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Original Research Paper

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COGNITIVE FUNCTION ASSESSMENT IN MILD TO MODERATE COPD PATIENTS THROUGH P300, ERP STUDY.

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ABSTRACT Event-related potentials (ERPs) provide a non-invasive method of studying brain neural activity, with P300 wave components reflecting the speed of cognitive processes. In our study we primarily focused on finding cognitive impairment in the initial stage of the Chronic obstructive pulmonary disease (COPD) through latency and amplitude study of P300 wave. We enrolled equal number (n = 35) of COPD cases and healthy controls. Mean value of Latency at Fz, Cz, Pz was significantly decreased in cases as compared to control group (p = 0.007, p = 0.001, p = 0.006 respectively). Similarly, mean averaged latency was also decreased in COPD vs controls (p = 0.008). Furthermore, a significant positive correlation between MEF25-75% and amplitude at Cz in the COPD cases (r = 0.3534, p = 0.037) was observed. The results obtained in our study suggests that the cognitive dysfunction is present even in mild to moderate COPD patients. The positive association between the spirometric parameters and P300 variables obtained in our study also suggests that with deterioration in lung functions there is decline in cognition.

KEYWORDS : COPD, Cognitive function, Event-related potentials, P300

INTRODUCTION

Although COPD is associated with progressive impairment of lung function, studies have revealed that it is in fact a complex multicomponent disease having different co-morbidities like heart diseases, pulmonary hypertension, lung cancer, osteoporosis, Anxiety and depression 1,2.

Studies have observed that COPD patients manifest with varying degrees of cognitive dysfunction 3. Previous studies have shown that individuals with reduced lung function perform worse in cognitive tests and have an increased risk of being hospitalized with a diagnosis of dementia 4,5. Smoking is another factor common in COPD patients which can effect brain functioning 6. Smaller grey matter volume and lower grey matter density is observed in the frontal region, occipital lobe and the temporal lobe including parahippocampal gyrus, in smokers than in non-smokers 7,8 .

Various methods have been put forward for assessing cognition in COPD patients. But a more objective identification of cognitive impairment can be achieved by Event-related potentials (ERPs). Event-related potentials (ERPs) provide a non-invasive method of studying brain neural activity, with P300 wave component reflecting the speed of cognitive processes. Neuronal activity in frontal lobe, inferior parietal lobe, hippocampus and locus coeruleus, correlates to the scalp recorded P300 wave 9. P300 is obtained during information processing tasks which involve attention, stimulus discrimination, memory, and related processes 9,10.

Most of the studies done for assessing the cognitive function in COPD patients were done on patients having hypoxemia or had exacerbation or most of them were under the severe category 11,12,13. The effects of COPD on cognition are thought to be related to systemic inflammation and chronic hypoxia 14. Hypoxic inflammation and oxidative stress leads to direct neuronal damage to brain resulting into various neurological manifestations according to various regions of brain involved. The inflammatory and hypoxic effects are present even in the initial stages and stable non hypoxemic COPD patients and assessing cognitive functioning in mild to moderate non-hypoxemic COPD patients has special relevance 14,15.

Considering the scarcity of data available pertaining to Indian population wherein cognitive decline is considered our study becomes more significant, especially because we assessed cognitive function in non-hypoxic stable mild to moderate COPD. For assessment of cognitive function we used ERP,P300 which provide a more objective assessment of cognitive decline, also the wave recordings at Fz, Cz and Pz could help us to understand more clearly the brain region getting effected.

MATERIALS AND METHODS

An observational cross sectional study was carried out in LHMC and SSKH in New Delhi, India. The study was approved by the institutional ethics committee (IEC) for human research. Thirty five (35) COPD cases as per GOLD 2010 guideline 16 were recruited from the medical clinic and ward. Thirty five (35) apparently healthy volunteers willing to participate in the study and satisfying the inclusion and exclusion criteria were included in the study. All participants were subjected to detailed history taking and thorough physical examination.

