ORIGINAL RESEARCH

Association Between COPD Severity, Hypoxemia, And Autonomic Neuropathy

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Received: 29 September, 2023 Accepted: 21 October, 2023

ABSTRACT

Introduction: Chronic Obstructive Pulmonary Disease (COPD) is a global health issue affecting not only the respiratory system but also the autonomic nervous system. The complex interaction between COPD severity, chronic hypoxemia, and autonomic neuropathy is vital to understanding and managing the disease. Hypoxemia in COPD, characterized by reduced oxygen levels, is correlated with increased sympathetic activity and alterations in heart rate variability.

Aim: The study aims to explore the relationship between COPD severity, hypoxemia, and autonomic neuropathy to improve diagnostic and therapeutic strategies.

Material and Methods: A detailed study was conducted on 39 participants with COPD at a tertiary care centre over 18 months. The cardiovascular autonomic function was assessed through various tests, including heart rate response during deep breathing, blood pressure monitoring during isometric handgrip exercises, and orthostatic and Valsalva manoeuvre tests. The participants' lung function and hypoxemia were also evaluated.

Results: The participants, predominantly male, exhibited a resting heart rate of 83.64±6.13 bpm, and systolic and diastolic blood pressure of 126.62±4.84 mm Hg and 83.28±3.45 mm Hg respectively. Autonomic function tests varied significantly with COPD severity. Significant correlations were found between FEV_1, SpO_2 and various autonomic function tests. In particular, decreased FEV_1 and SpO_2 levels were associated with altered blood pressure and heart rate responses during orthostatic and Valsalva manoeuvre tests.

Conclusion: The findings emphasize the importance of assessing cardiovascular and pulmonary parameters to understand the autonomic responses in COPD patients. Correlations between FEV_1, SpO_2, and autonomic function tests highlight the complex interplay between lung function, oxygen saturation, and autonomic responses. This insight can contribute to the development of targeted therapeutic and management strategies for COPD patients with autonomic dysfunction.

Keywords: COPD, Autonomic Neuropathy, Hypoxemia, FEV_1, SpO_2, Valsalva Manoeuvre, Orthostatic Test.

INTRODUCTION

Chronic Obstructive Pulmonary Disease (COPD) represents a pervasive global health concern characterized by progressive airflow limitation, with an estimated 251 million cases worldwide [1]. The prevalence and impact of COPD extend beyond pulmonary function, affecting multiple physiological systems, including the autonomic nervous system [2]. Emerging research has illuminated a complex interplay between COPD severity, chronic hypoxemia, and autonomic neuropathy [3]. The global prevalence of COPD continues to rise, burdening healthcare systems and individuals alike [1]. It is a major cause of morbidity and mortality, with exacerbations leading to a significant deterioration in the quality of life and increased healthcare utilization [4]. Additionally, COPD is intricately linked to comorbidities such as cardiovascular disease [2,3], making its management and understanding paramount in modern medicine. Hypoxemia in COPD represents a critical aspect of this multifaceted respiratory condition with profound implications. Chronic Obstructive Pulmonary Disease can lead to hypoxemia due to impaired airflow, ultimately resulting in inadequate oxygen supply to body tissues [5]. This lack of oxygen contributes to a spectrum of challenges, including diminished exercise tolerance, reduced skeletal muscle function, and a significantly decreased quality of life [6]. Beyond these immediate effects, hypoxemia in COPD patients can trigger severe organ damage, such as pulmonary hypertension, systemic inflammation, and polycythaemia, further complicating the clinical picture [7]. Understanding and managing hypoxemia in COPD is pivotal for enhancing patient well-being and is an imperative focus of research in the field of respiratory medicine. Studies have shown that COPD

severity can negatively affect autonomic responses, including heart rate modulation during tasks like the Valsalva manoeuvre (VM) and inspiratory capacity (IC) tests [2,8]. Furthermore, the presence of autonomic neuropathy tends to be more prevalent in individuals with moderate-to-severe COPD compared to those with milder forms of the disease [9]. Hypoxia, a hallmark of COPD, is one of the contributing factors to autonomic dysfunction in these patients. Reduced oxygen levels can lead to increased sympathetic activity and alterations in heart rate variability [10,11]. Furthermore, there is a correlation between the degree of hypoxemia and the severity of neuropathy, highlighting the intricate relationship between oxygen levels and autonomic neuropathy in COPD [12].

