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Original Article

Evaluation of Visual Evoked Potential (VEP) in Patients With Chronic Obstructive Pulmonary Disease (COPD)

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Abstract

Chronic Obstructive Pulmonary Disease (COPD), a progressive and partially reversible disease, has drawn world-wide attention for its moderate prevalence rate and causing central and peripheral neuropathy. Considering its severity in causing visual pathway impairment, the present investigation was carried out to find out the functional integrity of the visual pathway through visual evoked potentials (VEP) and to determine the factors influencing the condition in COPD patients. A total of 30 COPD patients of both sexes, classified according to the severity of the disease based on spirometric indices, were subjected to VEP testing and series of wave forms were measured and compared with equal number of control subjects. The latency of N75 and P100 were prolonged ($P<0.01$) and the P100 amplitude was reduced significantly ($P<0.01$) in COPD patients. Thus, the influence of COPD causing the optic neuropathy is apparent from the significant VEP changes. Non-invasive procedure can possibly be utilized as a routine screening test for COPD patients for better medical care.

Introduction

Chronic Obstructive Pulmonary Disease (COPD) is a progressive disease drawing attention all over the world, causing major health care burden. It is characterized by airflow limitation, with co-existence of chronic bronchitis and emphysema, and not fully reversible (1). As the disease advances, hypoxaemia develops due to ventilation perfusion imbalance during exacerbations (i.e. when paO_2 less than 60 mm of Hg) leading to the involvement of central nervous system (cranial nerves), besides causing peripheral neuropathy. The visual system in human being is highly sensitive to hypoxia (2) that its loss leads to incapacitate the life of a person.

Visual Evoked Potential (VEP) is more sensitive than EEG and psychometry in detecting clinically silent and unrecognized abnormality (3). It is more sensitive and less costly when compared to magnetic resonance imaging (MRI) in detecting the lesions affecting the visual pathway in front of the optic chiasma. The changes in the latency and amplitude of VEP waves, *viz.* N1 (N75), P1 (P100) and N2 (N145) reflect the degeneration in the quality of sight.

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Further, information on COPD with reference to cranial nerve involvement are limited in India which makes difficult to assess the magnitude of the problem nationwide. With these facts in mind, the present study was aimed at finding out the functional integrity of the visual pathway; determining the factors influencing the condition; and assessing the impact of COPD on VEP changes.

Materials and methods

It is a cross sectional study, conducted in the Institute of Physiology and Experimental Medicine, Madras Medical College, after clearing the norms of the Institutional Ethical Committee. Patients of both sexes in the age group between 30 and 55, having the features of COPD with normal vision were included. Diagnosis of COPD was done based on the GOLD criteria (1) and the patients were selected after performing the pulmonary function tests using spirometer (Super-Spiro) and the best of three consecutive tests was taken into consideration. According to GOLD criteria, in mild cases, the FEV_1 (forced expiratory volume in one second)/FVC (forced vital capacity) would be less than 0.70 with $FEV_1 \geq 80\%$. Similarly, the criteria for moderate ($FEV_1/FVC < 0.70$ with $50\% \leq FEV_1 \geq 80\%$ predicted), severe ($FEV_1/FVC < 0.70$ with $30\% \leq FEV_1 < 50\%$ predicted) and very severe ($FEV_1/FVC < 0.70$ with $FEV_1 \leq 30\%$ predicted or $FEV_1 < 50\%$ predicted + chronic respiratory failure) cases were fixed. Patients with other co-morbid conditions were excluded from the study. Control subjects were age- and sex-matched individuals with normal vision and normal pulmonary function tests with no signs of peripheral neuropathy.

With these criteria, a total of 60 individuals of both sexes were selected; of which, 30 (14 males and 16 females) were apparently normal, designated as “Group I” and the remaining were COPD patients (16 males & 14 females), as “Group II”. The patients were asked to sit comfortably in a chair with their footwear, in a quite darkened room 100 cm away from the screen and instructed to fix one of his eyes on a red focus, situated at the centre of the monitor. Each eye was tested separately while the other eye was kept covered with an opaque eye shield in order to prevent entry of light into that eye. The skin at the point of placement of electrodes was cleaned with spirit.