Age, sex, BMI, socioeconomic status (by modified Kuppuswamy's socioeconomic status scale)17 and number of years of education were matched in COPD group as compared to control group.

The inclusion criteria required that a patient be aged between 40 to 60 years of either gender having stable COPD. The exclusion criteria were: cancer, uncontrolled diabetes, subjects on lithium, propranolol, erythromycin, sedatives, significant cardiovascular

illness, history of tumour, epilepsy, head injury, dementia, morbid obesity, history of alcohol or substance abuse. Oxygen saturation was measured and the participants with oxygen saturation SaO2 >90% were only included in the study.

Informed written consent was obtained from all the cases and controls prior to participation in the study. Pulmonary function test and P300, ERP recording was conducted according to standard practice.

ASSESSMENT OF PULMONARY PHYSIOLOGY 16

All the COPD patients met the American Thoracic Society and European Respiratory Society criteria for COPD risk classification 18 . For the COPD patients the Short-acting bronchodilators were withheld for the previous 6 hours, long-acting bronchodilators for 12 hours, and sustained release theophylline for 24 hours. Standardized pulmonary function tests were performed in both cases and controls using the Ganshorn Mediegin Electronics System, Germany for recording the pulmonary function. The forced vital capacity (FVC), Forced expiratory volume in 1 second (FEV1), the ratio of FEV1 and FVC, Mid-expiratory flow25-75% (MEF25-75%) and Peak expiratory flow (PEF) were obtained.

A minimum of 3 acceptable IVC/FVC maneuvers were performed and the automated best spirometry recording of each individual was taken up for analysis. PFT volumes were presented in liters and flow rates in liters per second, as well as percentage of predicted values on basis of age, height, weight, ethnicity and sex according to ERS 1993 by Zapletal for Indian population.

The reversibility in PFT was tested after inhalation of a short-acting bronchodilator- i.e. after 400 µg of salbutamol through metered dose inhaler, connected to a spacer. The criteria for diagnosis of COPD included altered spirometric profile (FEV1 / FVC < 0.7) with reduced reversibility less than 12% reversal, as well as not more than 200 ml of increase in FEV1 post-bronchodilatation with salbutamol. Patients who were mild to moderate in severity according to the gold guideline16 (Mild: postbronchodilator FEV1 ≥80% , Moderate: postbronchodilator FEV1 ≥50% but <80% predicted) were further evaluated for their cognitive functioning.

AUDITORY EVENT- RELATED POTENTIAL, P300 MEASUREMENT[19]

The equipment used was SCHWARZER TOPAS EMG neurophysiological measuring system, a 4 channel EMG/NCV/EP system. The evoked potentials were recorded as per the guidelines of International Federation of Clinical Neurophysiologists (IFCN)19. Standardized conditions were maintained. Ag/AgCl disc electrodes were used. Active electrodes were placed at Fz, Cz, Pz using the 10-20 international system. A1 and A2 were the reference electrodes to be placed on each ear lobe. Ground was placed at Fz.

Stimulus and stimulation configuration – "oddball" acoustic paradigm was adopted with two categories of stimuli, the rare or the target stimulus and the frequent or the standard stimulus. 20% given at frequency of 4000 Hz were the rare stimuli and rest 80% of the tones were frequent stimuli given at frequency of 1000 Hz. The intensity for both was 65 dB and the stimuli were presented at the rate of one per second. The signals were in phase at the two ears. The time base was 100 ms/div and sensitivity was 10 µv/div. The bandpass of amplification was 0.05-20 Hz. In case any trial contained more than 10 per cent artefacts, the entire trial was rejected. The subject was instructed to avoid any bodily movement and fixate their eyes at a particular spot on wall in order to avoid artefacts due to eye movements and improve their concentration and attention to target stimulus during the P300 recording session. The subject was given a mechanical tally counter and asked to press the button when rare tone appeared. The P300 wave was identified as the largest positive peak occurring for all electrode sites after the N100-P200-N200 complex with latency between 250 to 400 msec. The latency and amplitude of the waveform were recorded.