Investigating the relationship between autonomic dysfunction and chronic obstructive pulmonary disease (COPD) is essential to comprehend its impact on patient health and quality of life. Understanding how COPD influences autonomic nervous system function can lead to improved diagnostic and therapeutic strategies, ultimately enhancing the well-being of individuals with this condition.Therefore, the present study aims to early determine the nature of autonomic imbalance in COPD patients.

MATERIAL & METHODS

In our study conducted at a tertiary care centre over 18 months, from February 2016 to August 2017, we focused on individuals diagnosed with Chronic Obstructive Pulmonary Disease (COPD) aged between 45 to 60 years who were capable of independent mobility and had a Post bronchodilator FEV1/FVC less than 70%.Those fitting into GOLD 4 criteria were excluded. [13] They were divided into 3 subgroups, based on the severity of COPD, as categorized on the basis of FEV1% (predicted) as per the GOLD classification.[13] GOLD 1 / mild (equal or more than 80%), GOLD 2 / moderate (equal or more than 50 – less than 80%) and GOLD 3 / severe (equal or more than 30 - less than 50%). A total of 39 participants were enrolled based on calculated sample size requirements. During the study, participants underwent a series of tests to assess their cardiovascular autonomic function, including heart rate response during deep breathing, blood pressure monitoring during isometric handgrip exercises, heart rate and blood pressure changes upon transitioning from lying down to standing (orthostatic test), and heart rate response to the Valsalva manoeuvre. Our objective was to investigate the relationship between the severity of COPD, the presence of hypoxemia, and autonomic neuropathy, using statistical analyses to discern connections. This research provides valuable insights into how COPD severity and hypoxemia may be linked to autonomic nervous system dysfunction, which could have important implications for COPD management. On the basis of the responses, the participants were categorized as per Ewing and Clark Classification:

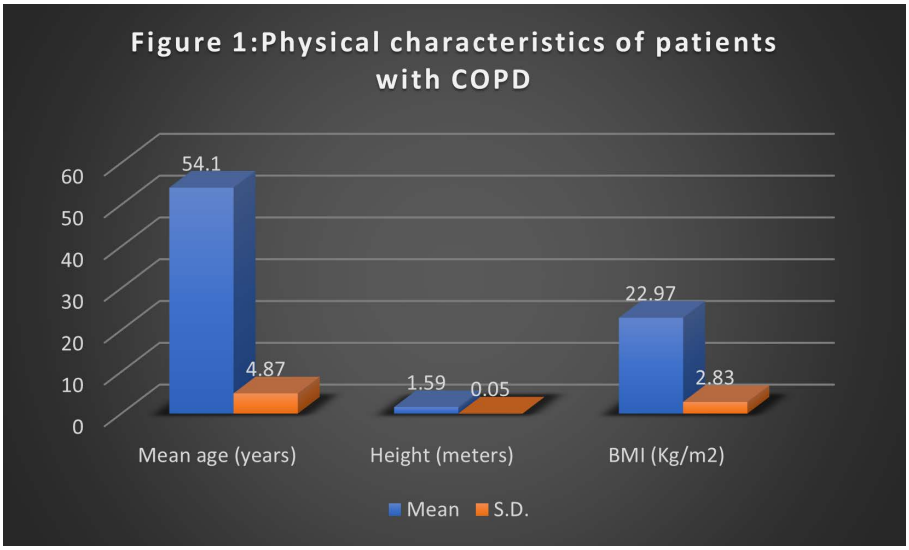
i. Normal: all responses in the normal range or one test borderline;
ii. Early involvement: one of the three heart rate tests abnormal or two tests borderline;
iii. Definite autonomic neuropathy: two or more abnormal tests. [14]

