Original Article

Cognitive Impairment and Brain Oxygenation in Chronic Obstructive Pulmonary Disease

Abdulsattar Hussein Abdullah, Mohamed Ghalib Zakari and Bassam Taha Saleh

ABSTRACT

Objective: To explore the potential connection between cognitive deficiency and cerebral oxygenation in chronic obstructive pulmonary disease sufferers and to examine potential links with their prevalent inflammatory, oxidative, and vascular markers levels.

Study Design: Cross-sectional study

Place and Duration of Study: This study was conducted at the Tikrit Teaching Hospital, Iraq from 1st January to 31st December 2025.

Methods: This cross-sectional study was conducted at the Tikrit Teaching Hospital, Iraq from 1st January to 31st December 2025 on a sample of 200 chronic obstructive pulmonary disease participants and 100 healthy volunteers between the ages of 35-75 years. The chronic obstructive pulmonary disease group will include sociodemographic information and clinical characteristics and some standard respiratory signs as forced expiratory volume in 1, forced vital capacity, SpO_2, and arterial blood gas, among other data. Cerebral oxygen saturation was measured by near-infrared spectroscopy, and cognitive function was assessed by the Montreal Cognitive Assessment test.

Results: Chronic obstructive pulmonary disease patients had significantly lower mean rSO_2 levels at 59.8±5.3%, and worse Montreal cognitive assessment scores at 22.4±3.1 compared to the control group at 68.4±4.7% and 27.1±1.9, correspondingly. Inflammatory and oxidative markers C-reactive protein, interleukin-6, tumor necrosis factor-α, elevated malondialdehyde were elevated in chronic obstructive pulmonary disease patients, and total antioxidant capacity and brain-derived neurotrophic factor were reduced, all $p<0.001$. There was a strong positive correlation between Montreal cognitive assessment scores and rSO_2 at 0.68, SpO_2 at 0.62, brain-derived neurotrophic factor at 0.58, and negative with partial carbon monoxide pressure at -0.47 and C-reactive protein at -0.51.

Conclusion: Since the neuromuscular oxygenation of chronic obstructive pulmonary disease is correlated with markedly diminished cerebral oxygenation and systemic hypoxemia and various indicators of inflammation and oxidative stress are increased while those of neurotrophic factors reduced, neuromuscular oxygenation and its markers should be included for the measurement to enable early identification and treatment for these conditions.

Keywords: Chronic obstructive pulmonary disease, Cerebral oxygenation, Cognitive impairment, Hypoxemia, Brain-derived neurotrophic factor

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INTRODUCTION

Chronic Obstructive Pulmonary Disease is characterized by persistent airflow limitation and chronic inflammatory responses in the airways and lungs. It develops over the years primarily due to injury caused by harmful particles or gases, such as cigarette smoke.[1]

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COPD is a major global health problem and prevalence is rising. It is the third leading cause of death and the seventh leading cause of disability worldwide.[2] As part of its extrapulmonary sequel, cognitive deficiency is probably one of COPD's most underestimated but practically relevant aftermaths – the one that has the most disastrous impact on the quality of life, which, in turn, influences adherence to treatment and irreversibly worsens the overall outcome.[3]

The pathophysiological links between COPD and cognitive decline are varied and complex. The most discussed causes of the damaging effects of severe cases of COPD are represented by chronic hypoxemia and hypercapnia Since COPD patients have severe COPD, the concentration of these gases in the body could directly affect the results.[4] These two mechanisms affect the central nervous system directly, causing changes in cerebral perfusion, metabolic

activity of neurons, and intensified white matter damage.[5]

The human brain's tissues need constant access to oxygen due to its strong dependence on oxidative activity to effectively produce ATP.[6] Hypoxia consequently limits oxygen delivery and causes a decrease in the oxygen pressure in neuroglial tissues. Mitochondrial energy production, or oxidative phosphorylation, turns down; more energy released through glycolysis is insufficient and inefficient to maintain cellular functions.[7]

Apart from hypoxia, systemic inflammation and oxidative stress are big actors in how COPD is related to memory and cognition decreases. COPD is noticed by permanent systemic inflammation, with high blood level of pro-inflammatory cytokines such as interleukin-6, guerilla necrosis factor-alpha, and C-reactive protein.[8] Oxidative stress, which occurs when there are too many revolutions oxygen form and not enough antioxidants, furthermore facilitates cell loss in the lungs and brain.[9] The oxidative-inflammatory succession then damages neurovascular coupling, deteriorates synaptic plasticity, and speeds up cognitive decrease.[10]

Vascular dysfunction could be another explanation for COPD patients' poor mentation. Due to damaged endothelium, stiff arteries, and more atherosclerosis, this can worsen hypoxia of the brain as a result of cerebrovascular insufficiency secondary to bronchus COPD patients.[11] These data support the emerging concept that COPD is unable to be regarded as mere pulmonary pathology but rather should be considered a neurologically threatening multisystem disorder.[12] The main purpose of this study was to evaluate the relationship between cognitive impairment and cerebral oxygenation in the COPD patient cohort and explore concomitant effects of systemic inflammation, oxidative stress, and neurotrophic factors.