The VEP test was performed using EMG, EP - MARK II (Recorders Medicare System) machine. The patients were asked to avoid oil or hair spray after hair wash and patients with refractory error were asked to wear their usual glasses. The FPz reference electrode was kept over the vertex (12 cm from the nasion), the Cz ground electrode over the forehead and Oz active electrode over the occiput (5 cm above the inion). The electrodes were connected to the preamplifier. The Filter range was 2 Hz 100 Hz with sweep speed, duration and sensitivity were 350 ms, 50 ms/D and 2 microvolts respectively. The amplification range was 20,000 1,00,000 with the number of epochs were 200 and with the electrode impedance kept below 5 Kilo ohms. Black and white checkerboard of 80% contrast was used with the stimulus type of pattern reversal. The size of pattern was 8 × 8 min with rate of stimuli 1-2 Hz. Full field was used with black and white colours. The focus was red with the mean luminance of the central field 50 cd/m2 and with the background luminance of 20-40 cd/m^2.

The visual stimulus was delivered by photo stimulator at frequency of 10 flashes/sec. The response obtained was displayed in the monitor and the peak latency, peak to peak amplitude of the positive and negative waves were measured.

The data collected were subjected to basic statistical analysis (4). Further analysis was done using SPSS for windows 10. The Student’s independent t-test and paired t-test were used to compare the means and standard deviations between the two groups as well as between the paired values respectively. The VEP abnormalities in COPD patients were correlated with patients’ characteristics including age, sex, duration of illness, quantum of smoking and spirometric indices (FEV_1, FEV_1/FVC%) and interpreted using SPSS version 16.0. The analyses of variance were also worked out to find the effects of severity of the COPD on VEP parameters.

Results

The COPD patients, subjected to pulmonary function test, were found to have a post-bronchodilator FEV_1 of less than 80 per cent of the predicted value, along with an FEV_1/FVC of not more than 70 percent. Further, they had only a marginal increase in the FEV_1 value (of less than 200 ml or less than 12 per cent) from the baseline value, after 20 minutes of inhalation of bronchodilator.

Characteristics of control and study populations

The severity of mild, moderate type-IIA and moderate type-IIB forms of the disease were found to occur in 17, 63 and 20 percent respectively in the sample population. The parameters considered as selection criteria for the study were compared between control and COPD groups and furnished in Table I. The parameters pertaining to pulmonary function viz. FEV_1/FVC and FEV_1 decreased highly significantly (P<0.01) in COPD patients.

Visual evoked potential (VEP)

The VEP variables between normal and COPD subjects are given in Table II. The latencies measured in response to stimulus were found to be prolonged highly significantly (P<0.01) in COPD patients than controls, except N145. While there was a highly significant (P<0.01) fall in the amplitude (N75 P100) in the COPD patients.

TABLE I: Comparison of parameters (Mean±SD) between control and COPD patients.

Sl. No.	*Variables*	*Normal*	*COPD patients*
1.	Age (years)	45.57±5.93 (30)	49.80±4.77 (30)
2.	Sex: Male (%)	46.67	53.33
	Female (%)	53.33	46.67
3.	Duration of disease (years)	–	15.03±5.15 (30)
4.	Quantum of smoking (pack years)	–	14.27±4.45 (11)
5.	BMI	22.94±1.50 (30)	21.31**±1.73 (30)
6.	FEV_1/FVC (%)	85.27±2.59 (30)	56.47**±6.35 (30)
7.	FEV_1 (%)	85.87±3.40 (30)	63.20**±12.22 (30)
8.	O_2 saturation (%)	96.97±1.33 (30)	91.07**±2.88 (30)
9.	Ophthalmic examination	Normal	Normal

Figures in parentheses indicate sample size; ** Highly significant (P<0.01).

TABLE II: Mean±S.D. of VEP variables between normal and COPD patients.