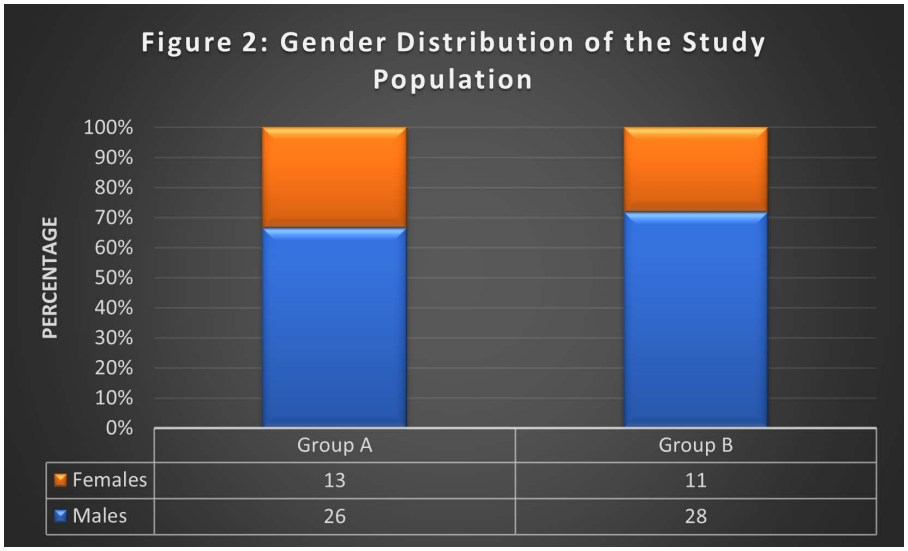
Proportions of participants with normal, borderline and abnormal responses, and absent, early and definitive autonomic neuropathy in the 3 subgroups of participants with COPD were compared using the Chi-square test and the autonomic responses were compared between the 3 subgroups (based on severity of COPD) using the analysis of variance (ANOVA).Coefficient of correlation was calculated using the Pearson's correlation test. Ethical considerations were upheld, with approval from the Institutional Ethics Committee and informed consent from all participants.

RESULTS

Table 1: Physical Characteristics and Gender Distribution (COPD Patients)

Characteristic	Mean ± S.D.
Mean age (years)	54.10 ± 4.87
Height (meters)	1.59 ± 0.05
BMI (Kg/m^2)	22.97 ± 2.83
Gender	Total Subjects (n=39)
Males	28 (71.79%)
Females	11 (28.21%)





Our study of 39 COPD patients observed a consistent average age of 54.10±4.87 years. The mean height was 1.59 ±0.05 meters, and the average BMI was 22.97 ± 2.83 Kg/m², indicating a relatively uniform physical profile within this patient group. Among the patients, 28 (71.79%) were males, while 11 (28.21%) were females. These findings provide essential insights into the characteristics and gender distribution among individuals affected by COPD.

Table 2: Resting Heart Rate, Blood Pressure, and Heart Rate Responses (COPD Patients)

Parameter	Resting Heart Rate	Systolic Blood Pressure	Diastolic Blood Pressure
Value (Mean +/- S.D.)	83.64 ± 6.13	126.62 ± 4.84	83.28 ±3.45

Table 2 presents essential cardiovascular parameters observed in COPD patients. This group's resting heart rate was 83.64 ± 6.13 beats per minute, indicative of their cardiac activity. Additionally, systolic blood pressure was noted to be 126.62 ± 4.84 mm Hg), while diastolic blood pressure averaged 83.28 ± 3.45 mm Hg.