STATISTICAL ANALYSIS

The data was subjected to statistical evaluation using Graph Pad Prism Version 6 software. Mean and standard error of mean (Mean ± SEM) of all the variables for both groups were calculated according to accepted statistical methods. Intergroup comparison was done using unpaired 't' test. Intergroup comparison for non-parametric data was done using Mann-Whitney U test. Correlations were assessed with Pearson correlation co-efficient and Spearman correlation co-efficient as and when applicable. The p-value < 0.05 was considered statistically significant.

RESULTS

The two groups were comparable with respect to their basic demographic profile (Table 1).

TABLE 1: The basic demographic profile of Case Group (COPD) and Control Group (healthy volunteer)

Parameters	COPD Group (N = 35)	Control Group (N = 35)	P Value
Age (Years)	52.5 ± 1.14	49.7 ± 1.07	0.08
Sex (Male/female), n	20/15	20/15	1.00
Height (Cm.)	161.0 ± 1.33	162.7 ± 1.66	0.41
Weight (Kg.)	57.6 ± 1.64	59.5 ± 1.75	0.43
B.M.I. (Kg/m2)	22.2 ± 0.59	22.4 ± 0.57	0.81
Years Of Education (Years)	9.2 ± 0.54	9.6 ± 0.56	0.66

Data are presented as mean±S.E.M.

No statistically significant difference was present between COPD cases and the control group (p = 0.89) with respect to socioeconomic distribution (Table 2).

TABLE 2: Socioeconomic status distribution of Case Group (COPD) and Control Group (healthy volunteer)

Parameters	COPD Group (N = 35)	Control Group (N = 35)	P Value
Upper	1	1	0.89
Middle (Upper And Lower)	18	20	
Lower (Upper And Lower)	16	14	

Comparing the two groups, significant difference was seen in the history of smoking, with 42.85% smokers in the COPD case group and 14.28% smokers in the control group (Table 3). Smoking pack-years were also significantly higher (p = 0.0002) in the COPD case group than the control group. No significant difference was seen between the two groups (p = 0.06) (Table 3) in the duration of exposure to biomass fuels.

TABLE 3: Smoking and chulha exposure history among Case (COPD) and Control Group (healthy volunteer)

Parameter	COPD Group (N=35)	Control Group (N=35)	P Value
Smoker	15	5	0.01**
Non-Smoker	20	30	
Packyears	14.1 ± 2.03	2.7 ± 0.09	0.0002***
Smoke Exposure	8	3	0.06
Non-Exposure	7	12	

Packyear data are presented as mean±S.E.M.

*p<0.05-significant, **p<0.01- highly significant, ***p<0.001-very highly significant

Between COPD case and control group comparison of spirometric profiles IVC, FEV1, FEV1/IVC, MEF25-75% and PEF was done. Significant difference was present in the IVC with COPD group showing deterioration (p = 0.04). Very highly significant decline in COPD group with respect to control group in parameters of FEV1, FEV1/IVC, MEF25-75% and PEF (p < 0.0001) (Table 4).

TABLE4: Pulmonary function test indices among Case (COPD) and Control Group (healthy volunteer)

Parameter	COPD Group (N=35)	Control Group (N=35)	P Value
IVC (Liters)	2.2 ± 0.11	2.7 ± 0.14	0.04*
FEV1(Liters)	1.3 ± 0.06	2.2 ± 0.09	< 0.0001****
FEV1/IVC (%)	61.1 ± 1.50	83.5 ± 1.18	< 0.0001****
MEF25-75% (Liters/Sec.)	1.0 ± 0.06	2.6 ± 0.12	< 0.0001****
PEF (Liters/Sec.)	2.7 ± 0.20	4.8± 0.31	< 0.0001****

Data are presented as mean ± S.E.M.

