=units; L=liters.

Table 2 shows the variables of autonomic modulation, low and high frequency, as well as the low/high ratio, in the moments before, after and 5 minutes after the 6MWT.

The results of the 6MWT, the distance covered (381 ± 129.20), predicted distance (514.82 ± 39.90) and percentage achieved (70.18 ± 20.05).

Table 2: Preliminary Six-Minute Walk Test (6MWT) characteristics of 11 COPD research participants.

V**ariables**	**Parameters**
BFPRÉ	
Initial (mean±SD)	140,91 ± 16,40
Final (mean±SD)	158,18 ± 14,70
After 5min (mean±SD)	138,19 ± 11,67
AFPRÉ	
Initial (mean±SD)	83,64 ± 6,74
Final (mean±SD)	88,18 ± 12,50
After 5min (mean±SD)	82,73 ± 6,46
BAPRÉ	
Initial (mean±SD)	80 ± 11,36
Final (mean±SD)	100,91 ± 12,20
After 5min (mean±SD)	84,18 ± 13,35
BFPÓS	
Initial (mean±SD)	19,82 ± 2,27
Final (mean±SD)	25,27 ± 5,74
After 5min (mean±SD)	23,09 ± 7,39
AFPÓS	
Initial (mean±SD)	96,45 ± 1,80
Final (mean±SD)	93,45 ± 4,76
After 5min (mean±SD)	96,36 ± 1,91
BAPÓS	
Initial (mean±SD)	0,64 ± 1,12
Final (mean±SD)	3,32 ± 3,56
After 5min (mean±SD)	2,59 ± 3,58
BF5PÓS	
Initial (mean±SD)	0,55 ± 1,29
Final (mean±SD)	3,27 ± 3,16
After 5min (mean±SD)	1,95 ± 2,91
Distance covered (m) (mean±SD)	381 ± 129,20
Predicted distance (m) (mean±SD)	514,82 ± 39,90
Percentage of predicted (%) (mean±SD)	70,18 ± 20,05

Legend. %=percentage; SD = standard deviation.

The functional capacity analyzed using the Duke Activity Status Index Portuguese version (DASI) was 22.67 ± 9.19, the mean estimate of peak oxygen was 20.41 ± 4.99 and the metabolic index was 5.52 ± 1.13. The activity of daily living analyzed by the London Chest Activity Scale (LCADL) was 21.64 ± 11.85. And the anxiety analyzed through the

State-Trait Anxiety Inventory (STAI) and the Beck Anxiety Inventory were, respectively, 49.82 ± 6.75 and 20.36 ± 12.90. All data are described in Table 3.

Table 3: Characteristics of the anxiety and tiredness questionnaires (LCADL, IDATE, BAI, DASI) of the 11 participants diagnosed with COPD.

Variables	**Parameters**
LCADL **(pts)** (mean±SD)	**21,64 ± 11,85**
IDATE **(pts)** (mean±SD)	**49,82 ± 6,75**
BAI **(pts)** (mean±SD)	**20,36 ± 12,90**
DASI **(pts)** (mean±SD)	**22,67 ± 9,19**
Mets (mean±SD)	**5,52 ± 1,13**
VO_2 (mean±SD)	**20,41 ± 4,99**

SD = standard deviation; pts = points.

Based on Pearson's correlation, when comparing the LCADL scale with the BAI, the relationship was positive and strong (r= 0.847; p=0.001) showing significance, where the higher the LCADL score, the greater the anxiety and the lower the physical performance.

When compared to the DASI that evaluates physical performance in relation to metabolic expenditure with the BAI, the relationship was negative and moderate (r= -0.632; p=0.037), where the lower the score, the greater the anxiety and the lower the performance in ADL's. Statistical significance was observed between the high pre-6MWT frequency and age, with a moderate negative correlation, where the higher the age, the lower the AFPré (r= -0.703; p=0.016). In the relationship between low frequency and high frequency pre with FEV^1, where it is related to the degree of obstruction, there was a positive and strong correlation, with significance (r=0.987; p=0.002).

4. Discussion

The study showed that there were more women than men, this can be explained by the small number of study participants, but also because women seek the health service more [24], since the prevalence of COPD is higher in men than in women [1]. As for smoking, it was observed in the sample that 90% of the patients were former smokers, which is related to the cause of COPD and a factor that decreases lung capacity, demonstrated by reduced values of spirometry and consequently physical capacity, detected by the test of the six-minute walk through the distance covered [1].

Schettino et al. [25], in their study, found that patients with COPD have chronic comorbidities, mainly cardiovascular ones such as congestive heart failure (CHF) and systemic arterial hypertension. The prevalence of cardiovascular comorbidities is five times higher in patients with COPD than in others who do not have the disease, with hypoxemia being one of the common pathophysiological mechanisms in patients with severe COPD and in cardiovascular disease. Hypoxemia, when associated with limited oxygen transport, can lead to complications of ischemic disease due to coronary stenosis.

The comorbidities found in the study are risk factors for cardiovascular diseases that affect autonomic modulation, including obesity, diabetes mellitus and SAH. In addition to cardiovascular diseases being comorbidities found in COPD, anxiety and depression are also among the most common [26-27].

Cases of depression are being even more significant in patients with COPD than even in people with cancer, AIDS, heart disease and chronic kidney disease. These rates are even higher in patients with acute exacerbation and oxygen-dependent patients. A high prevalence is also attributed to patients with COPD, women, who continue to smoke.

Patients with COPD associated with depression do not perform well on a six-minute walk test [28].

According to the study by Minghelli [30], groups of physically active elderly have a lower rate of anxiety and depression than sedentary ones. Showing that there is a correlation between more anxious patients and poor adherence to the 6MWT, which assesses physical capacity. A study demonstrated that patients with COPD had a decrease in both sympathetic and parasympathetic activity, related to a reduction in ANS functioning, showing that in patients with COPD there is a reduction in HRV, consequently its alteration [31].

This study has some limitations that must be considered. the interviews were started after the approval of the ethics committee of the Hospital de Messejana, with a reduced period for the completion of the course conclusion work, with that our initial sample had only 11 participants diagnosed with COPD and referred for the 6MWT. The interviews took place on 15 days with intervals of 2 times a week, according to the availability of the time offered by the hospital. Another predominant factor was the climatic conditions, where the place where the test was performed was exposed to these conditions, therefore, the exam was canceled and rescheduled by the institution's professionals.

However, considering these limitations, the study provides important indicators on heart rate variability in patients with COPD. Finally, as this is research of clinical importance, we will continue the collection to make it more relevant.

5. Conclusion

It can be observed that anxiety impacts on ADLs, where the greater the anxiety, the lower the ability to perform physical activities. The comorbidities found in COPD were found in the study participants, confirming this prevalence.

As this is a preliminary study, the questions will still be explored, the general objective has not been solved, but with the analysis it will be answered. The number of participants was also reduced, requiring a study with a larger number of participants and a longer collection time.

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Supplementary Materials: None.

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