Table 3: Heart Rate Response to Deep Breathing (E:I Ratio and ΔHR) (COPD Patients)

Response to Deep Breathing	E:I Ratio	ΔHR
Value (Mean± S.D.)	1.25± 0.07	20.81± 6.12

Table 3 highlights the heart rate responses of COPD patients to deep breathing. The E:I ratio was 1.25± 0.07, indicating their autonomic responses during this manoeuvre. Furthermore, the change in heart rate (ΔHR) was measured at 20.81± 6.12, shedding light on the dynamic aspects of heart rate regulation in these patients.

Table 4: Blood Pressure Response to Isometric Handgrip (ΔDBP) and Postural Change (Orthostatic Test - ΔSBP) (COPD Patients)

Response to Isometric Handgrip	ΔDBP	Orthostatic Test – ΔSBP
Value (Mean ± S.D.)	23.02 ± 5.43	19.31 ± 9.16

Table 4 outlines the blood pressure responses of COPD patients to isometric handgrip and orthostatic changes. The change in diastolic blood pressure (ΔDBP) during isometric handgrip was measured at 23.02± 5.43, while the change in systolic blood pressure (ΔSBP) during orthostatic testing was recorded at 19.31± 9.16.

Table 5: Heart Rate Response to Postural Change (Orthostatic Test - 30:15 Ratio) and Valsalva Manoeuvre (Valsalva Ratio)

Response to Postural Change	30:15 Ratio	Valsalva Ratio
Value (Mean ± S.D.)	1.21 ± 0.11	1.26± 0.21

Table 5 presents heart rate responses to postural change and the Valsalva manoeuvre in COPD patients. The 30:15 ratio during postural change was measured at 1.21± 0.11, reflecting autonomic modulation of heart rate. The Valsalva ratio, indicative of autonomic function during the Valsalva manoeuvre, was recorded at 1.26 (+/- 0.21).

Table 6: SpO_2 Difference between Hypoxemic &Normoxemic Groups and Comparison of Resting Heart Rate between Them

SpO_2 Groups	SpO_2	Resting Heart Rate
Hypoxemic Group	91.43 ± 0.53	84.57 ± 6.19
Normoxemic group	95.36 +/- 0.63	81.86 +/- 6.15

Table 6 highlights the differences between hypoxemic and normoxemic groups regarding SpO_2 levels and resting heart rates. In the hypoxemic group, SpO_2 was 91.43%± 0.53, while the resting heart rate averaged 84.57 ± 6.19 beats per minute & in the normoxemic group, SpO_2 was 95.36%± 0.63, while the resting heart rate averaged 81.86 ± 6.15 beats per minute.

Table 7: Proportion of COPD with absent, early, definite autonomic neuropathy as per disease severity

	GOLD 1	GOLD 2	GOLD 3	Total
Absent	5	4	1	10
Early	0	13	12	25
Definite	0	0	4	4
	5	17	17	39

Table 7 highlights the proportions of COPD patients with absent, early & definite autonomic neuropathy were compared to the 3 subgroups (based on severity of disease) of COPD patient by applying the Chi-square test and a p-value of 0.000175 was noted, which is statistically highly significant.