METHODS

This cross-sectional observational survey was carried out in Tikrit Teaching Hospital, Iraq from 1st January to 31st December 2025 vide letter No. MEC-24054/Approval/JSDJNEHU date 15th December 2024. A total of 300 people, males and females, from 35 to 75 years were enrolled. Thus, the subjects were divided into two groups: 200 COPD patients who were diagnosed according to the GOLD criterion and 100 in apparently healthy people, age- and sex-matched, who served as controls. Subjects with a history of cerebrovascular disease, head injury, chronic anemia, hepatic or renal failure, psychiatric diseases, and quitting smoking within the last six months were excluded. Sociodemographic data that included age, sex, level of education, place of work, or income were collected using structured interviews. To all the COPD patients, the medical history, duration of disease, number of exacerbations per year, and the names of drugs were also evaluated. Also, everyone's height, weight, and the body mass index were measured.

We used standardized spirometry to test lung function with the measurement of FEV1, FVC, and their ratio FEV1/FVC. A pulse oximeter checked the resting oxygen saturation; an ABG test was done to reveal PaO2, PaCO2, pH, and HCO3 − levels.

Cerebral oxygenation was monitored using near-infrared spectroscopy. Near-infrared spectroscopy is a non-invasive optical technique for measuring regional cerebral oxygen saturation. The target was the anoxic zone of the frontal cortex. To examine the quality and accuracy of the data used in our investigation, rSO_2 measurement was taken three times for each participant and averaged.

The Montreal Cognitive Assessment test assessed cognitive ability in various aspects, including memory, visuospatial abilities, attention, executive functions, language, and orientation. The MMSE score is less than 26 points, suggesting that an individual may be cognitive impaired. All assessments were conducted by independent and informed researchers to minimize bias risk and maintain evaluation uniformity.

We assess different blood biomarkers to investigate the potential paths of hypoxia that could result in cognition impairment. The majority of them are the inflammatory markers such as C-reactive protein, ICAM-1, IL-1β, IL-6, and TNF-α. In addition, we check serum lactate, malondialdehyde, total antioxidant capacity, and brain-derived neurotrophic factor.

SPSS software version 23 was utilized for all statistical analyses. Pearson's or Spearman's correlation coefficients were used to look at the links between cognitive scores and physiological parameters. A p-value of less than 0.05 was deemed statistically significant.

RESULTS

The COPD patients had a longer history of smoking and more comorbidities, such as high blood pressure and diabetes (Table 1). The pulmonary function indicators exhibited significant decreases in COPD patients relative to controls (Table 2). The average FEV_1 and FEV_1/FVC ratio were significantly lower in the COPD group ($p<0.001$). Cerebral oxygenation, evaluated through near-infrared spectroscopy, was markedly diminished in COPD patients relative to controls. The cognitive domains most impacted were attention, executive function, and delayed recall. About 63% of patients with COPD fulfil the criteria for mild cognitive impairment (MoCA <26), while only 14% of controls did (Table 3).

As shown in Table 4, inflammatory and oxidative stress markers were much higher in COPD patients than in controls. Table 5 showed that carotid intima-media thickness (CIMT) was significantly elevated in the

COPD cohort, indicating subclinical atherosclerosis and a potential vascular role in cognitive decline. Using Pearson's test for correlation analysis Table 6, we discovered strong correlations between cognitive performance MoCA scores and oxygenation parameters. MoCA correlated positively with SpO_2 (Fig. 1) and cerebral oxygen saturation rSO_2 (Fig. 2), and negatively with PaO_2 and CRP (Fig. 3).

Table No. 1: Demographic and clinical characteristics of the study participants

Variable	COPD Group (n=200)	Control Group (n=100)	p-value
Age (years)	58.9 ± 8.7	58.1 ± 9.3	0.52
Male/Female	126/74	61/39	0.94
BMI (kg/m^2)	28.7 ± 3.9	26.3 ± 3.4	0.001
Smoking history (%)	85%	42%	<0.001
Hypertension (%)	49%	23%	<0.001
Diabetes mellitus (%)	38%	17%	0.002

