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RESEARCH ARTICLE

Assessment of heart rate variability in participants with chronic obstructive pulmonary disease

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ABSTRACT

Background: Chronic obstructive pulmonary disease (COPD) is one of the main causes of morbidity and mortality worldwide. COPD kills half a million people in India every year, more than those who die due to tuberculosis, malaria, or Acquired immune deficiency syndrome, and 30 million people suffer with COPD in India.[1] The hypoxemia due to COPD might be associated with autonomic dysfunction which could be evaluated with heart rate variability (HRV). **Aims and Objective:** To determine the HRV in patients with COPD and to compare with normal individuals. **Materials and Methods:** This cross-sectional study was carried out in 30 COPD patients attending the Department of Pulmonology, SRM Medical College Hospital and Research Centre and 30 age and sex-matched healthy individuals as a control group. A detailed history from the participants, such as weight and height, was obtained, and HRV parameters such as mean RR, mean HR, successive normal sinus RR intervals >50 ms (NN50), the percentage of successive normal sinus RR intervals >50 ms (pNN50), root mean square of successive heartbeat interval differences (rMSSDs), high frequency (HF), low frequency (LF), and LF/HF were estimated using physio-pac instrument. **Results:** HRV parameters such as rMSSD, NN50, PNN50, LF, HF, and LF/HF ratio show significant differences between the COPD and control ($P < 0.05$), which indicates sympathovagal imbalance. **Conclusion:** HRV analysis shows that COPD participants have an autonomic imbalance suggestive of an increased sympathetic tone or decreased parasympathetic tone. Sympathetic overactivity may lead to cardiovascular disease development in patients with COPD.

KEY WORDS: Autonomic Dysfunction; Chronic Obstructive Pulmonary Disease; Heart Rate Variability

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is one of the several chronic diseases that are becoming increasingly problematic worldwide. Tobacco smoking is by far the major risk factor for COPD, and the prevalence of the disease in different countries is related to rates of smoking and time of introduction of cigarette smoking. Contribution of occupational risk factors is quite small but may vary depending on a country's level of economic development.[2]

A small number of cases, 1-2%, may be caused by a genetic condition, alpha1-antitrypsin deficiency, in which a deficiency in an elastase inhibitor causes elastic fibers of the lung to be broken down.[3] COPD includes chronic obstructive bronchiolitis with fibrosis and obstruction of small airways, and emphysema with enlargement of airspaces and destruction of lung parenchyma, loss of lung elasticity, and closure of small airways. Cardiac arrhythmia and sudden death are common and important causes of mortality in

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patient with COPD.[4] The quantification of the balance of parasympathetic and sympathetic nervous system (SNS) activity is important in understanding the pathophysiology of COPD and might be useful clinically in the treatment of a patient with COPD.[5]

The heart rate variability (HRV) has been widely used to assess the behavior of the autonomic nervous system (ANS). It is non-invasive and inexpensive and can be used to describe phenomena related to ANS in healthy and unhealthy participants.[6] It is a conventionally accepted term to describe the fluctuations in the intervals between consecutive heartbeats (RR intervals) and is directly related to the performance of the ANS on the sinoatrial node. It implies that an individual with low HRV has greater pre-disposition to develop cardiovascular problem.[7] Under physiological conditions, the greater HRV better is the health condition of the participant.[8] HRV analysis has been increasingly emphasized for being an important method for early diagnosis of cardiovascular diseases.[6]

In COPD, there occurs ventilatory limitation due to increase in pulmonary dead space and decrease in gas exchange. The hypoxic constriction, high pulmonary vascular resistance, and vascular damages lead to increase in right ventricle afterload. These changes cause the appearance of the cor pulmonale, which might lead to right heart failure in COPD patients. Along with cardiovascular changes, autonomic alterations also occur. These alterations can be evaluated by HRV. The abnormal HR adjustments, reflected by HRV alterations, may be related with the severity of disease. Heart autonomic dysfunction may lead to the occurrence of arrhythmias and sudden cardiac death in these patients. Since there were only a few studies which have analyzed HRV in COPD patients, we aimed to determine the HRV in patients with COPD and to compare with normal individuals.

MATERIALS AND METHODS

This cross-sectional study was carried out in 30 COPD patients attending the outpatient unit of the Department of Pulmonology, SRM Medical College Hospital and Research Centre. 30 age and sex-matched (males - 23, females - 7) healthy individuals were taken as control group. This study was approved by the Institutional Ethical Committee (IEC No; 152/IEC/2012) and conducted in accordance with the ethical guidelines for biomedical research on human participants by the Central Ethics Committee on Human Research, Indian Council of Medical Research (ICMR)-2000 and those as contained in "Declaration of Helsinki." Written informed consent was obtained from the participants after explaining to them the procedure. Participants with history of any cardiac diseases, hypertension, diabetes, neurological sequelae or associated respiratory diseases, history of alcohol abuse or taking vasodilator drugs, angiotensin converting enzyme inhibitors, antihypertensives and systemic corticosteroids, or medications that affect HR were excluded from the study. The control group (healthy individuals) included participants who presented normal pulmonary function tests.

