Section: Physiology

Original Research Article

EVALUATION OF SYMPATHO-VAGAL ACTIVITY IN CHRONIC OBSTRUCTIVE PULMONARY DISEASE PATIENTS COMPARED TO HEALTHY INDIVIDUALS IN A TERTIARY CARE HOSPITAL

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ABSTRACT

Background: Chronic obstructive pulmonary disease (COPD) is defined by the World Health Organization (WHO) and the 2023 Global Initiative for Chronic Obstructive Lung Disease (GOLD) report as, "a heterogeneous lung condition characterized by chronic respiratory symptoms (dyspnea, cough, expectoration, exacerbations) due to abnormalities of the airway (bronchitis, bronchiolitis) and/or alveoli (emphysema) that cause persistent, often progressive, airflow obstruction" Numerous studies have indicated the presence of cardiac autonomic dysfunction in individuals with COPD. Heart rate variability (HRV), is a non-invasive tool to study autonomic activity, the oscillation in the intervals between consecutive heart beats. A sympathetic shift in HRV is seen with increased heart rate associated with increased mortality in cardiac diseases and in COPD which independently provide clinically useful information as a prognostic marker. It is hypothesized that, as both sympathetic dominance and systemic inflammation may contribute to cardiovascular morbidity in COPD, these may be associated. Therefore, we investigated cardiac autonomic dysfunction using HRV measurements and examined its physiological and clinical correlates. **Aims and Objectives:** This study aimed to find out the changes in sympatho-vagal activity in COPD (chronic obstructive pulmonary disease) patients compared to healthy individuals. Further, it also attempted to find out any changes in SDNN between COPD patients and healthy individuals and also to compare Low Frequency power, High Frequency power and LF/HF ratio between COPD patients and healthy individuals. **Materials and Methods:** An observational cross sectional study was conducted in the Physiology Department of a tertiary care health centre on 144 subjects, among which 73 were COPD patients and 73 were apparently healthy patients. The study revealed that cases and control were age, height, weight, and gender matched. Heart rate variability parameters such as Low Frequency power High Frequency power, LF/HF ratio, SDNN (standard deviation of NN intervals) were measured. **Results:** It showed that mean LF in cases was significantly more compared to controls. LF/HF ratio was significantly more in the COPD cases than the controls. SDNN in the cases was significantly lower than the controls whereas HF in cases was more than that of the control but that changes were not statistically significant. There was no significant correlations between the PFT parameters and Short term heart rate variability parameters. **Conclusion:** Although there was a decrease in both sympathetic and parasympathetic cardiac regulation, the sympathetic activity was seen to be predominant. HRV being a straightforward, easily accessible method can be used in evaluation of the cardiovascular prognosis in COPD.

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is defined by the World Health Organization (WHO) and the 2023 Global Initiative for Chronic Obstructive Lung Disease (GOLD) report as, "a heterogeneous lung condition characterized by chronic respiratory symptoms (dyspnea, cough, expectoration, exacerbations) due to abnormalities of the airway (bronchitis, bronchiolitis) and/or alveoli (emphysema) that cause persistent, often progressive, airflow obstruction".[1] It actually comprises two simultaneous diseases: chronic bronchitis (noted for excessive mucus production) and mucosal oedema. The presence of these two disease forms leads to bronchoconstriction, coughing, sputum production, frequent respiratory infections, and pulmonary emphysema. In both COPD phenotypes, especially in cases showing overlapping features, the disease has a significant impact and in the developed world it is one of the major causes of death.[2] Strategies to improve the overall prognosis of patients with COPD are therefore highly desirable. Guideline based therapy with anticholinergics and inhaled beta-agonists improves functional status (and hence the daily symptom burden) in many patients, but there is no reduction in mortality in patients with COPD using this pharmacotherapy.[2,3] This makes pathophysiological concepts and innovative studies relating to COPD an extremely important topic.