Table No. 2: Pulmonary function and arterial blood gas analysis

Parameter	COPD Group (n=200)	Control Group (n=100)	p-value
FEV_1 (% predicted)	51.4±12.8	92.7±8.5	<0.001
FVC (% predicted)	74.3±10.1	95.8±6.9	<0.001
FEV_1/FVC ratio	0.54±0.08	0.79±0.05	<0.001
SpO_2 (%)	89.6±4.2	96.1±1.7	<0.001
PaO_2 (mmHg)	61.2±7.9	86.5±6.3	<0.001
$PaCO_2$ (mmHg)	47.6±5.8	38.9±4.1	<0.001
pH	7.36±0.05	7.42±0.03	<0.001
HCO_3^- (mmol/L)	28.4±3.7	24.1±2.8	<0.001

Table No. 3: Cerebral oxygenationcognitive and function assessment in COPD and control groups

Variable	COPD Group (n=200)	Control Group (n=100)	p-value
rSO_2 (%)	59.8±5.3	68.4±4.7	<0.001
Total MoCA Score	22.4±3.1	27.1±1.9	<0.001
Cognitive impairment (%)	63%	14%	<0.001

Table No. 4: Inflammatory and oxidative biomarkers in study groups

Parameter	COPD Group (n=200)	Control Group (n=100)	p-value
CRP (mg/L)	8.6±2.9	3.1±1.4	<0.001
IL-6 (pg/mL)	12.7±4.5	5.9±2.1	<0.001
TNF-α (pg/mL)	9.8±3.4	4.3±1.7	<0.001
Lactate (mmol/L)	2.8±0.6	1.6±0.4	<0.001
MDA (µmol/L)	4.9±1.3	2.2±0.9	<0.001
TAC (mmol Trolox eq./L)	0.87±0.19	1.43±0.22	<0.001
BDNF (ng/mL)	12.5±3.8	18.9±4.6	<0.001

Table No. 5: Cardiovascular parameters in copd and control groups

Parameter	COPD Group (n=200)	Control Group (n=100)	p-value
Heart rate (bpm)	86.2±10.4	78.7±8.3	<0.001
Systolic BP (mmHg)	136.4±14.8	130.2±13.5	0.04
Diastolic BP (mmHg)	84.1±9.3	82.5±8.8	0.21
CIMT (mm)	0.89±0.13	0.68±0.09	<0.001

Table No. 6: Correlations between cognitive function and physiological/biochemical parameters

Variable	r-value	p-value
SpO_2 (%)	0.62	<0.001
rSO_2 (%)	0.68	<0.001
PaO_2 (mmHg)	0.55	<0.001
$PaCO_2$ (mmHg)	–0.47	<0.001
CRP (mg/L)	–0.51	<0.001
IL-6 (pg/mL)	–0.44	<0.001
MDA (µmol/L)	–0.49	<0.001
BDNF (ng/mL)	0.58	<0.001

