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Assessment of Cardiac Autonomic Functions in Patients of Chronic Obstructive Pulmonary Disease in Relation To Severity and Duration of Disease

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Abstract: Chronic obstructive pulmonary disease (COPD) is a common and preventable disease that has great implications on global health. COPD could affect ANS due to recurrent hypoxemia, hypercapnoea, increased intrathoracic pressure swings due to airway obstruction, and increased respiratory effort, systemic inflammation and use of beta sympathomimetics. The present study was undertaken to assess the effect of severity and duration of COPD on cardiovascular autonomic nervous functions. Study was carried out on 100 diagnosed cases of COPD. They were divided as per severity into mild (n=34), moderate (n=51), severe (n=15) as per GOLD's criteria and as per duration of disease after diagnosis into < 5 yrs (n=35),5 - 10 yrs(n=52), >10 yrs (n=13). Tests done for parasympathetic function were Resting Heart Rate, E: I ratio, Valsalva ratio and 30:15 ratios. Tests done for sympathetic function were Handgrip test, orthostatic test and QTc interval. ANOVA test was used to compare different groups based on severity and duration of disease. Pearson correlation coefficient was used to find correlation between FEV1 and various parameters of autonomic functions. It was also used to find out co relation between duration of disease and autonomic functions Also based on the results of these tests, using Ewing's criteria they were classified into normal, early ,definite and severe cardiac autonomic neuropathy (CAN). We found that patients with COPD have cardiac autonomic dysfunction that correlated with severity and duration of disease. Also severity of CAN as per Ewing's criteria increases with severity and duration of disease. Thus it is advisable to screen all COPD patients for CAN to ensure appropriate remedial action to prevent complications and to improve life expectancy.
Keywords: cardiac autonomic neuropathy (CAN), hypoxemia, hypercapnoea, COPD, ANS

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a common and preventable disease that has great implications on global health. COPD has been defined as a disease state characterized by airflow limitation that is not fully reversible. It broadly consists of two pathological conditions i.e emphysema and chronic bronchitis. The airflow limitation is usually progressive with increasing dyspnoea and other respiratory symptoms with progressive deterioration of the health status [1].

The autonomic nervous system (ANS) by its sympathetic and parasympathetic divisions regulates heart rate and blood pressure and modulates most of the cardiovascular functions. Hence any abnormality in cardiovascular autonomic function can lead to cardiac arrhythmias and abnormal blood pressure changes at rest as well during postural change and exercise. It can lead to impaired exercise capacity and reduced health quality of life [2].

The high metabolic activity of autonomic nerves makes them extremely susceptible to hypoxemia and could cause a reversible impairment in electro physiological function. COPD could affect ANS due to recurrent hypoxemia, hypercapnoea, increased intrathoracic pressure swings due to airway obstruction, increased respiratory effort, systemic inflammation and use of beta sympathomimetics [3]. Cardiac arrhythmia particularly ventricular arrhythmia and sudden death is important cause of mortality in patients with COPD [4]. Early diagnosis of cardiac autonomic neuropathy (CAN) might be useful clinically in the proper

treatment of patients of COPD. Simple autonomic function tests can be used to detect autonomic dysfunction.

Unlike diabetes mellitus, the occurrence of autonomic neuropathy has received much less attention in COPD. To the best our knowledge there are very few studies done to evaluate the effect of severity and duration of COPD on cardiovascular autonomic function, so the present study was undertaken with following aims and objectives

- To assess the effect of severity of COPD on cardiovascular autonomic function.
- To assess the effect of duration of COPD on cardiovascular autonomic function.

MATERIAL AND METHODS

This study was a observational cross sectional comparative study conducted on 100 diagnosed patients of COPD. It was approved by Institutional Ethics Committee. All patients were enrolled with a written informed consent.Selection of COPD patients was done on the basis of spirometry done with RMS Helios Spirometer 702. FEV1 and FVC values were taken from post bronchodilator spirometry. Subjects taken were clinically stable with mild to severe COPD.

Inclusion criteria

- Age group 40 to 60 years.
- Only male subjects were included
- Smokers, ex smokers and non smokers were included.
- Only the subjects who were able to perform all the tests for cardiac autonomic neuropathy were included in the study.