*p<0.05-significant, **p<0.01- highly significant, ***p<0.001-very highly significant

Significant difference was present in the P300 latencies recorded at Fz, Cz and Pz. Similarly, mean averaged latency was delayed in COPD vs controls. No significant difference was seen in the amplitudes (Table 5).

TABLE 5: P300 Latency (in ms) and Amplitude in (uV) comparison between Case (COPD) and Control Group (healthy volunteer)

Parameter	COPD Group (N=35)	Control Group (N=35)	p Value
Latency At Fz	350.3 ± 6.09	327.6 ± 5.55	0.007**
Latency At Cz	354.6 ± 5.66	327.9 ± 5.61	0.001**
Latency At Pz	353.3 ± 6.17	329.1 ± 6.01	0.006**
Average Latency	352.2 ± 5.31	324.3 ± 5.66	0.008**
Amplitude At Fz	8.3 ± 1.11	9.0 ± 1.05	0.48
Amplitude At Cz	8.0 ± 0.97	9.7 ± 1.18	0.30
Amplitude At Pz	9.3 ± 0.68	10.9± 1.05	0.19
Average Amplitude	8.8 ± 0.83	9.7 ± 1.02	0.46

Data are presented as mean ± S.E.M.

*p<0.05-significant, **p<0.01- highly significant, ***p<0.001-very highly significant

Table 6 and 7 shows the intergroup comparison between the smokers and the non-smokers in the case and control group (ANOVA followed by post hoc Tukey's test). Significant difference in average latency was seen between non-smoker COPD cases and non-smoker controls (365.2 ± 12.97 vs 311.3 ± 8.51, p = 0.0489) and also in smoker COPD cases and non-smoker controls (348.9 ± 10.73 vs 311.3 ± 8.51, p = 0.0095).

Table 6: Shows mean values multiple comparison of latency in P300, ERP and smoking in case (COPD) and control group.

Parameter	Copd (ns) Vs Copd (s)		Copd (ns) Vs control (s)		Case(ns) Vs Control(ns)		Case(s) Vs Control(s)		Case(s) Vs Control(ns)		Control(s) Vs Control (ns)		p value
P300 latency (ms)	COPD (ns) N=5	COPD (s) N=15	COPD (ns) N=5	Co(s) N=5	COPD (ns) N= 5	Co (ns) N=15	COPD (s) N=15	Co (s) N=5	COPD (s) N=15	Co(ns) N=15	Co (s) N=5	Co (ns) N=15	
Fz	354.6 ± 14.57	352.0 ± 10.54	354.6 ± 14.57	312.0 ± 19.64	354.6 ± 14.57	317.1 ± 8.63	352.0 ± 10.54	312.0 ± 19.64	352.0 ± 10.54	317.1 ± 8.63	312 ± 19.64	317 ± 8.63	0.03*
Cz	357.4 ± 15.98	360.1 ± 8.22	357.4 ± 15.98	322.8 ± 18.45	357.4 ± 15.98	314.0 ± 8.46	360.1 ± 8.22	322.8 ± 18.45	360.1 ± 8.22	314.0 ± 8.46	322.8 ± 18.45	314.0 ± 8.46	0.97
Pz	365.2 ± 12.97	348.9 ± 10.73	365.2 ± 12.97	316 ± 17.44	365.2 ± 12.97	311.3 ± 8.51	348.9 ± 10.73	316 ± 17.44	348.9 ± 10.73	311.3 ± 8.51	316 ± 17.44	311.3 ± 8.51	0.77
Avg. latency	365.2 ± 12.97	348.9 ± 10.73	365.2 ± 12.97	316 ± 17.44	365.2 ± 12.97§§	311.3 ± 8.51	348.9 ± 10.73	316 ± 17.44	348.9 ± 10.73§	311.3 ± 8.51	316 ± 17.44	311.3 ± 8.51	0.004 **

* Significance in anova, § significance in Tukey's multiple comparisons test, s = smoker, ns = nonsmoker, Co = control
Data are presented as mean ± S.E.M.