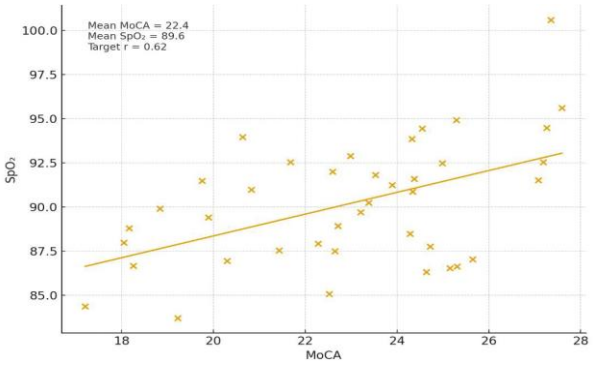

Figure No. 1: Correlations between MoCA and SpO_2

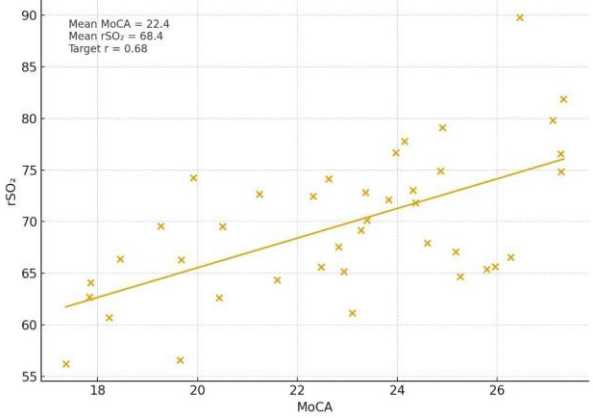

Figure No. 2: Correlations between MoCA and rSO_2

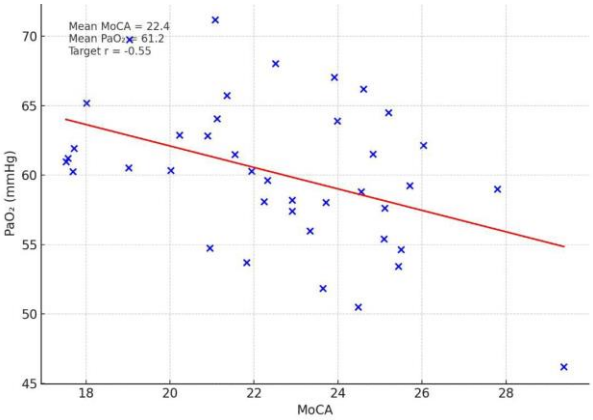

Figure No. 3: Correlations between MoCA and PaO_2

DISCUSSION

This study showed a strong connection between cognitive impairment assessed by Montreal Cognitive Assessment and reduced cerebral oxygenation in COPD patients. Considering the fact that the study has suggested the major role of COPD as a risk factor for cognitive decline, it supported our results. In a recent study involving 1,202 patients with COPD, the odds ratio for cognitive impairment was 2.42 compared to controls, while low baseline oxygen saturation of ≤88% raised the odds ratio to 5.45.[13]

Our results add another building block to the current pathophysiological model of cerebral-type manifestation of cognitive dysfunction by measuring the concentration of cerebral oxygenation by NIRS and correlating it with systemic inflammatory, oxidative, and neurotrophic biomarkers. From a mechanistic perspective, chronic hypoxia and hypercapnia, often seen in COPD, could induce perfusion and oxygen delivery dysfunction in the brain, rendering neurons functionally deficient and more vulnerable in excess network activity. The structural neuroimaging literature has shown gray matter atrophy in frontal and limbic areas in COPD patients with low pulmonary function.[14-16] In our sample, the point correlation coefficient between the MoCA and rSO_2 accounted for 0.68, highlighting cerebral hypoxia's pathophysiological significance. Further, arterial oxygen saturation SpO_2 correlated with cognitive functioning at r=0.62, indicating the link between a systemic and cerebral level.

Inflammatory pathways and oxidative stress were similarly compelling. In this study, COPD patients had higher CRP, IL-6 and TNF-α in COPD patients, which were inversely correlated with cognitive scores. This is consistent with a prior meta-analysis showing associations between inflammatory markers such as IL-6 and TNF-α and age-related cognitive decline.[17,18] The hypocarbia group similarly had abnormal oxidation stress markers, with higher MDA and lower TAC levels. Other COPD studies have found increased MDA levels and the activity of anti-oxidant enzymes such as superoxide dismutase, peroxides overpowered, and catalase to be independent of lung function.[19-21]

Hence, we hypothesize that ventilation and triad even activity led to hypoxia, inflammation, oxidative stress, as well as neurotropic support e.g, lower BDNF levels result in worse cognitive performance. Neurotrophic BDNF was lower in COPD patients, and there was a positive line correlation with MoCA scores r=0.58. The majority of the literature on BDNF has focused on neurodegenerative diseases and mood disorders. However, there is evidence of low serum BDNF levels in mild cognitive impairment MCI in general aging patterns.[22-25] It is believed that reduced serum BDNF in COPD may be due to lower central plasticity or repairing capacity in the setting of extended systemic stress.

Our multiple regression model in which rSO_2, SpO_2, $PaCO_2$, and BDNF all emerged as independent predictors of cognitive performance further substantiates the multi-factorial etiology of cognitive deterioration with our patients, the fact that cerebral oxygenation remained the strongest single predictor of cognitive performance irrespective of controlling for age, education, and disease severity suggests its importance. From a clinical perspective, evaluation of cognitive status and monitoring of cerebral oxygenation may play a role in early pre-emption. However, some limitations are also worth noting. The cross-sectional

nature of our design prohibits any causative conclusions, and it is likely that our findings might be reversed in terms of time directionality.

CONCLUSION

COPD patients frequently exhibit cognitive impairment, a condition closely related to the decline in cerebral oxygenation, hypoxemia, and increased pneumological dysfunction. Specifically, the diminished rSO_2, revealed in our study, proved to be the most powerful independent predictor of worse MoCA scoring, adjusting for the covariates. COPD-related neuropsychological alterations are likely to be attributed to chronic hypoxemia, CO_2 retention, systemic inflammation, free oxygen radicals, and the deficient activity of neurotrophic factors, such as BDNF. Examination of the cerebral oxygenation status can be used to identify the patients at risk of the cognitive deterioration and the necessity for the screening of the cognitive status of the COPD population.

Author's Contribution:

Concept & Design or acquisition of analysis or interpretation of data:	Abdulsattar Hussein Abdullah, Mohamed Ghalib Zakari
Drafting or Revising Critically:	Abdulsattar Hussein Abdullah, Bassam Taha Saleh
Final Approval of version:	All the above authors
Agreement to accountable for all aspects of work:	All the above authors

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