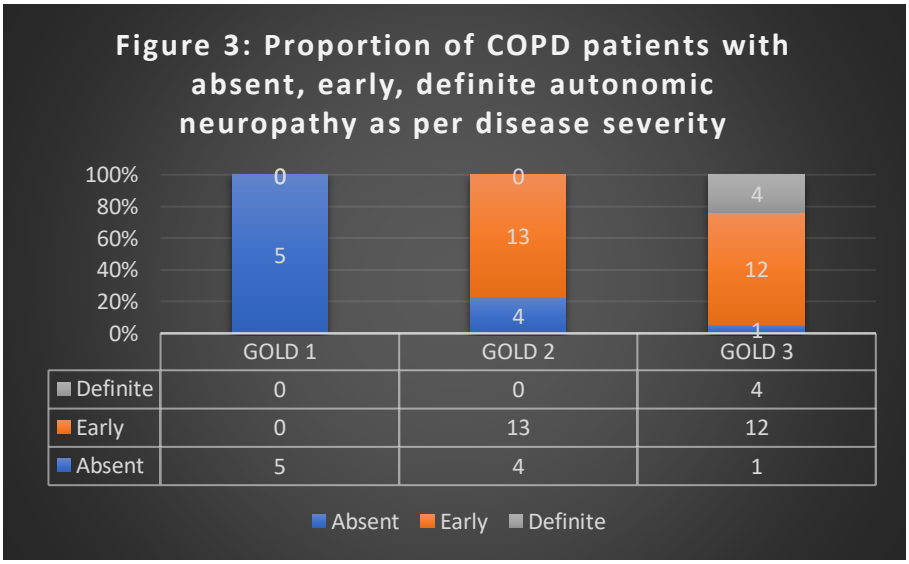


Table 8: Comparison of Autonomic Function Test Responses by Disease Severity

Parameters		GOLD 1 (n=5)	GOLD 2 (n=17)	GOLD 3 (n=17)	P Value
Heart rate response to Deep Breathing (Δ HR)	**Normal**	5	12	16	0.47
	Borderline	0	5	1	
	Abnormal	0	0	0	
Blood Pressure response to IHG (Δ DBP)	**Normal**	5	15	14	0.91
	Borderline	0	2	3	
	Abnormal	0	0	0	
Blood Pressure response to stural change (Orthostatic Test – ΔSBP)	**Normal**	5	1	0	<0.0001
	Borderline	0	15	12	
	Abnormal	0	1	5	
Heart rate response to postural change (Orthostatic Test - 30:15 Ratio)	**Normal**	5	17	17	0.33
	Borderline	0	0	0	
	Abnormal	0	0	0	
Heart rate response to Valsalva manoeuvre (Valsalva Ratio)	**Normal**	5	6	2	<0.0001
	Borderline	0	11	8	
	Abnormal	0	0	7	
Heart rate response to Deep Breathing Test (E:I Ratio)	**Normal**	5	12	12	0.73
	Borderline	0	5	5	
	Abnormal	0	0	0	

Table 8 summarizes autonomic function test responses in COPD patients categorized by disease severity (GOLD classification). Results indicate that heart rate response to deep breathing showed no significant differences across groups (p=0.47). Most patients exhibited normal blood pressure responses to isometric handgrip (p=0.91), but significant differences were observed in blood pressure responses to postural change (p<0.0001). Heart rate responses to postural change were similar across groups (p=0.33), while significant differences were noted in heart rate responses to the Valsalva manoeuvre (p<0.0001). Heart rate responses to the deep breathing test did not significantly differ (p=0.73).