The COPD patients and the healthy volunteers were well explained about the procedures of the proposed protocol and were familiarized with the equipment and the investigators. All participants were instructed to refrain from caffeine and/or any other stimulating beverage, to avoid moderate or excessive efforts on the day before the tests and to get a good sleep at night. The COPD patients were instructed to keep the medication prescribed by the doctor during the treatment. However, the use of inhalatory corticoids for 12 h or bronchodilators of short duration 6 h before the tests were interrupted. All procedures were carried out in an acclimatized room, at ambient temperature.

HRV analysis was performed using a computerized 8 channel polygraph (Model: Physiopac, Medicaid Systems, Chandigarh, India) in the research laboratory of the Department of Physiology, SRM Medical College Hospital and Research Centre. Cost of the analysis was borne by the investigator and the concerned department. There was no financial liability on the participant.

HRV represents the variations of R-R intervals (R-Ri) duration of the electrocardiogram, which depends on the sympathetic and parasympathetic nervous system (PNS). This method consists on a consists of a non-invasive autonomic assessment, and its analysis can be performed either in time domain (TD) or in the frequency domain (FD).

HRV parameters such as mean RR, mean HR, successive normal sinus RR intervals >50 ms (NN50), percentage of successive normal sinus RR intervals >50 ms (pNN50), root mean square of successive heartbeat interval differences (rMSSDs), high frequency (HF), low frequency (LF), and LF/HF were estimated.

All the data were entered in MS Excel spreadsheet, and the statistical analysis was done using SPSS version 17.0. The data were expressed as mean ± standard deviation. Descriptive tables were generated, and Student's *t*-test was used to demonstrate the findings. $P < 0.05$ was considered to be statistically significant.

RESULTS

In this study, we compared the HRV parameters between the COPD and healthy controls. Table 1 shows that there was no significant difference in the anthropometric data between the two groups, and they were comparable. When comparing the TD parameters of HRV between COPD and control (Table 2), there were significant differences in the parameters such as

rMSSD, NN50, and pNN50 between COPD and control group (P = 0.001). Table 3 compares the FD parameters (FFT-non-parametric spectrum power ms²) of HRV between COPD and control. There was a significant difference when comparing the values of LF, HF, and LF/HF ratio between the two groups with $P < 0.05$.

DISCUSSION

The results of our study indicate that there is sympathovagal imbalance in participants with COPD. The ANS and the balance between parasympathetic and sympathetic output play a key role in overall cardiovascular homeostasis. Cardiac arrhythmias are common in COPD patients due to autonomic dysfunction and poor prognosis has been noted in association with these arrhythmias, particularly ventricular arrhythmias. In addition, it is likely that abnormal activity of ANS can contribute to airway narrowing and may be relevant to the pathogenesis of COPD.[9,10] HRV measurement provides a non-invasive assessment of cardiovascular autonomic functions.[11,12]

Table 1: Comparison of anthropometric data between COPD and control group

Parameters	Mean±SD		*P* value
	Group I COPD (*n*=30)	Group II control (*n*=30)	
Age	43.72±4.42	43.72±4.34	0.99 NS
Height (cm)	158.34±7.92	159.47±5.42	0.53 NS
Weight (kg)	59.31±7.73	62.27±6.12	0.11 NS
BMI (kg/m²)	23.70±3.23	24.45±2.81	0.43 NS

NS: Not significant, COPD: Chronic obstructive pulmonary disease, SD: Standard deviation, BMI: Body mass index

Table 2: Comparison of time domain data between COPD and control group

Parameters	Mean±SD		*P* value
	Group I COPD (*n*=30)	Group II control (*n*=30)	
Mean RR (ms)	760±130	800±100	0.27 NS
Mean HR (bpm)	80.08±13.12	76.71±9.29	0.25 NS
rMSSD (ms)	15.45±7.12	17.89±1.82	0.001 S
NN50 count	4.10±4.53	7.60±4.52	0.001 S
pNN50%	1.76±1.96	4.57±3.67	0.001 S

S: Significant, NS: Not significant. COPD: Chronic obstructive pulmonary disease, HR: Heart rate, rMSSD: Root mean square of successive heartbeat interval differences, SD: Standard deviation

