

ORIGINAL ARTICLE

PATTERN OF COGNITIVE DYSFUNCTION IN DIFFERENT SEVERITY OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE

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ABSTRACT

Background: Cognitive dysfunction is an important systemic effect of Chronic Obstructive Pulmonary Disease (COPD). The study aimed to investigate cognitive functioning in specific cognitive domains in COPD patients with different severity of disease.

Materials & Method: Thirty one COPD patients with FEV1 \geq 50%, twenty nine COPD patients with FEV1<50% and thirty controls were matched for age, sex, education. Baseline cognitive functioning was compared between COPD patients with different severity of disease and controls using a detailed neuropsychological testing battery.

Statistical analysis: All three groups were compared by one way analysis of variance (ANOVA) for demographic and cognitive parameters. Pearson and Spearman rho correlation were done to assess relation between clinical, demographic characteristics and cognitive parameters.

Result: The group with COPD FEV1<50% scored significantly lower on Trail making B, copying landmark, memory, Stroop Colour Interference test ($p<0.001$) compared to the controls and COPD patients with FEV1 \geq 50%. Further, FEV1 showed significant correlation with MMSE, MOCA, Trail making B and copying landmark.

Conclusion: The decline in pulmonary function is associated with cognitive dysfunction and an impairment of cognition increases significantly with the advancement of the disease.

Keywords: Chronic hypoxia, Cognition impairment, COPD, Neuropsychological tests

INTRODUCTION

Cognition is a collective term for high-order neural processes that underpin information handling. In practice, cognitive abilities are mainly inferred from behaviour, which itself is determined by a wide variety of neurological, psychological and emotional factors.¹ The relationships between the many processes involved in an everyday cognitive task are complex, but cognitive ability is usually broken up into discrete domains, as it is rarely possible to study single domains in isolation.

Chronic Obstructive Pulmonary Disease (COPD) has been traditionally considered as a disease primarily affecting the lungs however its systemic effects have been increasingly recognized with di-

verse manifestations involving various body systems distant from the lung. The brain, in particular, may be vulnerable to the systemic effects of COPD.^{2,3}

Cognitive impairment has been demonstrated in 77% of patients with COPD and hypoxemia.⁴ Cognitive impairment in COPD has been associated with higher mortality and disability.^{5,6} The cognitive dysfunction is seen to increase with severity of disease and level of hypoxemia.⁷ Hypoxemia and hypercapnia both appear to aggravate cognitive dysfunction in COPD as suggested by neuroimaging studies which found that adults with severe COPD may develop alteration in brain perfusion due to hypoxemia leading to cognitive impairment.⁸

In COPD patients a decline has been seen primarily in reaction time, short and long-term memory, abstract reasoning skills and complex visual motor processes.

Although there exist a plausible link between COPD and cognitive impairment, the existing literature is limited by methodological issues such as diagnostic uncertainty, cross sectional design, small sample size, or lack of appropriate referent group. We hypothesised that there is relationship of level of hypoxemia and cognitive functioning.

The study aimed to assess prevalence of cognitive dysfunction in patients with COPD and also to assess cognitive impairments in patients with different severity of COPD.

MATERIALS AND METHODS

A hospital based prospective study was done on thirty one COPD patients with $FEV_1 \geq 50\%$, twenty nine with $FEV_1 < 50\%$ and thirty healthy controls. Controls were matched with COPD patients for age, level of education, IQ and socioeconomic background. Institutional ethical clearance was obtained for study by institutional review board. The purpose of the study was explained to both the groups and explicit written consent was obtained thereof.

The inclusion criteria for cases were

- Stable COPD patients who were diagnosed and staged as per GOLD (2013) guidelines⁹ with no exacerbation for past two months.
 - Age of 30-60 years.
 - Atleast Primary School Education.
- The controls were enrolled during the same study period as COPD patients, with normal spirometric pulmonary functions and without any lung disease (present or any time in past). Both the groups underwent a thorough clinical examination to rule out psychopathology, chronic debilitating medical disorders, endocrinal disorders, history of alcohol/drug abuse and any medication known to affect cognition and any co morbidity and/or complications of COPD.