Sl. No.	*Variables*	*Normal*	*COPD patients*
1.	N75 (in milli seconds)		
	Left eye	65.78±2.44	72.67**±2.47
	Right eye	65.53±2.76	72.81**±4.17
2.	P100 (in milli seconds)		
	Left eye	95.01±2.76	98.67**±2.63
	Right eye	95.28±3.12	99.18**±2.80
3.	N145 (in milli seconds)		
	Left eye	146.72±3.36	146.37^{NS}±4.43
	Right eye	146.57±3.10	146.40^{NS}±4.60
4.	N75 P100 (in micro volts)		
	Left eye	7.13±0.85	2.70**±0.64
	Right eye	7.44±0.87	2.72**±0.74

** Highly significant (p<0.01); ^{NS} Not significant.

Correlation of VEP variables

The correlation between the VEP variables and the characteristics of COPD patients revealed that the amplitude LN75-LP100 of both eyes were correlated positively with the spirometric indices (Tables III and IV). Statistically, the correlations were highly significant (P<0.01) and have been shown as scattered diagrams (Fig. 1 and 2).

Other correlations between the characteristics of COPD patients and VEP variables of left and right eye were not significant.

Severity of COPD with VEP

Analyses of variance (ANOVA) for the effect of severity of the disease on different wave forms were worked out and highly significant (P>0.01) differences were found among mild, moderate type-IIA and moderate type-IIB groups with respect to LN75-LP100 amplitude. In the diseased individuals, sex (male and female) and smoking (smokers and non-smokers) had not caused any significant difference in the VEP parameters.

In general, the factors such as sex and age were not observed to be the potential sources of variation

TABLE III : Correlation of variables of VEP wave forms recorded over left eye with age, pack years, duration and spirometric indices.

VEP variables		*Age*	*Pack years*	*Duration*	*FEV_1/FVC*	*FEV_1 percent*
LN 75	r	0.195	–0.361	–0.005	0.004	0.015
	p	0.301	0.275	0.980	0.985	0.937
LP 100	r	0.207	–0.422	0.230	0.437*	0.424*
	p	0.273	0.196	0.221	0.016	0.019
LN75-LP100	r	–0.148	–0.153	0.204	0.663**	0.656**
	p	0.436	0.654	0.280	0.000	0.000

r = Pearson's coefficient; p = Probability value; * denotes significant correlation at 0.05 level (2-tailed); ** denotes significant correlation at 0.01 level (2-tailed).