Table 7: Shows p value of multiple comparison of latency in P300,ERP and smoking in case (COPD) and control group.

PARAMETER	COPD (ns) Vs COPD (s)	COPD (ns) Vs CONTROL(s)	CASE(ns) Vs CONTROL(ns)	CASE(s) Vs CONTROL(s)	CASE(s) Vs CONTROL(ns)	CONTROL(s) Vs CONTROL (ns)	ANOVA p value
Fz	0.9991	0.2942	0.2341	0.1858	0.0707	0.9934	0.0339*
Cz	0.9986	0.3819	0.0795	0.1608	0.0035§	0.9576	0.9743
Pz	0.8276	0.1798	0.0362§	0.3440	0.0394§	0.9916	0.7763
Avg. latency	0.9881	0.1867	0.0489§	0.1438	0.0095§§	0.9978	0.0042**

* Significance in anova, § significance in Tukey's multiple comparisons test, s = smoker, ns = nonsmoker, Co = control

The latencies and amplitudes of P300 at Fz, Cz and Pz were studied for any correlation with the pulmonary function. Significant positive correlation was seen in amplitude at Cz and MEF25-75% in the COPD case group (r = 0.3534, p = 0.037)(Fig 1). Also, in female COPD cases (Fig 2,3) significant correlation was found between amplitude at Fz (r = 0.6616, p = 0.007), Cz (r = 0.7228, p = 0.002) and the ME 25-75% .

Fig 1:Positive correlation between P300 amplitude (at Cz) and MEF25-75% in cases.

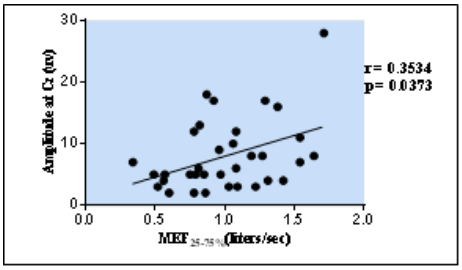


Fig 2: Positive correlation between P300 amplitude (at Fz) and MEF25-75%in female cases.

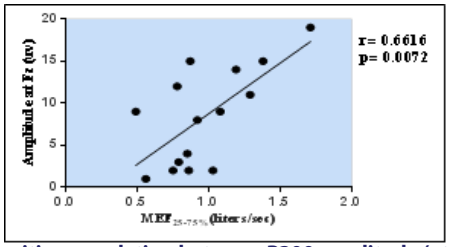
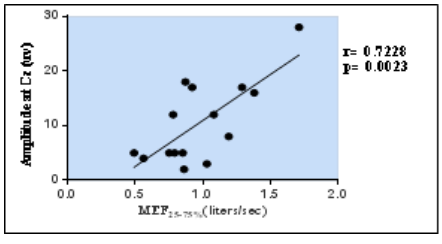


Fig 3:Positive correlation between P300 amplitude (at Cz) and MEF25-75%in female cases.



DISCUSSION

The study was conducted to measure cognitive deficits if any in the mild to moderate COPD cases by using Auditory Event Related Potential,P300 and to correlate the cognitive deficits with the pulmonary function abnormality in COPD. The finding of our study suggests that even mild to moderate severity of COPD also have a significant negative impact on cognition.

Studies done in the past have observed cognitive decline in COPD patients particularly among those having greater severity and hypoxemia11,12,13. In one of the study which included moderate to severe COPD patients mild cognitive impairment was found in 36% of the patients. In another study after the follow-up duration of 5.1 years COPD significantly increased the risk of non-amnestic mild cognitive impairment by 83% 20. Most of these studies have assessed the cognitive function through neuropsychological tests21,22,23.