Exclusion criteria

- Patients having very severe COPD or having acute dyspnoea of COPD.
- Patients with body mass index more than $25kg/m^2$.
- Patients who are alcoholic (present or ex).
- Patients with ischemic, rheumatic or any other heart disease, hypertension, diabetes, thyroid or any other endocrine disorders, electrolyte imbalance and any nervous system disease.
- Patients on β_2 agonist drugs would be asked to stop taking drug 24 hours before and those taking anti cholinergic drugs will be asked not to take it on the day of examination.
- Patients on drugs that prolong QTc interval such as amiodarone, quinidine, tricyclic anti-depressants etc.
- Patients of COPD were categorized into mild COPD, moderate COPD and severe COPD according to severity of COPD calculated by Global Initiative for Obstructive Lung Diseases (GOLD's) criteria [1].

GOLD's criteria

Stage I	Mild (n=34)	FEV1/FVC < 0.70 FEV1 > 80% predicted
Stage II	Moderate (n=51)	FEV1/FVC < 0.70 FEV1 50 - 80% predicted
Stage III	Severe (n=15)	FEV1/FVC < 0.70 FEV1 30- 50% predicted
Stage IV	Very severe (n=0)	FEV1/FVC < 0.70 FEV1 < 30% predicted or with chronic respiratory failure.

COPD patients were also categorized according to duration of disease from the time of diagnosis into 3 groups.

Group 1. COPD < 5 years (n=35)
Group 2. COPD 5-10 years (n=52)
Group 3. COPD > 10 years (n=13)

Tests for parasympathetic function [5]

- Resting Heart Rate.
- 2Effect of deep inspiration & expiration on heart rate (E:I ratio)
- Response of heart rate to Valsalva manoeuvre (Valsalva ratio).
- Change in heart rate immediately after standing (30:15 ratio)

Tests for sympathetic function[5]

- Rise in Diastolic BP during isometric exercise (Handgrip test).
- Fall in Systolic BP on standing (Orthostatic test).
- QTc interval.

Categorization of CAN

Based on the results of tests according to Ewing's criteria [6],CAN is categorized as follows-

Category of CAN	Criteria
Normal	All tests normal or one test borderline
Early	One of three heart rate tests abnormal or two borderline
Definite	Two heart rate tests abnormal
Severe	Two heart rate tests abnormal+ one or both BP tests abnormal

OBSERVATIONS AND RESULTS

Table-1: Comparison of autonomic function tests between Mild, Moderate and Severe COPD by ANOVA test

PARAMETERS	Mild COPD n= 34 Mean± S. D	Moderate COPD n= 51 Mean± S. D	Severe COPD n= 15 Mean± S. D	p value
Resting heart rate (per min)	82.41 ± 3.64	88.70 ± 12.69	89.93 ± 11.25	0.011*
E : I ratio	1.15 ± 0.09	1.13 ± 0.066	1.12 ± 0.074	0.015*
Valsalva ratio	1.32 ± 0.172	1.10 ± 0.149	1.00 ± 0.189	0.008*
30:15 ratio	1.04 ± 0.106	1.00 ± 0.043	0.98 ± 0.056	<0.001**
Hand grip test (mm of Hg)	15.88 ± 3.96	14.03 ± 2.84	11.93 ± 3.78	<0.001**
Orthostatic test (mm of Hg)	15.11 ± 9.17	17.52 ± 10.02	19.20 ± 3.788	0.037*
QT_C(sec)	0.41 ± 0.02	0.43 ± 0.021	0.47 ± 9.435	0.041*

* < 0.05: - statistically significant and ** < 0.001:- statistically high significant.

Table 1 shows comparison of different autonomic function tests according to severity of COPD by using ANOVA test. Mean values of Resting heart rate, E:I ratio, Valsalva ratio, fall in systolic blood pressure during orthostatic test & QTc interval showed significant difference in the values within the groups. Resting heart rate, fall in systolic blood pressure, QTc interval were maximum in severe COPD group, while E:I ratio and Valsalva ratio were lowest in severe COPD group.30:15 ratio &rise in diastolic blood pressure during hand grip test showed highly significant difference in the values within the groups ($p<0.001$),being lowest in severe COPD

Table-2: Correlation between FEV1 and different parameters of autonomic function tests.