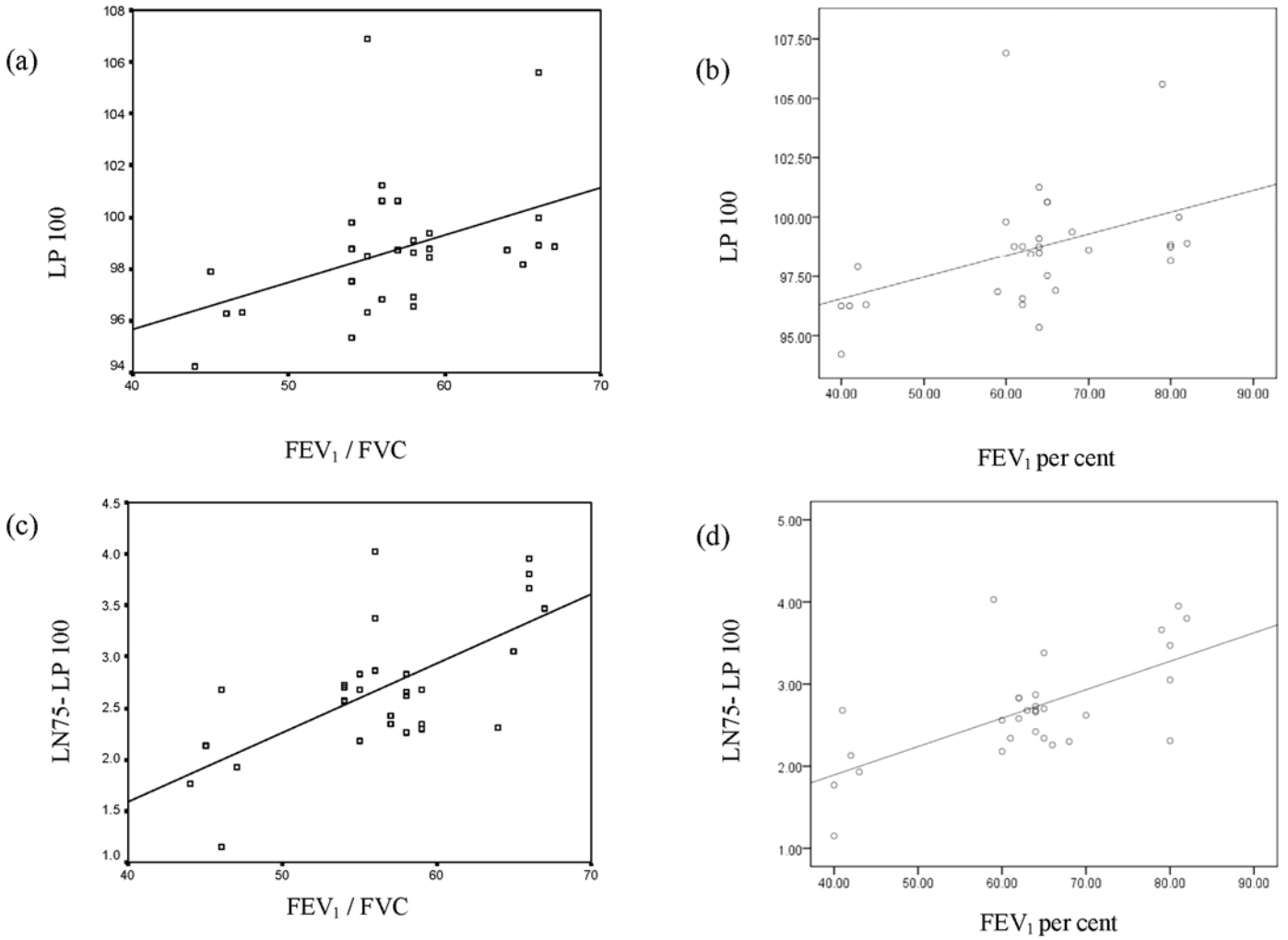

Fig. 1 : Scattered plot diagram showing correlation between VEP variables of left eye. (a) A significant positive correlation between LP100 latency and FEV_1/FVC index; (b) A significant positive correlation between LP100 latency and FEV_1 percent; (c) A highly significant positive correlation between LN75-LP100 amplitude and FEV_1/FVC index; (d) A highly significant positive correlation between LN75-LP100 amplitude and FEV_1 percent.

TABLE IV : Correlation of variables of VEP wave forms recorded over right eye with age, pack years, duration and spirometric indices.

VEP variables		*Age*	*Pack years*	*Duration*	*FEV_1/FVC*	*FEV_1 percent*
RN 75	r	–0.246	–0.102	–0.008	0.338	0.341
	p	0.190	0.766	0.969	0.067	0.065
RP 100	r	0.077	–0.669*	0.087	0.384*	0.354
	p	0.687	0.024	0.648	0.036	0.055
RN75-RP100	r	–0.021	–0.192	0.141	0.715**	0.716**
	p	0.912	0.573	0.457	0.000	0.000

r = Pearson's coefficient; p = Probability value; * denotes significant correlation at 0.05 level (2-tailed); ** denotes significant correlation at 0.01 level (2-tailed).