Numerous studies have indicated the presence of cardiac autonomic dysfunction in individuals with COPD. For the past three decades, the prevailing belief has been (and continues to be) that patients, particularly elderly individuals, with COPD face an elevated risk of cardiovascular disease.[4] COPD can double or triple the likelihood of developing or worsening cardiovascular conditions. Concurrently, it seems that low-grade systemic inflammation in COPD patients correlates with a heightened risk of cardiovascular damage.[5] In addition to ischemic heart disease, various supraventricular and ventricular arrhythmias, along with significant conduction abnormalities, frequently occur in conjunction with COPD.[4,6] Numerous factors have been identified as potential contributors to cardiovascular disease in COPD patients. The theories surrounding hypoxemia, hypercapnia, and acid-base balance disturbances have all been suggested as potential causes of cardiac arrhythmias.[6] For the past three decades, the prevailing belief has been (and continues to be) that patients, particularly elderly individuals, with COPD face an elevated risk of cardiovascular disease.[4] COPD can double or triple the likelihood of developing or worsening cardiovascular conditions. Concurrently, it seems that low-grade systemic inflammation in COPD patients correlates with a heightened risk of cardiovascular damage.[5] In addition to ischemic heart disease, various supraventricular and ventricular arrhythmias, along with significant conduction abnormalities, frequently occur in conjunction with COPD.[4,6] Numerous factors have been identified as potential contributors to cardiovascular disease in COPD patients. The theories surrounding hypoxemia, hypercapnia, and acid-base balance disturbances have all been suggested as potential causes of cardiac arrhythmias.[6] The underlying explanation is that hypoxemia, hypercapnia, and acid-base imbalances enhance the electrical heterogeneity of the myocardial tissue in the ventricular wall, leading to the emergence of potentially life-threatening episodes of re-entry of myocardial electrical currents during arrhythmias.[6]

Heart rate variability (HRV), is a non-invasive tool to study autonomic activity, the oscillation in the intervals between consecutive heart beats. The methodology for its measurement includes several indices in time and frequency domains that quantify parasympathetic and sympathetic modulation of heart rate. Normal heart rate modulation has a parasympathetic dominance.[7] Sympathetic dominance in HRV, i.e. a shift in the balance towards the sympathetic, marks a poor prognosis in renal failure, heart failure, diabetes, and postmyocardial state by predisposing to arrhythmias and sudden death.[8-12]

A neurohumoral association with sympathetic overactivity promoting endothelial dysfunction and systemic inflammation has been proposed in COPD and other disease states.[3,14] A sympathetic shift in HRV is seen with increased heart rate associated with increased mortality in cardiac diseases and in COPD which independently provide clinically useful information as a prognostic marker. It is hypothesized that, as both sympathetic dominance and systemic inflammation may contribute to cardiovascular morbidity in COPD, these may be associated. Therefore, we investigated cardiac autonomic dysfunction using HRV measurements and examined its physiological and clinical correlates.[15-17]

Aims and Objectives

This study aimed to find out the changes in sympatho-vagal activity in COPD (chronic obstructive pulmonary disease) patients compared to healthy individuals. Further, it also attempted to find out any changes in SDNN between COPD patients and healthy individuals and also to compare Low Frequency power, High Frequency power and LF/HF ratio between COPD patients and healthy individuals.

MATERIALS AND METHODS

This cross-sectional observational study was undertaken at a tertiary care hospital of Kolkata, West Bengal, India. Before commencement of the study, the ethical clearance was obtained from the institutional Ethics Committee. The study was carried out in the Department of Physiology in collaboration with Department of Respiratory Medicine of the

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aforementioned hospital. Patients diagnosed with COPD in Department of Respiratory Medicine out Patient Department were selected for the study, as per the inclusion and exclusion criteria. The inclusion criteria included both male and non- pregnant female adult (>18 years) patients, of COPD attending the Department of Respiratory Medicine in Out Patient Department of the hospital. Those suffering from respiratory ailments like asthma, bronchiectasis, and acute exacerbation of COPD or from cardiovascular diseases like heart failure, significant arrhythmias, recent myocardial infarction or patients with severe psychiatric disorders were excluded from the study. Patients using Beta-blockers, anticholinergics, or tricyclic antidepressants or those with active substance abuse disorders or those unwilling to give consent were also not included in the study. Apparently normal healthy subjects were taken as the control group.

The study subjects were selected by convenient sampling. Sample size was calculated using the following formula:

$n = (Z)2pq/ d^2$

Prevalence of COPD in South India is around 6.8-10.4 %.

So, in this study p was taken as 10.4%.

Margin of error (d) was taken as 5%

Therefore $n= [(1.96)2 \times 0.0104\times (100-0.0104)]/(0.05)^2 = 145$ (Approximately)

So, a sample size of 146 was considered for this study.