All the patients were subjected to post-bronchodilator spirometry (Vitalograph Compact Buckingham, England) and were staged as per GOLD guidelines, 2013⁹. The spirometric parameters recorded were FEV_1 (litres), FVC (litres), FEV_1/FV Cratio (percent predicted), FEF 25%

75% (litres/sec) and peak expiratory flow (PEFR) (litre/sec). Based on FEV_1 two subgroups were formed one with $FEV_1 \geq 50\%$ and another with $FEV_1 < 50\%$.

Cognitive impairment was evaluated by validated psychometric questionnaire.

These neuropsychological tests assessed cognitive domains of memory, verbal tasks, attention, executive functioning and mental flexibility. A Psychometric Test Battery was performed in a fixed sequence and lasted for approximately 50 minutes.

- Monteral Cognitive Assessment Test (MOCA)¹⁰
- Standardized Mini Mental Status Examination (MMSE)¹¹
- Digit Symbol Substitution Test of Wesher Adult Intelligence Scale¹²
- Trail Making Test B of Haldstead Reirtan B¹³
- Stroop Color Interference Test¹⁴

The study population was subdivided into two group based on severity of the disease: group 1 with mild to moderate COPD with $FEV_1 \geq 50\%$ and group 2 with severe and very severe COPD with $FEV_1 < 50\%$.

Statistical Analysis: Statistical analysis was done using SPSS version 18, statistical software (SPSS, Inc., Chicago, USA). Comparisons between means were carried out by parametric (two-tailed t-test) and nonparametric tests (Mann Whitney test), while analysis of variance (ANOVA) was used to compare mean values across the COPD with different severity ($P < 0.05$ indicated statistical significance). The Pearson Correlation analyses were used to find the association between parametric variables with normal distribution.

RESULT

The mean age of the study population was 62 ± 1.14 year. The demographic characteristics of study population, controls and the two groups of COPD are summarized in table 1.

The Group of COPD patients with $FEV_1 \geq 50\%$ included 11 patients of stage I, 20 patients in stage II, while Group with $FEV_1 < 50\%$ included 21 patients with stage III and 8 patients in stage IV of COPD as per GOLD staging. The three groups were statistically similar with respect to age, sex, smoking, education level and BMI ($p > 0.05$).

Table 1: Demographic characteristics in the control group and mild-to-moderate and severe COPD groups

Variable	Control (n=30)	COPD patients with FEV1≥50% (n=31)	COPD patients with FEV1<50% (n=29)
Age (Years)	62±1.18	64±2.12	61±2.22
Sex(M/F)	19/11	15/16	18/11
Education(1-6)	4	4	4
Smoking (Packs/Year)	36.45±14.48	36.66±10.14	38.94±12.34
FEV1% predicted	104±12.24	62.12±2.24*	48±1.2±4.42*,+
FVC% predicted	94.24±10.12	74.46±8.86*	52±18±6.64*,+
FEV1/FVC	90.12±8.84	62.14±6.24*	48.14±11.24*,+
BMI (Kg/m2)	20.13±0.74	21.14±2.1	18.21±0.7
FFMI (Kg/m2)	20.18±0.21	19.94±0.28	12.22±2.22
Resting SpO2	98.1±1.25	96±2.22*	90.12±1.22*

ANOVA, analysis of variance; Data are presented as means ± SD ; *P < 0.01 vs. control group; +P < 0.01 vs. mild-to moderate group. BMI=Body Mass Index, COPD=Chronic Obstructive Pulmonary Disease, Education (0-6) score 1=primary school 6=university.

