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# Evaluation of Autonomic Dysfunction in Underweight, Normal Weight, Overweight and Obese Patients with Chronic Obstructive Pulmonary Disease

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## Abstract

**Background:** Though there are several studies available on effects of obesity on cardiac autonomic dysfunction and effects of COPD on cardiac autonomic dysfunction separately but search on combined effect of obesity and COPD on cardiac autonomic dysfunction fails to produce results. Therefore there was a need to evaluate the changes in autonomic dysfunction with increasing BMI in patients with COPD.

**Objective:** The aims of this study were 1) to compare autonomic dysfunction in patients with COPD with increasing BMI, 2) to correlate autonomic dysfunction in patients with COPD with increasing BMI.

**Methodology:** In the present study, 42 subjects were categorized into underweight, normal weight, overweight and obese category. Non invasive cardiac autonomic function tests were carried out in these subjects.

**Results:** The mean ± SD age of underweight, normal weight, overweight, and obese patients with COPD were 57.667 ± 5.1640, 61.007 ±8.8991, 55.800±6.6106 and 56.200±7.1204 respectively. It was found that there was no correlation between BMI and autonomic dysfunction responses in patients with COPD. All four cardiac autonomic function test came out to be non significant statistically [Karl Pearson correlation (r), ns- p >0.05]. Multiple comparisons between underweight, normal weight, overweight, and obese patients with COPD for cardiac autonomic responses, $FEV_1$, PEF were statistically non significant.

**Conclusion:** In present study, although the results have shown that there was definite autonomic neuropathy in patients with COPD with increasing BMI, there was no significant difference in autonomic dysfunction with increasing BMI in patients with COPD.

***Keywords:*** *Forced expiratory volume ($FEV_1$), Peak expiratory flow rate (PEF), Obesity, Chronic Obstructive Pulmonary Disease.*

## Introduction

The chronic obstructive pulmonary disease (COPD) is characterized by persistent airflow limitation that is usually progressive and associated with an enhanced chronic inflammation response of the airways. It has been estimated that in 2030, COPD will become the third biggest cause of death.[1,2]

Previous studies show that in COPD patients, cardiovascular autonomic neuropathy (CAN) is a common consequence and has been shown to negatively affect the cardiovascular and autonomic nervous system.[3, 4] Previous studies have demonstrated that COPD patients have depressed heart rate variability (HRV), indicating increased sympathetic activity at rest[5,6] and Bronchoconstriction, hypoxia, hypercapnia, weight loss and systemic inflammation are other associated features.[7, 8] Studies on adults show that the HRV is decreased in overweight young adults especially men indicating sympathovagal imbalance. No changes were

observed in HRV in underweight group. Changes in the autonomic nervous activity begin in the overweight and may become more prominent in the obese thus indicating increased cardiovascular risk. [9] But the number of studies that analysed the autonomic functions in obese adult population is still limited.

Available data suggests that obesity is more prevalent in patients with COPD than in the general population, depending on the severity of chronic airflow limitation. [10, 11] Obesity is an independent risk factor for cardiovascular disease and mortality[12,15.] Autonomic neuropathy is another complication in obese patients.[16,17] But limited literature is available to examine the relation between increasing body mass index (BMI) and cardiac autonomic function tests in patients with COPD. Hence, this study on the evaluation and correlation of autonomic function in the underweight, normal weight, overweight and obese patients with COPD was undertaken

## Materials and Method

**Subjects:** 42 COPD subjects on the basis of BMI were categorized into 6 underweight, 26 normal weight,5 overweight and 5 obese category. Written informed consent was taken from the subjects and approval was obtained from the Institutional ethical committee. Procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national).

**Parameters Measured:** Autonomic function tests were employed to evaluate the integrity of both parasympathetic and sympathetic innervations of the heart in all the groups.

**(A) Parasympathetic Function Tests:** Blood pressure was recorded from OMERON digital sphygmomanometer and heart rate beat to beat changes can be measured from a continuous running ECG record (lead II).

1. Valsalva maneuver: The heart rate response to valsalva maneuver i.e forced expiration against resistance to assess baroreceptor integrity was assessed. The valsalva ratio was calculated as the ratio of longest R-R interval after maneuver to shortest R-R interval during maneuver. [16]
2. Heart rate variation (HRV) with respiration was measured in supine position. Resting ECG was recorded and baseline heart rate was measured. The subject was asked to breathe in deeply at a rate of 6 breaths per minute allowing 5 seconds each of inspiration and expiration. The expiratory (E) to inspiratory (I) ratio was calculated as the sum of 6 longest R-R interval, divided by 6 shortest R-R intervals. [16]

**B. Sympathetic function tests:**

1. **Cold pressor test (CPT):** Subject was asked to immerse his hand in cold water maintained at 4-6 degree Celsius and blood pressure measurement was made from other arm. Failure of systolic BP to rise by 16-20 mm Hg and diastolic BP by 12-15 mmHg was indication of autonomic neuropathy.[16, 17]
2. **Blood pressure response to standing:** After blood pressure measurement in supine position the subject was made to stand. Blood pressure was recorded in 30 second interval. Difference between readings of blood pressure in lying position and then after standing was calculated.[16,17]

**Statistical Analysis:** SPSS 21.0 software and graph pad prism 3.0 for windows were used. Co-efficient of correlation in bivariate relationship was obtained using the Karl Pearson correlation test. The autonomic responses were compared between underweight, normal weight, overweight and obese COPD using the multiple analysis of variance (MANOVA Tukey). A "p" value of <0.005 was considered as statistically significant.

