National Journal of Physiology, Pharmacy and Pharmacology

RESEARCH ARTICLE

Heart rate variability in chronic obstructive pulmonary disease and its correlation with disease severity in South Indian population

Ganesan R[1], Gaur G S[2], Karthik S[2], Vishnukanth G[3]

[1]Department of Physiology, Melmaruvathur Adhiparasakthi Institute of Medical Sciences and Research, Kancheepuram, Tamil Nadu, India, [2]Department of Physiology, Jawaharlal Institute of Postgraduate Medical Education and Research, Puducherry, India, [3]Department of Pulmonary Medicine, Jawaharlal Institute of Postgraduate Medical Education and Research, Puducherry, India

Correspondence to: Ganesan R, E-mail: ganeshraj2511@gmail.com

Received: December 19, 2019; **Accepted:** January 13, 2020

ABSTRACT

Background: Cardiovascular diseases associated with chronic obstructive pulmonary disease (COPD) account for 50% of COPD deaths. Autonomic dysfunction and poor pulmonary function increase the cardiovascular risk in COPD patients. Severity of COPD can be assessed by forced expiratory volume in 1 s. Autonomic balance can be assessed by heart rate variability (HRV). There are variations in the reports of COPD patients regarding the level or onset of dysfunction is a sympathetic or parasympathetic system in them. **Aims and Objectives:** In our study, we intended to assess HRV parameters such as, total power (TP), high frequency normalized units (HFnu), low frequency normalized units (LFnu), LF/HF ratio, mean HR, root mean square of the successive differences (RMSSD), NN50, and pNN50 among different stages of COPD and also to identify the association of these HRV parameters with disease severity. **Materials and Methods:** It is a cross-sectional study done on (n = 130) male stable COPD patients. Anthropometric parameters, HRV parameters, and pulmonary function test were assessed. Later, based on the Global Initiative for Chronic Obstructive Lung Disease stage criteria (mild, moderate, severe, and very severe), they were divided into four subgroups. Data were analyzed by SPSS 19.0 version software. Kruskal–Wallis test was used to find a statistical difference between the groups. Correlations between the variables were done using Spearman correlation test. **Results:** LF/HF ratio (2 ± 0.5) was increased when compared to reference value reported by the previous studies. TP, HFnu, and RMSSD levels were significantly decreased in very severe, severe, and moderate COPD patients when compared to mild COPD patients. The mean HR, LFnu, and LF/HF ratio levels were significantly increased in very severe, severe, and moderate COPD patients when compared to mild COPD patients. TP, HFnu, and RMSSD levels negatively correlated with disease severity and mean HR, LFnu, and LF/HF ratio positively correlated with disease severity. **Conclusion:** We have noted that cardiac autonomic dysfunction in the form of increased sympathetic and reduced parasympathetic activity occurs in COPD patients and the association was more prominent when the disease severity increased.

KEY WORDS: Chronic Obstructive Pulmonary Disease; Cardiovascular Risk; Forced Expiratory Volume in 1 s; Heart Rate Variability; Sympathovagal Balance

Access this article online	
Website: www.njppp.com	Quick Response code
DOI: 10.5455/njppp.2020.10.01005202013012020	

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is characterized by irreversible airflow obstruction, seen as decline in forced expiratory volume in 1 s (FEV1).[1] All over the world, 65 million people were estimated to have COPD and in India, burden of COPD is 14.84 million.[2-4] India has

the highest mortality rate of COPD (64.7%).[5] Cardiovascular diseases (CVD) associated with COPD account for 50% of COPD deaths.[6-8] Autonomic dysfunction and poor pulmonary function increase the cardiovascular risk in COPD patients.[9,10]

FEV1 is used to assess pulmonary function in COPD patients and also in staging them.[11] Sin *et al*. showed that the lower the FEV1, the higher the risk of CVD.[12] The levels of FEV1 were reduced in low-grade systemic inflammatory conditions such as in COPD.[13] Since low-grade systemic inflammation is associated with atherosclerosis; reduced FEV1 might be a significant risk factor for cardiovascular morbidity and mortality, independent of cigarette smoking, total cholesterol, and hypertension.[14,15]

COPD is a systemic disease, negatively affects autonomic nervous system and causes cardiac autonomic dysfunction.[16] Autonomic dysfunction in COPD is attributed to increased intrathoracic pressure swings caused by airway obstruction, increased respiratory effort, hypoxemia, hypercapnia, systemic inflammation, and use of beta-sympathomimetics. Autonomic dysfunction in COPD patient's causes endothelial dysfunction, arterial stiffness, and left ventricular hypertrophy and can also modulate further inflammatory reactions, thereby predisposing them to CVD.[17] Heart rate variability (HRV) is a non-invasive method designed to study beat-to-beat variation in HR which is obtained from R-R interval in electrocardiogram.[18,19] Autonomic balance between sympathetic and parasympathetic system can be assessed by HRV. Reduced HRV is also an index for cardiovascular risk as it is linked to many cardiovascular risk factors that increase the state of demise.[20] There are variations in the reports of COPD patients, regarding the level or onset of dysfunction is the sympathetic or parasympathetic system. There is also a paucity of literature in revealing the association between HRV and disease severity.