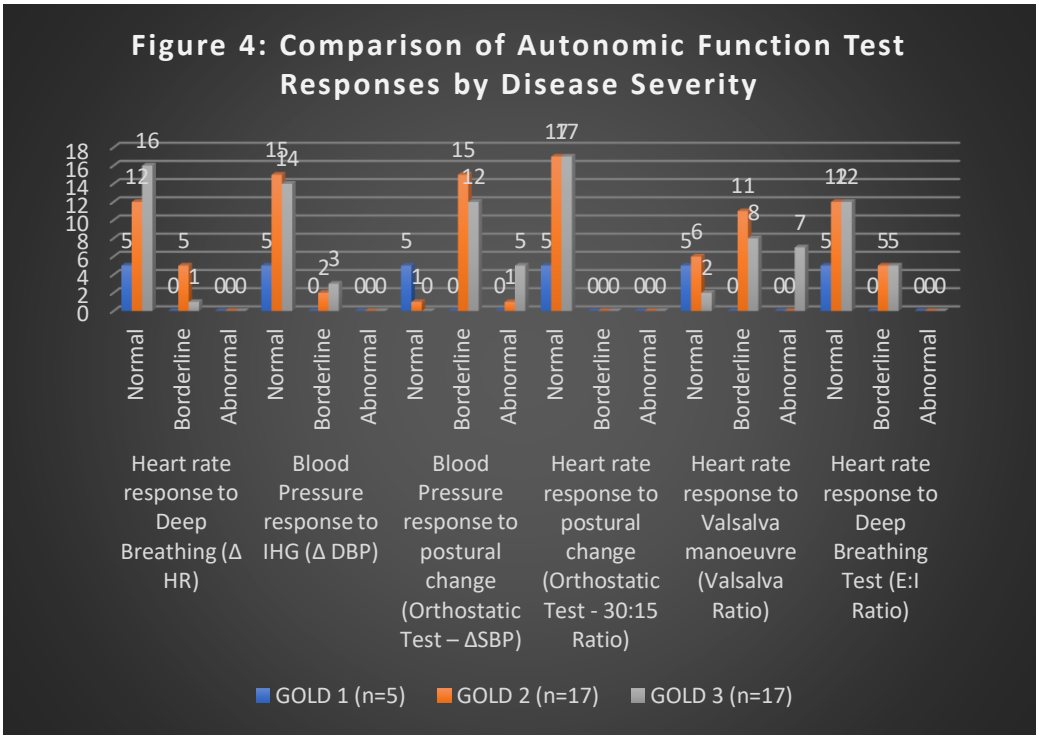


Table 9: Correlation of Physiological Parameters with Autonomic Function Tests (COPD Patients)

Parameters	ΔSBP Orthostatic Test	E:I Ratio	Δ HR	30:15 Ratio Orthostatic Test	Δ DBP IHG	Valsalva Ratio
FEV_1	-0.61	0.12	0.08	0.14	0.35	0.76
SpO_2	-0.59	0.09	0.07	0.23	0.29	0.65

Table 9 illustrates the correlation coefficients between various physiological parameters and autonomic function tests among COPD patients. Notably, forced expiratory volume in one second (FEV_1) exhibited significant negative correlations with ΔSBP Orthostatic Test (-0.61, $p<0.0001$) and positive correlations with Δ DBP IHG (0.35, $p<0.05$) and Valsalva Ratio (0.76, $p<0.0001$). Similarly, oxygen saturation (SpO_2) displayed significant negative correlations with ΔSBP Orthostatic Test (-0.59, $p<0.0001$) and positive correlations with E:I Ratio (0.09, $p<0.05$), Δ HR (0.07, $p<0.05$), and Valsalva Ratio (0.65, $p<0.0001$).