Table 3: Comparison of frequency domain (FFT-non-parametric spectrum power n.u) data between COPD and control group

Parameter (power n.u)	Mean±SD		*P* value
	Group I COPD (*n*=30)	Group II control (*n*=30)	
LF (n.u)	74.1±11.08	58.02±4.45	0.016 S
HF (n.u)	22.6±5.4	27.98±6.4	0.004 S
LF/HF	3.38±1.3	1.4±0.4	0.0001 S

S: Significant, COPD: Chronic obstructive pulmonary disease, SD: Standard deviation, n.u: Normalized unit, LF: Low frequency, HF: High frequency

In our study, as shown in Table 2, the HRV analysis revealed that COPD patients had a significant decrease in the TD parameters such as rMSSD, NN50, and pNN50 ($P < 0.05$). In the TD, statistical methods were used to quantify the variation of the standard deviation or the differences between successive R-Ri. rMSSD is most common TD measure of short-term HRV and measures parasympathetic modulation of HRV. NN50 is the number of interval differences of successive NN intervals that are >50 ms. NN50 correlates highly with rMSSD and measures parasympathetic modulation of HR. pNN50 is the fraction of NN50 intervals as a proportion of a total number of NN intervals and also correlates highly with rMSSD. Our findings show that there was a decrease in parasympathetic activity. However, though statistically not significant, we did observe an increase in mean HR and decrease in mean RR in participants with COPD when compared with controls (Table 2).

The FD analysis decomposes the variability in HF, LF, and very low frequencies (VLF) bands. The VLF components, with frequencies lower than 0.04 Hz, do not have a defined physiological explanation and are related to a renin-angiotensin-aldosterone system and thermoregulation. The LF, between 0.04 and 0.15 Hz, is mediated by the parasympathetic and SNSs, with predominance of the last. The HF band, between 0.15 and 0.40 Hz, corresponds to the respiratory modulation and is mediated only by the PNS.

LF nu in patients with COPD was significantly greater ($P < 0.05$) than in normal participants. HF nu was significantly lower in patients with COPD than in normal participants ($P < 0.05$) implying a decreased parasympathetic response. Our result is in concordance with Scalvini et al.[13] Decreased parasympathetic nervous system activity and increased sympathetic activity will lead to reduce the HRV. Specially, HF activity is linked to the parasympathetic system. LF activity reflex is mixed by both SNS and PNS activity.[14] In our study, the results of LF, HF, and LF/HF ratio shows sympathetic overactivity or parasympathetic under activity in participants with COPD since the values for LF is increased, HF is reduced, and LF/HF ratio is increased in COPD (Table 3). These results were consistent with previous observations that autonomic nervous dysfunction exists in COPD.[5,10]

In patients with COPD the hypoxia, oxidative stress, physical inactivity, systemic inflammation, and high intrathoracic

pressure might cause an increase in sympathetic activity. According to Heindl et al.[15] and Hardy et al.,[16] patients with COPD often develop hypoxia which may be present intermittently (e.g., during exacerbations or related to desaturations during sleep) or sustained in more severe cases. According to Tamisier et al.,[17] acute exposure to hypoxia increases chemoreflex activation of sympathetic outflow in healthy humans and sustained hypoxemia causes a long-lasting increase in muscle sympathetic nerve activity, as recorded directly from muscle fascicles of the common peroneal nerve via intraneural microelectrodes in healthy humans. Scalvini et al.[13] and Stein et al.[18] observed sympathetic overactivity in both hypoxemic and normoxemic patients with COPD.

Our study is in concordance with Parati et al.[19] that HRV represents an index of autonomic control of the heart and is reduced in patients with overactivity of the SNS. Our results are contrary to Volterrani et al.,[5] who observed that those patients with COPD showed reduced HRV at rest compared to the healthy control participants and in addition, patients with COPD had a depressed HRV response to both the sympathetic and vagal stimuli. The findings of the Copenhagen City Heart Study[20,21] suggested that the etiology of arrhythmia in patients with COPD is multifactorial and includes a number of risk factors such as hypoxemia, acidosis, and reduced forced expiratory volume in 1 second. However, a direct association between arrhythmias and sympathetic activity in patients with COPD has not been established yet. As COPD is a disease with high morbidity and mortality and coexists with cardiovascular disease, it is necessary to give a higher level of care to these patients.

CONCLUSION

In our study, the HRV analysis of COPD and control shows that COPD participants had an autonomic imbalance suggestive of an increased sympathetic tone or decreased parasympathetic tone. Sympathetic overactivity may lead to cardiovascular disease development in patients with COPD. Thus, the HRV analysis done to predict the autonomic imbalance will be helpful for planning the novel therapeutic and preventive approaches in the care of the patient with COPD.

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