Independent variable	Dependent variable	Pearson's Correlation Coefficient "r"	p-value and Statistical Significance
FEV1	Resting HR	-0.2995	0.002*
	E: I Ratio	0.0848	0.4013
	Valsalva Ratio	0.3861	< 0.001**
	30:15 Ratio	0.2594	0.009*
	Hand Grip Test	0.3585	0.0002**
	Orthostatic Test	-0.1301	0.152
	QTc	-0.6410	< 0.001**

* < 0.05:- statistically significant and ** < 0.001:- statistically highly significant.

To correlate autonomic deficit with severity of disease Pearson's correlation analysis was performed. The different parameters of autonomic function tests are kept as dependent variables while FEV1 is kept as independent variable. It showed significant positive linear correlation between FEV1 and Valsalva ratio , 30: 15 ratio and Hand Grip Test .There was significant negative linear correlation between FEV1 and Resting heart rate and QTc E: I ratio and Orthostatic test were not significantly correlated with FEV1.

Table-3: Categorization of CAN based on Ewing's criteria.

No.	Category	Mild COPD n= 34	Moderate COPD n= 51	Severe COPD n= 15
1.	Normal	91.17% (n=31)	1.96% (n=1)	0% (n= 0)
2.	Early	8.82% (n=3)	72.54% (n=37)	13.33% (n=2)
3.	Definite	0% (n=0)	23.52% (n=12)	73.33% (n=11)
4.	Severe	0% (n=0)	1.96% (n=1)	13.33% (n=2)

As shown in table 3 when patients of Mild, Moderate and Severe COPD groups were classified on the basis of degree of CAN by using Ewing's criteria. It shows that as the severity of COPD increases, percentage of patients having definite and severe CAN increases.

Table-4: Comparison of autonomic function tests in relation to duration of COPD

PARAMETERS	COPD < 5 yrs (n= 35)	COPD 5-10 yrs (n= 52)	COPD > 10 yrs (n=13)	p value
Resting heart rate (beats per min)	82.51 ± 3.641	88.78 ± 12.766	90.00 ± 11.195	0.011*
E : I ratio	1.15 ± 0.091	1.13 ± 0.065	1.12 ± 0.077	0.020*
Valsalva ratio	1.12 ± 0.169	1.11 ± 0.148	1.10 ± 0.204	0.008*
30:15 ratio	1.04 ± 0.104	1.00 ± 0.044	0.98 ± 0.051	0.007*
Hand grip test (mm Hg)	15.94 ± 3.925	13.84 ± 2.831	12.07 ± 4.050	0.001*
Orthostatic test (mm Hg)	15.37 ± 9.162	17.30 ± 9.892	19.84 ± 10.015	0.034*
QT_C(sec)	0.41 ± 0.026	0.44 ± 0.022	0.47 ± 0.023	< 0.001**

* < 0.05: - statistically significant and ** < 0.001:- statistically high significant.

Table 4 shows comparison of different autonomic function tests according to duration of COPD by using ANOVA test. All the parameters of autonomic functions showed significant change between the groups, being maximally affected in COPD having duration of more than 10 yrs.

Table-5: Correlation of Duration of COPD with the different parameters of autonomic function tests by Pearson's correlation coefficient.

Independent variable	Dependent variable	Pearson's Correlation Coefficient "r"	p-value and Statistical Significance
Duration of COPD	Resting HR	0.2650	0.0077*
	E: I Ratio	-0.1218	0.2273
	Valsalva Ratio	-0.3861	< 0.001**
	30:15 Ratio	-0.2377	0.0173*
	Hand Grip Test	-0.3220	0.0011**
	Orthostatic Test	0.1107	0.2729
	QTc	0.5305	< 0.001**

* < 0.05:- statistically significant and ** < 0.001:- statistically highly significant.