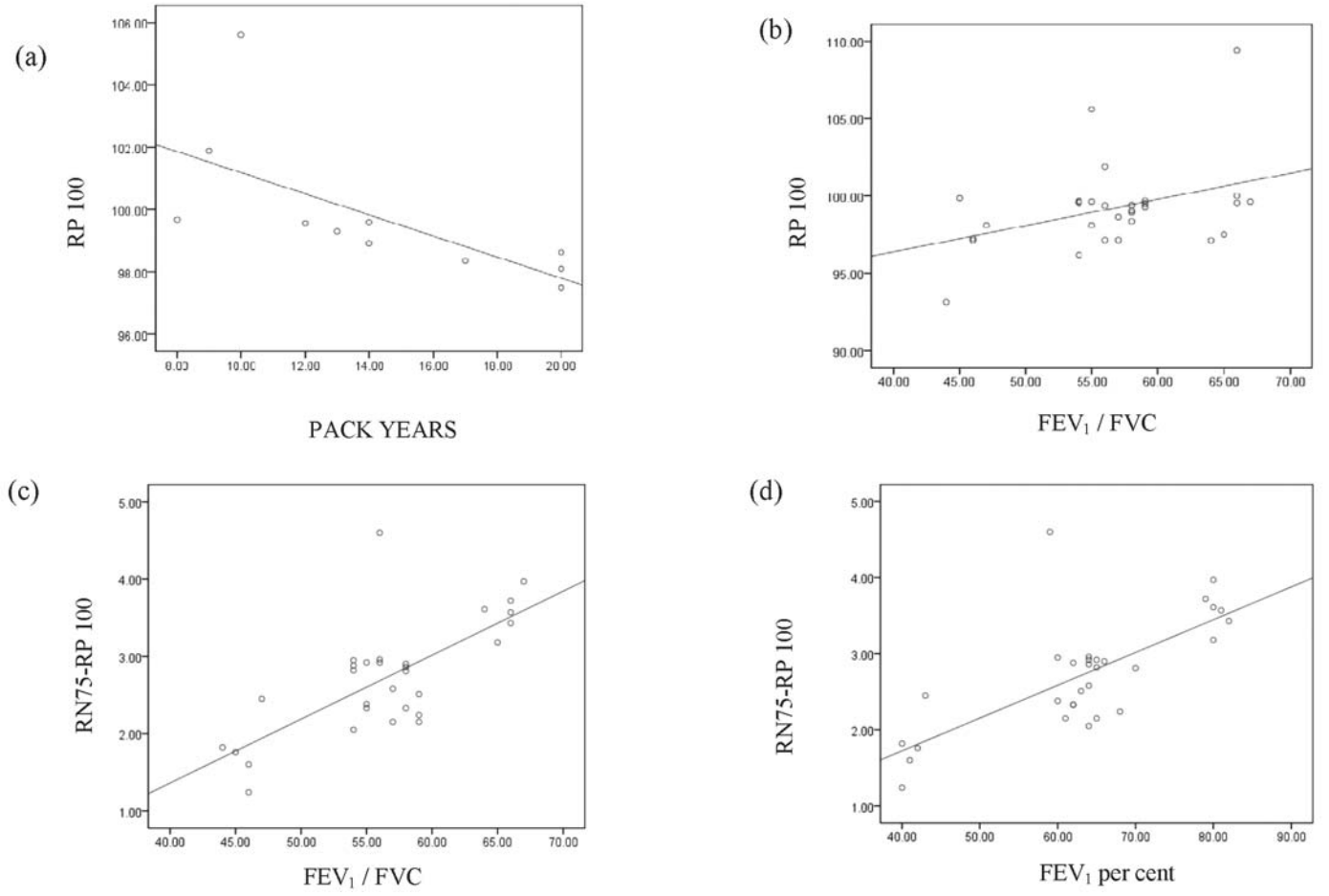

Fig. 2 : Scattered plot diagram showing correlation between VEP variables recorded in right eye. (a) A significant negative correlation between RP100 latency and smoking pack years; (b) A significant moderate positive correlation between RP100 and FEV_1/FVC index (c) A highly significant positive correlation between RN75-RP100 amplitude and FEV_1/FVC index (d) A highly significant positive correlation between RN75-RP100 amplitude and FEV_1 percent.

in the VEP parameters according to the independent Student's t-tests performed among the healthy volunteers.