DISCUSSION

In our study involving 39 COPD patients, we observed consistent physical characteristics: an average age of 54.10 years, a height of 1.59 meters, and a BMI of 22.97 kg/m². Gender distribution showed that 71.79% were males and 28.21% were females. The resting heart rate was 83.64 bpm, systolic blood pressure was 126.62 mm Hg, and diastolic blood pressure was 83.28 mm Hg. Heart rate responses to deep breathing (E:I Ratio) averaged 1.25, and the change in heart rate (ΔHR) was 20.81. During isometric handgrip, the change in diastolic blood pressure (ΔDBP) was 23.02, and during orthostatic testing, the change in systolic blood pressure (ΔSBP) was 19.31. Heart rate responses to postural change (30:15 Ratio) were 1.21; during the Valsalva manoeuvre, the Valsalva Ratio was 1.26. SpO_2 levels and resting heart rates differed between hypoxemic and normoxemic groups. Lastly, correlation analyses revealed significant relationships between FEV_1, SpO_2, and various autonomic function tests, shedding light on the connections between lung function, oxygen saturation, and autonomic responses in COPD patients.In our study of 39 COPD patients, the average age was 54.10 years, with a narrow standard deviation, reflecting consistency within our patient group. Patients had an average height of 1.59 meters and a mean BMI of 22.97 Kg/m².Comparing our findings to existing research, our average age corresponds with previous studies, which also reported that COPD patients are typically in their mid-50s [15]. Additionally, our study's gender distribution, with a higher proportion of males, aligns with the general trend in COPD, where males are more commonly affected [16].In our study, COPD patients exhibited a resting heart rate of 83.64 bpm, in line with expectations for this patient group. This finding correlates with the study by Byrd et al., which also observed elevated resting heart rates in COPD patients [17]. Furthermore, our study revealed systolic blood pressure of 126.62 mm Hg and diastolic blood pressure of 83.28 mm Hg. These values align with the observations made by Christofaro et al., who demonstrated a relationship between elevated resting heart rate and increased systolic and diastolic blood pressure [18].Our study found an E:I ratio of 1.25 during deep breathing, indicative of autonomic responses in COPD patients. This result corresponds with previous research suggesting altered autonomic function in COPD patients [2]. The change in heart rate (ΔHR) during deep breathing (20.81 bpm) underscores the dynamic aspects of heart rate regulation, as supported by studies emphasizing the importance of assessing dynamic heart rate responses in COPD [19].Our findings revealed significant changes in blood pressure during isometric handgrip and orthostatic testing. The increase in diastolic blood pressure (ΔDBP) during isometric handgrip (23.02 mm Hg) aligns with studies emphasizing the relationship between cardiovascular disease and COPD [18,20]. Similarly, the change in systolic blood pressure (ΔSBP) during orthostatic testing (19.31 mm Hg) is consistent with the importance of assessing blood pressure responses in COPD patients [20,21].Our study reported a 30:15 ratio of 1.21 during postural change and a Valsalva ratio of 1.26. These findings reflect autonomic modulation of heart rate during these manoeuvres, consistent with the observations made by Osailan et al., who assessed cardiovascular autonomic neuropathy using similar reflex tests [22].In our study, hypoxemic COPD patients exhibited lower SpO_2 levels (91.43%) and higher resting heart rates (84.57 bpm). These results are consistent with the study by Luo et al., which highlighted the relationship between low heart rate and mortality in cardiovascular diseases [23].Our study categorized COPD patients by disease severity using the GOLD classification and assessed autonomic function test responses. We found that heart rate responses to deep breathing did not significantly differ across disease severity groups, which is in line with the study by Dawson et al. that also observed consistent heart rate measurements across pulse oximeters [24].However, significant differences were noted in blood pressure responses to postural change, with a p-value of less than 0.0001. Similarly, heart rate responses to the Valsalva manoeuvre showed significant differences across disease severity groups with a p-value of less than 0.0001. This is consistent with the importance of assessing autonomic function in COPD patients, as emphasized in studies related to hypoxemia and its effects on heart rate [25].Table 7 highlights the proportions of COPD patients with absent, early &

definite autonomic neuropathy were compared to the 3 subgroups (based on severity of disease) of COPD patient by applying the Chi-square test and a p-value of 0.000175 was noted, which is statistically highly significant, which is consistent with the findings of Chhabra et al [26].Table 9 reveals correlations between physiological parameters and autonomic function tests among COPD patients. Notably, FEV_1 exhibited significant negative correlations with ΔSBP Orthostatic Test and positive correlations with Δ DBP, IHG and Valsalva Ratio. These findings correspond to the importance of lung function in autonomic responses, as supported by previous studies highlighting the impact of lung capacity on oxygen saturation and heart rate [27].Additionally, SpO_2 displayed significant negative correlations with ΔSBP Orthostatic Test and positive correlations with E:I Ratio, Δ HR, and Valsalva Ratio. This suggests the interplay between oxygen saturation and autonomic function, aligning with studies emphasizing the relationship between oxygen levels and physiological responses [1,28].In conclusion, our study's findings regarding autonomic function in COPD patients are consistent with existing research, emphasizing the significance of assessing lung function and oxygen saturation in understanding autonomic responses.

CONCLUSION

Our findings emphasize the critical role of assessing parameters such as heart rate, blood pressure responses, and lung function when delving into the autonomic responses of this patient group. Notably, we've uncovered significant correlations between FEV_1, SpO_2, and various autonomic function tests, shedding valuable light on the intricate relationships between lung function, oxygen saturation, and autonomic responses in individuals with COPD. These findings underscore the relevance and importance of our research in contributing to the broader understanding of COPD and its impact on autonomic functions.

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