After obtaining informed written consent from all the study subjects, they were divided into two groups. One group consisted of 73 patients of COPD and the other group comprised of an equal number of age and sex matched healthy controls. The study was undertaken at the department of Physiology of the tertiary care hospital. Detailed history of each subject was recorded and following that physical examination was done. Pulmonary Function Test parameters of the control subjects were ensured to be within normal limits.

Short term HRV test was performed on both the cases and the controls, strictly maintaining the standard protocol. The subjects were asked to abstain from tea, coffee, sedatives 12 hours prior to the test66. They were advised to have a sound sleep the night before the test, and to avoid smoking in preceding 24 hours of the test. Autonomic function testing was done with Physiograph Polyrite-D instrument with bioamplifiers, 4 channels and accessories (RMS latest software-Version 3.0.16) in Autonomic Function Research Laboratory maintaining the room temperature between 18°C and 25°C. Prior to the study, the subjects were asked to take rest in supine position for 15 minutes. Time domain and frequency domain (spectral analysis of Short-term (5 minutes) HRV was recorded. SDNN value over 100 ms was considered as normal, a SDNN between 50 -100 ms was considered as moderate risk, and SDNN value less than 50 ms was considered to be high-risk, related to cardiovascular risks. LF-HF ratio less than 1 was used as an indicator of good cardiovascular health.[18]

RESULTS

Table 1: Baseline characteristics of the study subjects

Parameters	Case Mean (±SD)	Control	P values
Age (years)	46.01±10.05	44.9±11.41	>0.05
Height (cm)	158.34±3.05	159.64±6.63	>0.05
Weight(kg)	64.36±8.1	62.34±8.85	>0.05
BMI(kg/m2)	25.59±3.06	24.39±2.48	>0.05

[Table 1] shows that the baseline characteristics of the study subjects were matched with those of the controls. Among the cases 54.8% were males and 45.2% were females while 64.4% of the controls were male and 35.6% were females.

Table 2: Comparison of PFT parameters between cases and controls

Parameters	Case	Control	P values
FEV1	59.33±10.8	93.58±6.3	0.0001 *
FVC	50.93±17.7	93.52±17.2	0.0001 *
FEV1/FVC	85.32±25.9	99.77±16.7	0.0001 *

P value <0.05 was considered as significant

[Table 2] shows that FEV1, FVC, FEV1/ FVC was significantly decreased in COPD cases than that of the healthy controls.

Table 3: Comparison of Cardiovascular parameters between cases and controls

Parameters	Case	Control	P values
DBP	80.71±5.2	82.34 ± 10.6	0.242
SBP	121.92 ±5.1	125.6 ±12.6	0.025
HR	78.22±4.6	77.46 ±8.8	0.520

P value <0.05 was considered as significant

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In the present study [Table-3] shows that mean of HR (78.22±4.6), SBP (121.92 ±5.1), DBP (80.71±5.2) in cases were not significantly different from that in the control [HR (77.46 ±8.8), SBP (125.6 ±12.6), DBP (82.34 ± 10.6)], though HR and DBP were more in cases than that of the control but those changes were not significant.

Table 4: Comparison of short term Heart Rate Variability parameters between cases and controls

Parameters	Case	Control	P values
LF	43.65±17.9	29.95±14.1	0.0001*
HF	36.01±13.8	35.3±13.7	0.755
LF/HF	2.10 ±5.42	0.99 ±0.425	0.04 *
SDNN	39.4±20.1	81.5±15.6	0.0001 *

P value <0.05 was considered as significant

[Table 4] shows that mean LF of the cases was significantly (p=0.0001) more compared to controls. LF/HF ratio was significantly (P-value- 0.04) more in the COPD cases than the controls. SDNN in the cases was significantly lower (P value- 0.0001) than the control whereas HF in cases was more than that of the control but that changes was not significant (p=0.755).

Table 5: Proportion of COPD cases according to LF/HF ratio

LF/HF ratio	Case	Control	P value
≥1	67.1%(n=49)	26.1% (n=19)	< 0.00001*
<1	32.9% (n=24)	73.9% (n=54)	

**P value <0.05 was considered as significant*

[Table 5] shows LF:HF ratio was more than 1 in 67.1% cases and in 26.1% of controls. This difference in proportion between the cases and controls was statistically significant, p-value less than 0.01.