## Result

**Table 1: Frequency of different responses to tests of autonomic dysfunction according to severity of COPD**

| Test | Under Weight N=6 | Normal Weight N=26 | Over Weight N= 5 | Obese N=5 |
|---|---|---|---|---|
| **Valsalva ratio <1.20- abnormal, 1.20-1.45, borderline, and >1.45-normal** | | | | |
| Abnormal | 2(33%) | 8(31%) | 3(60%) | 1(20%) |
| Borderline | 1(17%) | 11(42%) | 2(40%) | 3(60%) |
| Normal | 3(50%) | 7(27%) | 0(0) | 1(20%) |

| Test | Under Weight N=6 | Normal Weight N=26 | Over Weight N= 5 | Obese N=5 |
|---|---|---|---|---|
| **Heart rate variation (HRV) after deep breathing <10 beats- abnormal, 10-15 beats –borderline, and >15 beats –normal** | | | | |
| Abnormal | 6(100%) | 10(38%) | 3(60%) | 3(60%) |
| Borderline | 0 | 11(42%) | 1(20%) | 2(20%) |
| Normal | 0 | 5(19%) | 1(20%) | 0 |
| **BP response to posture change** | | | | |
| Abnormal | 1(17%) | 1(4%) | 0 | 0 |
| Borderline | 2(33%) | 8(30%) | 2(40%) | 0 |
| Normal | 3(60%) | 17(67%) | 3(60) | 5 (100%) |
| **BP response to Cold pressor test** | | | | |
| Abnormal | 3(50%) | 18(70%) | 3(60%) | 18(70%) |
| Normal | 3(50%) | 8(30%) | 2(40%) | 8(30%) |

**Table 2: Correlation between BMI and autonomic tests responses**

| | BMI | | |
|---|---|---|---|
| | **Pearson Correlation** | **P Value** | **Significance** |
| Valsalva Maneuver | -.17 | .28 | NS |
| Heart rate variation after deep breathing | -.05 | .75 | NS |
| FEV1 | .01 | .97 | NS |
| PEF | .19 | .23 | NS |
| SBP to posture change | -.25 | .12 | NS |
| DBP to posture change | -.08 | .61 | NS |
| SBP to cold pressor test | -.02 | .90 | NS |
| DBP to cold pressor test | -.08 | .60 | NS |

SBP- Systolic blood pressure, DBP- Diastolic blood pressure, $FEV_{1}$. Forced expiratory volume in 1 second, PEF-Peak expiratory flow rate. There were no correlation between BMI and autonomic dysfunction responses in patients with COPD. [Karl Pearson correlation (r), ns- p >0.05] given in Table 2.

**Table 3: Between groups MANOVA analysis**

| Group | | Mean | Std. Deviation | F value | P Value |
|---|---|---|---|---|---|
| Valsalva Maneuver | 1 | 1.3427 | .38015 | 0.572 | 0.637 |
| | 2 | 1.2440 | .12442 | | |
| | 3 | 1.1580 | .06058 | | |
| | 4 | 1.3533 | .20906 | | |
| Heart rate variation after deep breathing | 1 | 12.846 | 7.8470 | 1.46 | 0.24 |
| | 2 | 8.600 | 4.0373 | | |
| | 3 | 11.800 | 7.3959 | | |
| | 4 | 6.950 | 2.1107 | | |
| $FEV_{1}$ | 1 | 37.62 | 10.534 | 0.599 | 0.62 |
| | 2 | 40.60 | 13.939 | | |
| | 3 | 44.00 | 13.435 | | |
| | 4 | 43.17 | 18.192 | | |

| Group | | Mean | Std. Deviation | F value | P Value |
|---|---|---|---|---|---|
| PEF | 1 | 34.50 | 12.791 | 1.039 | 0.386 |
| | 2 | 45.60 | 16.319 | | |
| | 3 | 40.00 | 9.055 | | |
| | 4 | 40.33 | 21.528 | | |
| SBP to posture change | 1 | 9.54 | 7.223 | 0.316 | 0.814 |
| | 2 | 6.60 | 2.408 | | |
| | 3 | 8.60 | 5.550 | | |
| | 4 | 10.17 | 8.010 | | |
| DBP to posture change | 1 | 5.69 | 4.028 | 0.451 | 0.718 |
| | 2 | 4.40 | 2.881 | | |
| | 3 | 6.80 | 7.791 | | |
| | 4 | 8.33 | 12.258 | | |
| SBP to cold pressor test | 1 | 12.50 | 9.378 | 0.275 | 0.843 |
| | 2 | 15.00 | 9.618 | | |
| | 3 | 15.80 | 6.979 | | |
| | 4 | 15.17 | 13.630 | | |
| DBP to cold pressor test | 1 | 7.15 | 5.548 | 0.177 | 0.911 |
| | 2 | 5.80 | 2.775 | | |
| | 3 | 5.80 | 3.271 | | |
| | 4 | 6.67 | 4.676 | | |

Multiple comparisons between underweight, normal weight, overweight, and obese patients with COPD for cardiac autonomic responses. $FEV_1$, PEF were statistically non-significant (MANOVA Tukey, P>0.05) given in table-3.