Table 2: Clinical characteristics on neuropsychology battery of test in controls and subgroups of COPD with different severity of disease

Parameter	Controls	COPD with FEV1≥50%	COPD with FEV1<50%
Orientation	5.5±0.7	5.2±1.4	4.8±1.2
Attention	5.4±0.4	4.8±1.2*	3.6±1.2
Language	4.2±0.8	3.6±1.0	2.8±0.9+
Memory (Delayed Recall)	3.9±0.4	2.9±0.8	2.4±0.4+
Conceptual	1.4±0.1	1.2±0.2	0.8±0.4
Copying landmark	4.2±0.4	3.6±1.2*	2.8±0.4*
Color-Stroop	22.5±0.76	26.4±4.12	32.4±6.42
Time In Sec Error	2.2±0.96	3.23±0.30	9.24±4.44
Trial B sec	94±52.24	122.24±73.56*	223.44±26.56*,+
Digital Symbol Substitution Test n/time	47.14±1.12	42.44±1.68	28.42±2.24
MOCA Score	28.54±1.58	24.41±3.52*	18.70±2.14*,+
MMSE Score	28.78±0.98	26.16±2.22*	22.16±2.24*,+

*P < 0.01 vs. control group; +P < 0.01 COPD group with FEV1<50% vs. COPD patients with FEV1≥50% group. Data are presented as means Mean± SD.

Table 2 summarizes that the cognitive scores for copying landmark, Trail making B and were significantly lower in the COPD patients with FEV1≥50% (p < 0.01) and COPD patients with FEV1<50% (p < 0.01) groups compared with the control group. On analysis the two subgroups of COPD we observed that the score on MOCA and MMSE were significantly lower in the COPD group with FEV1<50% than in the COPD group with FEV1≥50% (p < 0.01).

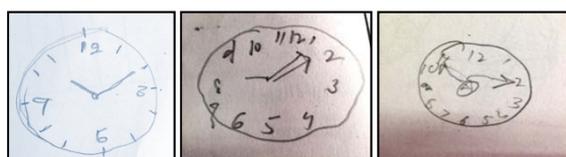


Fig1: Drawing of clock by control group (a), COPD patients with FEV1 with ≥50% (b) and COPD patients with FEV1<50%(c).

Fig 1 shows the impairment of drawing of clock subtest on MOCA by COPD subgroups compared to controls. The relatively preserved cognitive domains of memory (delayed recall after 20 minutes) and verbal task (naming, word generation and fluency) of group of COPD with FEV1≥50% were affected in COPD group with advanced form of disease with FEV1<50%.

The Strength of association of severity of disease with neuropsychology battery test to assess various cognitive domains in COPD patients was done by Pearson correlation coefficient. The correlate of lung function indexes such as FVC, FEV1, FEV1/FVC ratio, with the cognitive battery of test revealed, that there was a statistical significant FEV1 had stronger association compared to resting oxygen saturation with MMSE (r=0.68 vs r=0.42), MOCA (r=0.78 vs r=0.56), copying landmark (r=0.65 vs r=0.32) as summarized in table 3. Trail making B had a significant inverse correlation with all FVC, FEV1/FVC (p<0.01) and baseline saturation (p<0.001).

Table3: Correlation between parameters of severity of COPD and psychometric tests in the whole study population.

Parameters	MMSE Score	MOCA Score	Trial making B	Copying landmark	Color stoop interference
FEV1	0.68**	0.78**	-0.32**	0.65**	0.14
FVC	0.44	0.66*	0.12*	0.44	0.12
FEV1/FVC	0.24*	0.46*	0.01*	0.04	0.22
Resting SpO2	0.42**	0.56**	-0.22**	0.32**	0.24

Analysis by Pearson correlation coefficient: *p is significant at p<0.01,**p is significant at p<0.001(2 tailed).

Fig 2: Scatter plot to depict correlation of between the FEV₁ (litres) and MMSE score and MOCA scores in study population.