To correlate autonomic deficit with duration of disease Pearson's correlation analysis was performed. The different parameters of autonomic function tests are kept as dependent variables while duration of disease is kept as independent variable. It showed significant positive linear correlation between duration of COPD resting heart rate and QTc interval. There was significant negative linear correlation between duration and E: I ratio, 30: 15 ratio and rise in diastolic BP by Hand Grip Test . E: I ratio and Orthostatic test are not significantly correlated with Duration of COPD.

Table-6: Categorization of CAN based on Ewing's criteria

No.	Category	COPD < 5 yrs. n= 35	COPD 5-10 yrs. n= 52	COPD > 10 yrs. n= 13
1.	Normal	85.71% (n=30)	3.84% (n=2)	0% (n=0)
2.	Early	14.28%(n=5)	67.3% (n=35)	15.38% (n=2)
3.	Definite	0% (n=0)	25% (n=13)	76.92% (n=10)
4.	Severe	0% (n=0)	3.84% (n=2)	7.69% (n=1)

As shown in table 6 maximum patients of duration less than 5 yrs were in normal category, maximum % of patients having duration of illness between 5-10 yrs were having early CAN and majority with duration more than 10 yrs were having definite CAN as per Ewing's criteria.

DISCUSSION

So looking at the results of these parameters we can conclude that as the disease becomes more severe and of long duration there is gradual decrease in parasympathetic as well as sympathetic activity. Our results correlate with findings of many other studies- Chabra *et al*. [7] observed that there was significant difference between values of Valsalva ratio, 30: 15 ratio and orthostatic test among Mild, Moderate and Severe COPD groups. Stewart *et al*. [8] compared values of autonomic function tests among moderately hypoxic (arterial PO_2> 60 mm Hg), severely Hypoxic (arterial PO_2< 60 mm Hg) and hypercapnic (arterial PO_2< 55 mm Hg and PCO_2> 45 mm Hg) COPD patients. He found that there was significant difference between the values of Valsalva ratio, E: I ratio and 30: 15 ratio among these group. Chen *et al.* [9] did HRV studies in COPD and found correlation between FEV1/FVC and parameters of HRV. Scalvini *et al.* [10] found that COPD patients with chronic respiratory insufficiency there was derangement in ANS which was partially reversed by O2 administration.

The high metabolic activity of autonomic nerves makes them extremely susceptible to hypoxemia and could cause a reversible impairment in electro physiological function [7, 8]. There is increased frequency of hypoxic episodes (exacerbation) due to increased obstruction as the severity of disease increases. Along with hypoxia there can also be increase in systemic inflammation in more severe and chronic cases. Increased oxidative stress due to increasing systemic inflammation [10] also could be the reason for more dysfunction in severe and chronic cases. Alpha 1 anti- trypsin deficiency in COPD patients can also be the cause of autonomic dysfunction [11].

COPD patients also showed prolonged QTc interval. In severe and long duration COPD patients it was abnormally increased which can lead to serious and sometimes fatal complications such as ventricular arrhythmia and sudden death.

Smoking itself is independent risk factor for CAN in COPD patients. Also smoking is the main cause of COPD, so it leads to worsening of CAN in COPD. But as per some studies association between smoking and CAN is much weaker than between hypoxaemia & CAN [8].

APPLICATIONS OF THE STUDY

Our findings show that even if patients were asymptomatic there was sub clinical autonomic neuropathy. Out of 100 patients only 10 complained of postural dizziness, rest of the patients were not having any symptoms of autonomic neuropathy. Therefore all COPD patients should be screened for CAN, as symptoms can arise late during the course of disease. Measurement of simple autonomic function tests and QTc interval might identify patients at risk during anaesthesia, septicaemia or hypoxaemia. This will ensure appropriate remedial action and thus improve life expectancy in patients with COPD.

Limitations of the study

Newer techniques for measuring autonomic functions like the computer aided power spectral analysis of heart-rate variability could not be done because of limitations in resources and cost. We did not take into consideration arterial oxygen tension for determining the degree of hypoxia in COPD patients.

SUMMARY AND CONCLUSION

In conclusion patients with COPD have cardiac autonomic neuropathy that correlates with severity and duration of disease. All COPD patients should be screened for CAN to ensure appropriate remedial action and thus improve life expectancy in patients with COPD

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