## Discussion

The role of BMI in the pathogenesis of COPD is not clear. In previous researches it has been found that both, parasympathetic as well as sympathetic divisions have been found to be affected in the adult obese population as compared to the non- obese adult population.[16,17] Whereas Chabra S K et al reported a reduction in both parasympathetic and sympathetic function in subjects with normal BMI with or without hypoxemia.[4] Among patients 21.4% had no evidence of autonomic neuropathy while 28.6% had early neuropathy and 28% had definite neuropathy. The relationship between autonomic neuropathy and BMI was not given by Chabra S K et al. The results of the present study found that there was definite autonomic neuropathy in normal weight COPD population similar to Chhabra S K et al. Amongst all the groups of COPD population in our study 90% have definite or early autonomic neuropathy and 10% have no evidence of autonomic neuropathy (Table-1).

Wu J et al compared autonomic dysfunction in underweight, normal weight, overweight and obese adults. The study compared HRV (hear rate variation during forced breathing) and HF (high frequency spectrum) power and correlated SDNN (the standard deviation of the average NN intervals) autonomic dysfunction in underweight, normal weight, overweight and obese adults. HRV and HF power were statistically significant for obese (p=o.o1) but there were non-significant results for underweight and overweight (P= 0.86, 0.15 respectively). There was no significant independent correlation of SDNN with underweight (p=0.41), overweight (p =0.80) and obesity (p= 0.43) group. It was concluded that underweight was not a correlate of any indices of Cardiac autonomic function (CAF) but over weight and obesity were independently associated factors of altered CAF.[18]

In our present study, we compared autonomic dysfunction in underweight, normal weight, overweight and obese COPD population. Parasympathetic function tests were statistically non- significant between underweight, normal weight, overweight, and obese COPD patients (P-0.64, P-0.24 respectively, table-3). Sympathetic function tests i.e BP response to postural change and BP response to cold pressor tests also were

statistically non-significant between underweight, normal weight, overweight and obese COPD patients. (P-0.8, P-0.84, table-4). We also found non- significant correlation between BMI and autonomic function tests (table-2)

In present study most of the underweight COPD population have definite or borderline autonomic neuropathy (table-1) which was different from the results of study of W u J et al. [18] This may be the reason that COPD patients have enhanced sympathetic tone at rest and are less able to respond to sympathetic and parasympathetic stimuli in comparison to healthy persons. Previous study show that resting muscle sympathetic nerve activity is significantly higher in patients with COPD as compared to age and sex matched healthy control subjects. [11]

Studies show that plasma nor-epinephrine was elevated in patients with emphysema compared with healthy controls. Altered lung inflation reflexes may also mediate sympathetic activation in COPD.[19,20] Sympathetic activation with its chronotropic effects may be responsible for elevated heart rate response seen in COPD patients.[20]

In underweight COPD patients, neuro-humoral activation caused by sympathetic activation may be a cause of skeletal muscle dysfunction. This seems to involve the diaphragm and accessory respiratory muscles, with aggravation of ventilation disturbances characteristic for COPD. Chronic hypoxemia seems to play a role in sympathetic activation, even in healthy subjects.[21]

The results of this study show that there was non-significant (weak positive, r-0.006) correlation for $FEV_1$ and PEF with increasing BMI [ $FEV_1$(P-0.62, P-0.97), PEF(P-0.39,P-0.23) respectively, table-2]. Lad U et al found in their study that there was positive correlation in underweight male and female with $FEV_1$ and overweight male, and female had negative correlation with $FEV_1$.[21]

## Conclusion

There were several studies available on effects of obesity on cardiac autonomic dysfunction and effects of COPD on cardiac autonomic dysfunction. But till date no study is available on combined effects of obesity and COPD on cardiac autonomic dysfunction. Therefore present study was done on evaluation of autonomic dysfunction with increasing BMI in patients with COPD. In present study, although the results have shown that there was definite autonomic neuropathy in patients with COPD with increasing BMI, there was no significant difference in autonomic dysfunction with increasing BMI in patients with COPD. Furthermore, in several studies we found that irrespective of the stages of the disease, underweight was an independent risk factor for cardiovascular complication and mortality. In mild and moderate COPD the best prognosis is found in normal weight or over weight subjects. In severe COPD, over weight, and obesity, is associated with better survival (obesity paradox, prognostic). Therefore we suggest that patients with COPD in the normal to overweight range have better prognosis.

**Limitations of the Study:** Our study was constrained by the small size of the sample available. The morbidly obese were not included in our study.

**Conflict of Interest:** The authors do not have any conflicts of interest to declare.

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