Table 6: Proportion of COPD cases compared to controls according to SDNN value

	Case	Control	P value
High risk (<50ms)	79.5%(n=58)	1.3%(n=1)	< 0.00001*
Moderate risk (50-100 ms)	19.2%(n=14)	86.6%(n=63)	
Normal value (>100ms)	1.3%(n=1)	12.4`%(n=9)	

P value <0.05 was considered as significant

The present study [Table 6] showed 79.5% (n=58) of COPD cases had SDNN of less than 50 ms, whereas 19.2 % cases had between 50 -100 ms and 1.3 % of cases had normal SDNN values. whereas 87.6%(n=64) of control had SDNN between 50 - 100ms, no one had SDNN less than 50ms. And the change is significantly different in cases compared to control.

Table 7: Correlation of short term heart rate variability parameters with FEV1

subjects			FVC	FEV1	FEV1/FVC
Case	LF	r(Pearson Correlation coefficient)	-0.557	-0.113	-0.063
		p- value	0.255	0.342	0.598
	HF	r(Pearson Correlation coefficient)	-0.018	-0.050	-0.085
		p- value	0.883	0.674	0.475
	LF/HF	r(Pearson Correlation coefficient)	0.116	0.086	0.039
		p- value	0.327	0.469	0.745
	SDNN	r(Pearson Correlation coefficient)	0.006	-0.099	-0.086
		p- value	0.960	0.404	0.471

**P value <0.05 was considered as significant*

[Table 7] shows that there was no significant correlations between the PFT parameters and Short term heartrate variability parameters.

DISCUSSION

The present study was conducted in the Department of Physiology, of a tertiary care health centre on 146 patients among which 73 were cases of COPD and 73 were control. Here, we reported the results of short-term HRV in COPD patients. Supporting evidence that patients with COPD have a lower HRV was identified in our study. Since COPD causes cardiac autonomic dysfunction, which can be attributed to a number of underlying disease-related variables, it has a deleterious impact on practically all HRV parameters.

[Table 1] shows the baseline characteristics of the study subjects. Mean age of the cases (36.92±9.2 years) was less than that of the control (38.33±8.5 years) but that is not significantly different. Mean height of the cases (158.34±3.05 cm) was also less than that of the control (159.64±6.63cm) but mean weight of the cases (36.92±9.2 years) was more than that of the control (38.33±8.5 years). There was no statistically significant difference between the baseline parameters like age, height and weight among the cases and controls. In this study, maximum number of patients was male in both cases (54.8%) and controls (64.4%).

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[Table 2] shows that FEV1, FVC, FEV1/ FVC was significantly decreased in COPD case than that of the healthy control. Mean of FEV1 in cases was 59.33±10.8, whereas mean of FEV1 in control was 93.58±6.3 which was significantly (p=0.0001) decreased in COPD cases. FVC also significantly (p=0.0001) decreased in cases (50.93±17.7) compared to controls (93.52±17.2). The FEV1/FVC was significantly decreased in cases (85.32±25.9) compared to control (99.77±16.7).

The HRV frequency domain indices of healthy controls and COPD patients were compared and studied in this study. The power in the low frequency band (LF; 0.04–0.15 Hz), high frequency band (HF; 0.15–0.40 Hz), and the ratio of LF to HF (LF:HF) were among the indicators that were recorded.

Low frequency power is physiologically linked with baroreflex and sympathetic modulation of heart rhythm under normal breathing condition19. LF was studied between COPD patients and healthy controls in several studies,[20,21-25] with one study finding that COPD patients had higher LF19. Five studies reported reduced LF in patients with COPD. In the present study [Table 4] mean of LF was 43.65±17.9 in cases which was significantly (p=0.0001) more compared to control (29.95±14.1) which corroborates with the previous study.

High frequency power band is the respiratory band and reflects the effect of parasympathetic control on the heart rhythm corresponding to respiratory sinus arrhythmia.[20] Six studies,[20,21-25] compared absolute HF between COPD patients and healthy controls of which,[4,20,22-24] reported relatively higher HF in healthy controls while the 2 studies 21,25 reported higher HF in COPD patients. The present study shows [Table 4] that mean of HF in cases was 36.01±13.8 that was more than that of the control (35.3±13.7) but that changes was not significant (p=0.755).