Hence, in this study, we intended to assess the pulmonary function tests (PFTs), HRV parameters in male COPD patients and also to correlate HRV parameters with disease severity.

MATERIALS AND METHODS

Study Design

This was a cross-sectional study conducted in 130 male COPD patients from January 2016 to July 2017. The sample size was estimated conveniently based on logistics, time, and budget. We have decided to include 130 male COPD patients attending the department of pulmonary medicine during the study period. It was designed to assess the PFTs, HRV parameters in male COPD patients and also to correlate HRV parameters with disease severity. The study was conducted in the Department of Physiology, JIPMER, in Collaboration with the Department of Pulmonary Medicine, JIPMER. Before the start of the study, approval from JIPMER Scientific Advisory Committee and Institute Ethics Committee for human studies was obtained.

Selection of Subjects

Male COPD patients (Global Initiative for Chronic Obstructive Lung Disease [GOLD] – Stages I–IV) aged between 35 and 60 years attending JIPMER pulmonology OPD were included in the study. COPD patients who cannot maintain oxygen saturation above 88% and COPD patients with systemic complications such as coronary heart disease, arrhythmia, stroke and alcoholics, diabetic, hypertensive patients, and tobacco chewers were excluded from the study. Subjects were health educated about the disease and are motivated to know their disease severity and cardiovascular risk associated with their disease.

Experimental Design

The study was carried out in pulmonary function testing laboratory and autonomic function testing laboratory in the Department of Physiology, JIPMER, between 9 am and 1 pm. The laboratory conditions were quiet, the temperature of 25–27°C and adequate lighting provided. The subjects were explained clearly about the study protocol in their native language and written informed consent was obtained from them. The participants were asked to have light breakfast around 7 am and come for tests around 9 am as the subjects will have difficulty in performing PFT and HRV with the full stomach. The subjects were told to refrain from smoking, drinking caffeinated beverages, and the morning dose medications for COPD at least 12 h before the recording. In case of any adversity in health, such as fever, exacerbation of COPD, poor sleep, or physical discomfort, tests were postponed, and the subjects were asked to report on another convenient day. Subjects were also asked to stop taking medications affecting their attention such as psychotropic drugs (sedatives and antihistamines). In the study group, PFTs such as FEV1, forced vital capacity (FVC), FEV1/FVC (using Spirolab III), and HRV parameters such as total power (TP), high frequency normalized units (HFnu), low frequency normalized units (LFnu), LF/HF ratio, mean HR, root mean square of the successive differences (RMSSD), NN50, and pNN50 (using PowerLab 8/30 ML 870 data acquisition system [Australia]) were studied. Later, subjects were classified into four subgroups based on GOLD stage criteria into mild, moderate, severe, and very severe COPD.

Statistical Analysis of Data

SPSS version 19 was used for statistical analysis. The data were subjected to Kolmogorov–Smirnov normality test. The continuous data such as age, duration of illness, anthropometric parameters (height, weight, waist circumference [WC], hip

circumference [HC], waist–hip ratio [WHR], and waist–height ratio [WhtR]), HR, and blood pressure were expressed as mean with standard deviation and the intergroup differences in mean between mild, moderate, severe, and very severe COPD groups were compared using one-way ANOVA test. HRV parameters were expressed in median with interquartile range and the intergroup differences between mild, moderate, severe, and very severe COPD groups were compared using Kruskal–Wallis test. The correlation between HRV and disease severity was done using Spearman correlation test. The difference was considered statistically significant, if $P < 0.05$.

RESULTS

All the anthropometric, PFT, and HRV parameters were assessed in 130 COPD patients after obtaining informed consent from them and the data were analyzed.

Comparison of Parameters among Different Stages of COPD

Demographic characteristics

The mean age, duration of illness, anthropometric indices (height, weight, body mass index [BMI], WC, HC, WHR, and WhtR) of the study group are given in Table 1.

HR and blood pressure parameters

The mean HR, systolic blood pressure, diastolic blood pressure, pulse pressure, and mean arterial pressure of the study group are given in Table 2.

No significant difference was noted among the four subgroups of COPD.

HRV parameters

Comparison of HRV parameters among patients in different COPD severity groups was done using Kruskal–Wallis test and the *post hoc* (Dunn's) test was performed to find a significant difference among the groups.