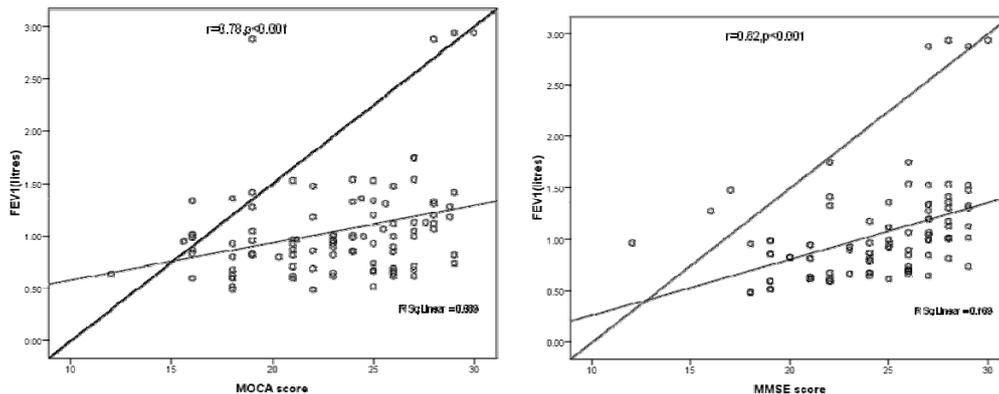


Fig 2 shows the strength of association of MMSE and MOCA score with FEV1 in the study population.

DISCUSSION

Chronic obstructive pulmonary disease has been found to cause a general cognitive decline affecting specially the cognitive functions of learning, visuospatial and constructional abilities, executive functions, and language skills.^{15,16} In our study, we tested this hypothesis and found that severity of disease have greater effects on cognitive domains than the milder form of disease.

The incidence of cognitive impairment in patients with COPD varies in different studies

from 12% to 88% according to specific diagnostic criteria adopted, the methods used for assessing the impairment, and the number of subjects investigated.⁶

In our present study, we observed that although all the domains of cognition were variably affected psychomotor processing with visuospatial and motor constructional abilities, were the most affected cognitive functions which can be attributed to frontal hypoperfusion in patients with COPD.^{8,16}

We observed that in early stages of COPD, cognitive impairment is often limited to attention problems and information processing speed but as dis-

ease progresses the impairments become more severe and diffuse. Memory and language which were intact in early stages of the disease were impaired in patients with severe form of disease (table 2).

These findings agree with those of previous studies^{1,5,9} suggesting that the regions of brains implicated in encoding, consolidation, storage and retrieval of information (transentorhinal, parahippocampal gyrus and entorhinal cortexes) are affected by chronic hypoxemia. This cumulative loss of neurons and their connections results in hippocampal atrophy in the early stage of the disease, while the structural change converts to the functional deterioration in the later stage.^{17,18}

Some researchers reported that the FVC, FEV1 and DLCO in patients with COPD are correlated with cognitive dysfunctions¹⁹,while others have failed to find significant association between lung parameters (FEV1, FVC) and cognitive impairment.^{20,21}

LIMITATIONS OF THE STUDY

Our study had several limitations that should be acknowledged. First, our sample size was small, which may partially account for weak association between some measures in our study. Although participants were stringently selected to avoid the

influence of possible confounding variables, such as diabetes, cerebro-vascular disease and major chronic diseases, there is a possibility that other chronic or subclinical diseases which were not included in the analysis may also have contributed to cognitive decline.

We did not perform neuroimaging studies in our study population to identify regions of brain which play a critical role in the neural control of cognitive function. However, it was costly and is not usually recommended for COPD patients.

CONCLUSION

In the present study, we found a highly significant correlation of baseline oxygen saturation and FEV1 with trail making, copying landmark, MMSE score, MOCA score. Thus suggesting that low lung functioning may contribute to cognitive disorders by decreasing the oxygen delivery to brain neurons with the risk of cognitive impairment increases with decreasing oxygen desaturation.

Based on our observation; we would like to suggest that a routine inclusion of the neuropsychological battery of test can be helpful for planning therapeutic and optimal care programs for COPD patients with cognitive impairment. We hope that our study help to implicate the importance of the assessment of cognition in subjects suffering from COPD.

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