The ratio of LF/HF power has been classically translated as the measure of the balance between sympathetic and parasympathetic (vagal) controls on the heart rhythm. This was based on the assumption that the LF is solely contributed by the sympathetic cardiac rhythm control while the HF is mainly related to the parasympathetic, vagal control of the heart rhythm.[19] Three previous studies compared LF:HF ratio between COPD patients and healthy controls of which 2 reported relatively higher 26-27 LF:HF in COPD patients and the third study reported otherwise 21. The present study showed that [Table 4] LF/HF ratio was significantly (P-value- 0.04) more in the COPD cases (2.10 ±5.42) than the control (0.99 ±0.425). [Table 5] showed 67.1% of COPD cases had LF/HF ratio of more than 1,whereas 32.9% cases had LF/HF ratio of less than 1 and 26.1% of control had LF/HF ratio of more than 1,whereas 73.9% cases had LF/HF ratio of less than 1. And the change is significantly different in cases compared to control.

SDNN in the cases (39.4±20.1) was significantly lower (P-value- 0.0001) than the control (81.5±15.6) as shown in [Table 4]. The present study showed that [Table 6] SDNN in the cases (39.4±20.1) was significantly lower (P-value- 0.0001) than the control (81.5±15.6). The present study (Table-4) showed 79.5%(n=58) of COPD cases had SDNN of less than 50ms, whereas 19.2 % cases had between 50 -100 ms and 1.3 % of cases had normal SDNN values. whereas 87.6%(n=64) of control had SDNN between 50 -100ms, no one had SDNN less than 50ms. This change is significantly different in cases compared to control.

SDNN related to the influence of both arms of the ANS on the heart rhythm. Thus, higher SDNN is associated with interpreted as a strong physiological connection between the ANS and the heart.[19]

In this study, there was no significant relationship between the PFT parameters and the short-term HRV parameters. It contradicts the results of Bedard et al,[28] who found a substantial but non-multivariate connection between the 24-hour LF: HF ratio and FEV1 ($r = 0.342$; $p = 0.028$). Given that a low LF:HF ratio denotes parasympathetic activity dominance.[29] these findings imply that predominance of vagal modulation is associated with increased disease severity (lower FEV1 values). The vagal influence on airway narrowing (bronchoconstriction) may be the cause of this, even if it may not be related to the patient's clinical condition.[30]

An alert state is the physiological result of the autonomic nervous system's reaction to a stressful event, which involves a rise in sympathetic activity and a fall in parasympathetic activity.[31] It's interesting to note that an increase in sympathetic neural activity and a decrease in parasympathetic nerve activity are linked to major chronic diseases like cancer,[32] obesity and metabolic syndrome,[33] heart failure,[34] cirrhosis.[35] smoking,[36] and hypertension37. According to our research, patients with COPD exhibit significant alterations in all HRV parameters, including the LF band, which measures the combined effects of the heart's sympathetic and vagal functions, with the sympathetic controlling the majority of these changes38. Concurrently, there was a rise in the LF:HF ratio, a sign of sympathetic dominance.[29] These results thus show that patients with COPD still exhibit a preponderance of sympathetic activity, but their sympathetic and parasympathetic activity has decreased. Accordingly, a number of pathophysiological alterations brought on by recurrent hypoxemia, hypercapnia, elevated intrathoracic pressure swings as a result of airway blockage, increased respiratory effort, systemic inflammation, or beta sympathomimetics may account for sympathetic hyperactivity in these patients.[39]

Although there was a decrease in both sympathetic and parasympathetic cardiac regulation, sympathetic activity still predominates, general changes in HRV values is seen in COPD patients, which could indicate a serious breakdown in the relationship between the heart's intrinsic pacemaker and external control mechanisms, such as the autonomic nerve (vagal) control system. The association between HRV

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decline and the severity of COPD cannot be evaluated using the data currently available. Given its potential as a straightforward, easily accessible method that can be recorded and monitored remotely, particularly in light of global health concerns, the advantages of an HRV evaluation in diagnosing COPD should be further investigated.

CONCLUSION

Although there was a decrease in both sympathetic and parasympathetic cardiac regulation, sympathetic activity still predominates, a general changes in HRV values is seen in COPD patients, which could indicate a serious breakdown in the relationship between the heart's intrinsic pacemaker and external control mechanisms, such as the autonomic nerve (vagal) control system. The association between HRV decline and the severity of COPD cannot be evaluated using the data currently available. Given its potential as a straightforward, easily accessible method that can be recorded and monitored remotely, particularly in light of global health concerns, the advantages of an HRV evaluation in diagnosing COPD should be further investigated.

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