In HRV, the TP and HFnu were significantly less ($P < 0.005$) and LFnu and LF/HF ratio were significantly high ($P < 0.005$) [Table 3] in very severe, severe, and moderate COPD patients when compared to mild COPD patients.

The time-domain indices of HRV such as mean HR and RMSSD were significantly decreased ($P < 0.005$) [Table 3] in very severe, severe, and moderate COPD patients when compared to mild COPD patients. Correlation between the time-domain indices and frequency-domain indices of HRV with disease severity is shown in Table 4.

Table 1: Demographic characteristics of the study participants (n=130)

Variables	Mean±SD
Age (years)	53.37±5.65
Duration (years)	6.92±2.57
Height (cm)	161.33±7.72
Weight (kg)	55.06±9.60
BMI (kg/m^2)	21.15±3.47
Waist (cm)	89.00±8.39
Hip (cm)	108.77±16.02
Waist–hip ratio	0.82±0.09
Waist–height ratio	0.55±0.04

The values are expressed in mean with SD. BMI: Body mass index, SD: Standard deviation

DISCUSSION

In our study population of 130 male COPD patients, anthropometric parameters such as height, weight, BMI, WC, HC, WHR, and WhtR were assessed. Later, the mean height, weight, BMI (20.1, 20.8, 21, and 22,), WC, HC, WHR (0.81, 0.82, 0.83, and 0.85), and WhtR (0.55, 0.54, 0.55, and 0.55) were compared among the four subgroups of COPD patients. We found that none of the anthropometric parameters showed statistical significance among the four subgroups of COPD patients. In our study group of COPD patients, HRV parameters such as LFnu, HFnu, TP, LF/HF ratio, RMSSD, mean HR, NN50, and pNN50 were assessed. We found that the mean LF/HF ratio (2 ± 0.5) was increased when compared to reference value reported by the previous studies.[21] In supine rest, raised levels of LF/HF ratio suggested that there is a sympathovagal imbalance in the form of sympathetic predominance and reduced vagal activity.[21] However, other indices of parasympathetic activity such as TP, HFnu, RMSSD, and mean HR were unaltered.[22]

Our findings were similar to the study done by Chhabra *et al*. and Taranto-Montemurro *et al*.[23,24] They found an increased LF/HF ratio in COPD patients and concluded that there is sympathetic dominance in COPD patients. In the study done by Chen *et al*., the rest HRV in COPD patients was normal as that of the control subjects.[25] However, their sample size was only 30 COPD patients and HRV recording done 6 h after the use of bronchodilators. In our study, the sample size was 130 male COPD patients and HRV recording done with our subjects deprived of medications for 24 h. A study done by Volterrani *et al*., in 31 male COPD patients found that there is increased HFnu and decreased LFnu. They concluded that there is increase in parasympathetic activity and decrease in sympathetic activity in COPD patients and postulated that increase in vagal activity is the reason for decrease in FEV1 and increase in bronchoconstriction in COPD patients.[26] This study had been done with relatively younger individuals aged from 31 years. Exclusion of pulmonary diseases with vagal dominance like bronchial asthma was also not properly explained. In the present study, we compared the HRV

Table 2: Comparison of basal heart rate and blood pressure among COPD patients

Cardiovascular parameters	Total (*n*=130)	Mild COPD (*n*=18)	Moderate COPD (*n*=41)	Severe COPD (*n*=44)	Very severe COPD (*n*=27)	*P*-value*
HR	76.7±9.7	67.41±3.43	74.72±3.09	78.50±4.77	85.93±4.30	0.062
SBP	120±13.8	106.25±4.24	116.53±4.85	120.97±5.23	130.58±6.05	0.091
DBP	75.9±13.4	66.76±3.68	71.25±5.44	79.05±6.43	86.08±4.90	0.104
PP	43.34±9.58	39.49±4.45	45.28±6.85	41.92±8.93	44.49±9.21	0.066
MAP	90.9±10.58	79.92±3.26	86.35±4.15	93.03±4.36	100.90±3.06	0.045

Values are expressed as mean (SD); comparison of variables between groups done using ANOVA. *P<0.05 is statistically significant among the four groups of COPD. HR: Heart rate (bpm), SBP: Systolic blood pressure (mmHg), DBP: Diastolic blood pressure (mmHg), PP: Pulse pressure (mmHg), MAP: Mean arterial pressure (mmHg), COPD: Chronic obstructive pulmonary disease

Table 3: Comparison of HRV and blood pressure variability parameters at rest among COPD patients