In our study we used P300 for cognitive function assessment. We found significant delay in latencies at Fz, Cz and Pz ($p = 0.007$, $p = 0.001$, $p = 0.006$ respectively) in the COPD cases as compared to control group. Moreover, the average latency was also significantly delayed ($p = 0.008$) (Table 5). However, no significant difference was seen in the P300 amplitudes. A delayed P300 latency signifies the substantial deficit in the vital region of brain associated with cognition. P300 is a sensitive measure of the capacity to allocate attention resources, stimulus discrimination, memory, and related processes. The latencies of ERPs components track the time course of processing activity in milliseconds whereas amplitude indicates the extent of allocation of neural resources to specific cognitive processes 9. P300 is an index of neural activity in multiple brain regions involved in cognition. P300 is considered to be associated with neural activity in frontal lobe, inferior parietal lobule, hippocampus, medial temporal lobe and locus coeruleus 9. P300 component of ERP is generated in psychological task related to cognitive processes such as attention allocation, stimulus discrimination and memory 9,10. Our study shows the presence of neurophysiological deficits in COPD cases as shown by delay in P300 latency.

The finding in present study are in concordance with some earlier works that have also shown similar results. Kirkil et al. in their study found shorter latency in the control group as compared to the COPD cases with no significant difference in the amplitude 12. In a study done on Indian population the P300 latency was found significantly prolonged and the amplitude significantly decreased in the stable COPD patients as compared to the control group 24. Previous studies have shown that P300 is a more sensitive test to discern cognitive impairment 25. Findings suggest that it can be a useful tool in the diagnosis of dementia 26. Tahan et al. from their study concluded that P300 is a more sensitive test than MMSE as a marker of cognitive derangement in respiratory failure patients with hypoxemia 27.

In our study we found positive correlation between the deterioration in pulmonary function and cognitive decline. Significant positive correlation was seen in amplitude at Cz and MEF25-75% in the COPD case (Fig 1). Flow limitation in medium-sized airways decreases flow rates in the mid portion of the expiratory flow-volume loop. MEF25-75% is useful in assessing the presence and severity of obstruction 28,29. Earlier studies have shown positive association between pulmonary function and cognitive test performance 30. Weuve et al. studied the association between rate of decline in FEV1 over the past 12 years and subsequent cognitive performance and found inverse relation between the two 31. Schaub et al. found significant increase in the risk of dementia among subjects with reduced PEF, FEV1, MEF50% and MEF25% 32. Also in our study among the female COPD cases (fig. 2 and 3) significant correlation was found between amplitude at Fz ($r = 0.6616$, $p = 0.007$), Cz ($r = 0.7228$, $p = 0.002$) and the MEF25-75%. The association of lung function with cognitive deterioration is stronger in women than in men.The reason could be early onset of the disease, more lung function reduction and more severity of the disease 33.

When the COPD cases and controls were divided into smoker and non-smoker groups and intergroup comparison was done, no significant difference between smoker and non-smoker on each group was seen (Table 6 and 7). Hence the effect of smoking on cognitive decline may not be that significant as the disease process itself. Also a more concrete conclusion can only be drawn on a larger sample size.

Hypoxemia in COPD is known to cause structural alternation in brain areas like parietal cortex, prefrontal and hippocampus 34,35. In our study we have not included patients with clinical cyanosis and hypoxemia. But even in non-hypoxemic patients with resting oxygen saturation ≥ 90%, episodes of oxygen desaturation during daily activity, nocturnal desaturation and obstructive sleep apnea can cause brain damage 14. This could be one of the possible explanation of cognitive impairment found in COPD cases in our study. The other possible cause could be systemic inflammation, which is seen even in mild to moderate cases. Systemic inflammation is associated with cerebral microstructural disintegration that predominantly affects frontal pathways and corresponding executive function 36.

Our study results are especially important because we studied mild to moderate cases and found the presence of cognitive impairment in them. Moreover, we can say that impairment in cognition probably starts earlier in the disease course as we had included relatively younger patients in study population. The results are noteworthy in planning the management of the patients early in the course of COPD, since the cognitive impairment may go unrecognized until it becomes more severe later and also it would put a greater challenge in providing care to the patient.

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