CORRELATION OF VISUAL EVOKED POTENTIAL CHANGES WITH SEVERITY OF COPD

Asha Shrivastava*, Rashmi Dave, Brajesh Sharma***, Sanjeev Shrivastava******

*Professor, **JR III, ***JR II, ****Assistant Professor, Gandhi Medical College, Bhopal 462 001

ABSTRACTS: Background & Objectives: Present study was aimed to assess VEP abnormalities in stable COPD patients and correlate the changes with severity of COPD .**Methods**: Study comprised of 60 healthy adults and 60 stable COPD patients (30-70 years) with no clinical neuropathy or visual impairment. Duration of illness, pack years and spirometric indices (FEV1%, FEV1/FVC, PEFR %) were assessed. Severity of COPD was classified as per WHO GOLD criteria. VEP was recorded using RMS EMG MKII. Latency and amplitude of P100 wave were analysed. Significant abnormality was defined as variations beyond mean ± 3SD from healthy adults. **Results**: Observations revealed significantly prolonged P100 latency and decreased P100 amplitude bilaterally in COPD patients compared with controls. With increasing severity a trend towards decrease in P100 amplitude was observed in 38% cases, a characteristic feature of axonal loss, in 52% cases axonal loss was associated with demyelination from moderate to very severe grades of COPD. Positive correlation between P100 amplitude and spirometric indices and negative correlation with pack years could be established.**Interpretation & conclusion**: Observation suggests that hypoxemia of COPD, by inducing changes in arterial blood gases may be implicated for the impairment in visual evoked responses.

Keywords: VEP, hypoxemia, demyelination, axonal loss

Author for correspondence: Dr. Rashmi Dave, Department of Physiology, Gandhi Medical College, Bhopal – 462001.E- mail: rdave1987@gmail.com

Introduction:

Chronic obstructive pulmonary disease (COPD) is a lung disease characterized by chronic obstruction of lung airflow that interferes with normal breathing and is not fully reversible. It is defined by the Global Initiative for Chronic Obstructive Lung Disease (GOLD), as "A preventable and treatable disease with some significant extra pulmonary effects that may contribute to the severity in the individual patient. Its pulmonary component is characterized by airflow limitation that is not fully reversible. The airflow limitation is usually progressive and associated with an abnormal inflammatory response of the lung to noxious particles or gases."[1]

COPD has been identified to have multisystem involvement with significant extra pulmonary manifestations.[2]

Smoking, long lasting COPD, airway obstruction is believed to affect ponto medullary portion of brain by altering blood gases causing hypoxemia, hypercapnia and respiratory acidosis.[3]Association of COPD patients with peripheral neuropathy has been reported in previous studies.[4, 5]

VEP waveform is generated in striate, peristriate occipital cortex and thalamocortical volleys[6]. It indicates the functional aspects of the optic nerve, optic chiasm and tracts, lateral geniculate bodies and geniculocalcarine projection to visual cortex[7]

COPD is a progressive disease in which hypoxemia occurs due to VP mismatch. Visual receptors are sensitive to hypoxia.[8]

Various studies have reported VEP changes in stable COPD patients. [2, 3]

With this background the study was undertaken to evaluate VEP changes in COPD patients and to correlate these changes with severity of disease, pack years and spirometric indices.

Material and Methods:

The study was conducted in Department of Physiology in collaboration with Department of Pulmonary Medicine. The study was approved by the Gandhi Medical College (Approval no. 14593-94/MC/7/2014). 112 clinically diagnosed COPD patients underwent detailed clinical and

neurological examination. 75 non-alcoholic male patients not suffering from diabetes mellitus, hypertension, uraemia, asthma, unstable angina, any neuropathy and not on any neurotoxic drug were selected for the study. These patients were subjected to spirometric investigation and ophthalmological examination to exclude any eye pathology. 68 patients having normal visual acuity and colour vision were selected. 8 patients who refused investigations were not included.

Participants were divided into 4 subgroups mild, moderate, severe and very severe grade of COPD. Severity of COPD was assessed according to the WHO GOLD criteria.[9]

In each subgroup 15 patients who met the inclusion criteria and volunteered for the study were chosen. The COPD patients were either current smokers (76.6%) or non-smokers (23.3%).Smoking pack years were calculated using Dr N J Masters and Catherine Tutt smoking pack year calculator.[10]

For the selection of healthy volunteers to serve as control attendants of the patients willing to be investigated were subjected to spirometric investigation and ophthalmic examination. 60 age and sex matched healthy non-smoker attendants were selected. There was no evidence of any neurologic deficit/peripheral neuropathy and visual impairment in these subjects on clinical examination and detailed history. On spirometric investigation FEV1/FVC was more than 70%. The exclusion criteria of the patient group were also used for the controls.

All participants were informed about the study and written consent was obtained.

Spirometric tests were done by using RMS – Helios 401 spirometer and the best of three consecutive tests was taken into consideration. Certain drugs used by COPD patients were restricted for a period as advised by the treating Physician. Forced Vital Capacity (FVC), Forced expiratory volume in 1 second (FEV_1),the ratio of FEV_1/FVC, peak expiratory flow rate (PEFR),forced expiratory flow during the middle half of FVC (FEF 25-75) were measured. Pre and Post bronchodilator study was done in all COPD cases. Post Bronchodilator response was marked by significant irreversibility in COPD.

VEP was recorded using RMS EMG EP MAK II. Skin is prepared by abrading and degreasing. Recording, ground and reference electrodes were placed at Oz (as per 10-20 international system of EEG electrode placement), vertex (Cz), Fpz or 12 cm above nasion respectively. Electrode impedance was kept below 5 Ω.