HRV parameters	Total (*n*=130)	Mild COPD (*n*=18)	Moderate COPD (*n*=41)	Severe COPD (*n*=44)	Very severe COPD (*n*=27)	*P*-value*
Frequency domain						
TP	979.5 (317)	1348.39 (240)	1074.28 (119)	898.93 (195)	645.35 (163)	0.000
LFnu	55 (10)	47.79 (9.10)	51.34 (8.13)	58.92 (14.58)	62.79 (9.23)	0.000
HFnu	43 (6)	50.80 (6)	46.24 (4)	41.35 (4)	41.42 (5)	0.001
LF/HF	2 (0.15)	0.89 (0.21)	1.62 (0.07)	2.24 (0.78)	2.92 (0.09)	0.002
Time domain						
Mean HR	78 (8)	68.60 (4)	76.43 (4)	81.36 (6)	88 (5)	0.001
RMSSD	16 (11)	31 (4)	21 (5)	13 (4)	8 (4)	0.003
NN50	28.5 (18)	29 (21)	28 (17)	30 (19)	27 (13)	0.912
pNN50	12 (7)	14.45 (5)	12.80 (12)	12.35 (6)	12 (11)	0.901

Values are expressed as median (interquartile range); comparison of variables between groups done using Kruskal–Wallis test. *P<0.05 is statistically significant among the four groups of COPD. TP: Total power (ms^2), LF: Low frequency (ms^2), HF: High frequency (ms^2), nu: Normalized units, Mean HR: Mean heart rate (bpm), RMSSD: Root mean square of the successive differences NN intervals (ms), NN50: Number of pairs of adjacent NN intervals differing by more than 50 ms, pNN50: Percentage of NN50. HRV: Heart rate variability, COPD: Chronic obstructive pulmonary disease

Table 4: Correlation of disease severity with HRV in COPD patients (*n*=130)

HRV parameters	Disease severity	
	Spearman correlation (ř)	*P*-value
LFnu	0.841	0.005
HFnu	−0.731	0.002
LF/HF ratio	0.844	0.004
TP	−0.913	0.012
Mean HR	0.902	0.006
RMSSD	−0.931	0.004

Correlation between variables is done using Spearman's correlation test. *P<0.05 is statistically significant. TP: Total power (ms^2), LF: Low frequency (ms^2), HF: High frequency (ms^2), nu: Normalized units, Mean HR: Mean heart rate (bpm), RMSSD: Root mean square of the successive differences NN intervals (ms), HRV: Heart rate variability, COPD: Chronic obstructive pulmonary disease

parameters among four subgroups of COPD and found that mean HR, LFnu, and LF/HF ratio levels were significantly increased ($P < 0.005$) and TP, HFnu, and RMSSD levels were significantly decreased ($P < 0.005$) in very severe, severe, and moderate COPD patients when compared to mild COPD patients. Increased sympathetic activity is depicted by Increased LFnu, LF/HF ratio and reduced parasympathetic activity is depicted by decreased HFnu, TP, RMSSD and increased mean HR. At supine rest, there is a sympathovagal imbalance in the COPD patients in the form of elevated sympathetic and declined parasympathetic tone which increased as the disease severity is increased. Kiviniemi *et al*. and Thayer *et al*. showed that the reduction in TP of HRV was associated with cardiac mortality and morbidity.[27,28] This was further supported by increased resting HR in COPD patients, as resting HR is the index of vagal tone and Jensen *et al*. showed that increased HR was associated with increased CV comorbidities.[29] These findings suggested that among the COPD patients, moderate, severe, and very severe COPD patients had more sympathetic dysfunction and increased cardiovascular risk when compared to mild group of COPD patients.

In our study, when we associated HRV parameters with disease severity, we found that mean HR ($r = 0.902$), LFnu ($r = 0.885$), and LF/HF ratio ($r = 0.844$) levels positively associated and TP ($r = −0.913$), HFnu ($r = −0.731$), and RMSSD ($r = −0.931$) levels were negatively associated with the disease severity. Our study had similar findings as that of the study done by Handa *et al*.[30] There is no association between rest HRV and disease severity according to the study done by Camillo *et al*. and concluded that decreased

HRV might not be associated with disease severity.[31] This study was done only in 31 COPD patients which might be less to show the association of HRV with disease severity.

CONCLUSION

From our findings, we have noted that cardiac autonomic dysfunction in the form of increased sympathetic and reduced parasympathetic activity occurs in COPD patients and the association was more prominent when the disease severity increased. The previous studies showed that reduced HRV could be used for assessing cardiovascular risk. Hence, COPD patients are prone to cardiovascular risk and among the COPD patients –moderate, severe, and very severe group of patients have increased cardiovascular risk than mild group of COPD patients.

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How to cite this article: Ganesan R, Gaur GS, Karthik S, Vishnukanth G. Heart rate variability in chronic obstructive pulmonary disease and its correlation with disease severity in South Indian population. Natl J Physiol Pharm Pharmacol 2020;10(03):209-214.

Source of Support: Nil, **Conflicts of Interest:** None declared.