Discussion

All the COPD patients included in the present study

had irreversible or partially reversible airflow limitation which is one of the defining characteristics of COPD (GOLD criteria), as distinguished from reversible obstructive airway disease as per the recommendations of CIBA Symposium (5) and American Thoracic Society (ATS) Committee on Diagnostic Standards (6). However, most of the earlier studies did not have conformity regarding the reversibility criteria as recommended; but were taken into consideration in the present study.

Characteristics of study subjects

The mean age of COPD patients observed in the present study was 45.57 years who ranged from 36 to 55 years. But, the earlier studies (7-10) were carried out only in the older patients (with the mean age of 64.0±6.5, 61.5±8.8, 59.4±9.4 and 62.1±9.9 respectively) who might have had the age-related VEP changes which would not have been, hither to, ruled out. Therefore, it could be confirmed in the present study that the COPD is also affecting the middle age group and the evidence of central neuropathy noticed in the patients are disease-driven rather than age-related. The incidence of COPD observed even in the younger age could be attributed to genetic cause, as already proven by many studies that alpha$_1$-anti trypsin deficiency is one of the common causes for COPD. Moreover, the COPD patients were almost equally distributed between sexes and the sex-wise incidence of disease was not seen. However, according to GOLD (1), there is an increasing trend of COPD in females though it has plateaued in males.

Visual evoked potential

Significant increase in N75 latency in COPD patients (Table II) may be attributed to synaptic delay or altered neuronal processing in optic nerve which is in accordance with the suggestion of Singh *et al*. (11). The P100 latency is the most consistent one having least variable peak when compared with the N75 and N145. In the present study, the latency of P100 in COPD patients was prolonged for a duration of 3.66 and 2.99 milliseconds than normal individuals in left and right eyes respectively, with highly significant probability value (P<0.01). This finding is in agreement with the recent studies by Gupta *et al*. (12) and Demir *et al*. (13). Sezer *et al*. (10) also showed that P100 value was altered in COPD patients and further hypothesized that the elevations in latencies of both N and P waves were brought about by the hypoxia, hypercapnea and acidosis, resulting from COPD. Since, N145 wave is generated from extra-striate visual cortex, the insignificant result obtained in our study confirms the irrelevance of N145 wave getting affected by the COPD.

The amplitudes of P100 in COPD patients were found to be 2.70±0.64 microvolts in left and 2.72±0.74 in right eyes. The highly significant reduction exhibited in this parameter indicates the influence of COPD on VEP measurements; which is in agreement with the earlier studies [Ozge *et al*. (9); Sohmer *et al*. (14); and Gunn *et al*. (15)]. This reduction is attributed to hypoxaemia and acidosis resulting in optic nerve damage by harming vaso-nervosum which leads to neuronal hyperpolarization and decreased excitability. On the contrary, this parameter was unaltered in COPD patients as reported by Gupta *et al*. (12) and Demir *et al*. (13). The finding of independency of factors *viz*. disease duration, smoking and age on COPD corroborates with the observation of Ozge *et al*. (9).

Correlation of VEP variables

The positive significant (P<0.05) relationships observed between LP100 latency and spirometric indices (FEV_1/FVC and FEV_1 percent) are contrary to our expectations. However, the correlation coefficients for the spirometric indices and the amplitude (N75P100) were found to be positive and highly significant (P<0.01; Table III). This correlation was further strengthened by ANOVA which showed highly significant differences existing among mild, moderate type IIA and moderate type IIB patients. The equal amount of exposure of non-smokers to the passive smoking and pollution from automobiles and biomass or domestic fuel would be the possible reason that brings out no difference in the VEP parameters between smokers and non-smokers.

In conclusion, the abnormal VEP parameters in COPD patients found in this study strongly supports

the fact of polyneuropathy, resulting from acidosis, hypercarbia and airway obstruction. These effects should be considered while determining management strategies and follow up procedures for COPD patients. Still, overall changes were in the direction of poorer function and these results suggest physiologically significant impact of chronic hypoxemia and the need for further study to evaluate thoroughly the potential risk factor for visual pathway dysfunction.

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