VEP test was performed in a specially equipped electro diagnostic procedure room (darkened, sound attenuated room). Initially, the subjects were made to sit comfortably approximately 100 cm away from the pattern-shift screen. Subjects were placed in front of a video monitor displaying black and white checkerboard pattern. The checks of alternate black/white to white/black at a rate of approximately twice per second. Every time the pattern alternates, the subject's visual system generates an electrical response that was detected and recorded by surface electrodes, which were placed on the scalp overlying the occipital and parietal regions with reference electrodes on the midline of frontal region (Fz). The subjects were asked to focus his gaze onto the centre of the screen. Each eye was tested separately (monocular testing).

Channel 1: Oz- FPz
Channel 2: Oz-A1 A2
Ground: Cz
Recording conditions
Band pass: 1-300 Hz
Analysis time: 250 ms
Number of epochs: 200 Stimulation
Black and white checkerboard or vertical grafting
Contrast- 50-80%
Full field size >8%
Size of pattern 14 × 16 min
Rate of stimuli 2 Hz
Mean luminance of the central field 50 cd/m2
Background luminance 20-40 cd/m2

P100 latency, amplitude and interocular latency difference was recorded in the study population.

Statistical Analysis: All values were expressed as Mean ± Standard deviation. Student t test and one way ANOVA were used to compare groups. Bivariate correlations between variables were evaluated by Pearson's correlation. Statistical analysis was done using SPSS-16.0 (Statistical package for Social science)

Result:

TABLE NO 1 RELEVANT BASELINE CHARACTERISTICS OF STUDY POPULATION

S.No	VARIABLES		COPD Patients N=60				
		CONTROLS N=60	**ENTIRE GROUP N=60**	**MILD N=15**	**MODERATE N=15**	**SEVERE N=15**	**VERY SEVERE N=15**
1.	AGE (years)	53.1 ± 13.4	54.5 ±11.4	55 ± 11.9	56.1±12.5	52.3±8.8	54.6 ± 12.0
2	BMI (Kg/m2)	24.1 ± 2.5	23.9±4.2	24.4±3.8	23.1±4.0	23.3±4.4	24.9 ± 4.6
3	PULSE (bpm)	73.4 ± 4.1	81.7±11.8	82.93±9.2	75.4±15	82.0±9.8	86.6 ± 10.4
4	R RATE (PM)	14.2 ± 1.9	18.0±3.5	18.6±4.1	17.4±2.7	18.2 ± 4.2	18 ±2.9
5	SBP (mmHg)	113.2 ± 4.9	129.3±9.1	129.2±9.1	128.3 ± 10.5	130.6 ± 8.4	129.3 ± 9.5
6	DBP (mmHg)	73.4 ± 2.9	83.5±6.6	84.1±9.1	80.8 ± 6.7	84.6 ± 4.9	84.5 ± 4.6
7	Pack years	-	29.5 ± 25.3	23.7 ± 15.8	25.8 ± 21.2	30.9 ± 34	37.9 ± 30

All the vital parameters in COPD patients were found to on higher side as compared to controls. Quantum of smoking was more in patients of severe and very severe subgroup as compared to mild and moderate subgroup of COPD.

Table 2: Spirometric indices and Saturation of oxygen of controls and COPD patients

	FEV_1(% predicted)	FEV_1/FVC (%)	FVC (% predicted)	PEFR (% predicted)
CONTROLS(n=60)	95.97 ± 34.21	88.88 ± 11.07	92.53 ± 24.34	88.7 ± 39.6
*COPD PATIENTS (n=60)	53.58 ± 26.45	52.92 ± 11.3	73.38 ± 20.57	45 ± 18.97
t	7.59	17.6	4.65	7.7
p	0.0001	0.0001	0.0001	0.0001
COPD SUB-GROUPS				
Mild (n=15)	90.26±13.4	62.6±6.98	90.13±19.56	59.93±16.31
Moderate(n=15)	62.53±6.92	53.52±9.74	86.4±12.83	48.2±20.65
Severe (n=15)	35.86±4.03	50.23±10.83	65.73±8.72	38.73±16.89
Very severe (n=15)	25.66±2.60	45.33±10.37	51.26±9.01	33.13±9.77

*Post bronchodilator irreversibility (<12%)

All the respiratory parameters of COPD patients were found to be significantly decreased as

compared to control groups. FEV1/FVC was <70% in all COPD patients.

*COPD patients were classified as mild, moderate, severe, very severe grade on the basis of % FEV1 predicted (>80%, 79-50%, 49-30%, <30% respectively)

The spirometric indices in 4 subgroups of COPD patients were gradually reduced from mild to very severe grade, as was expected.

	Right Latency (ms)	Left latency (ms)	Right amplitude(mV)	Left amplitude (mV)
CONTROLS(n=60)	98.07 ±5.02	98.57±5.02	6.2±2.08	5.64±2
COPD PATIENTS (n=60)	110.11±6.87	110.29±6.81	3.18±1.9	3.05±1.7
t	**10.38**	**10.73**	**8.3**	**7.64**
p	**0.0001**	**0.0001**	**0.0001**	**0.0001**
COPD SUBGROUPS				
Mild (n=15)	108.65±3.01	109.08±3.24	4.66±2.21	4.34±2.07
Moderate (n=15)	111±5.87	111.23±5.46	2.99±1.76	2.92±1.39
Severe (n=15)	111.02±6.46	110.75±6.38	2.64±1.44	2.90±1.38
Very severe (n=15)	109.78±10.46	110.12±10.56	2.42±1.38	2.04±1.1
f	0.39	0.26	**5.79**	**5.83**
p	0.75	0.84	**0.002**	**0.002**

Table no 3: Latency and amplitude of P100 wave measurements in study population

The mean latency of P100 wave of the right as well as left eye was found to be statistically prolonged as compared to the corresponding eye in healthy control group ($p<0.0001$).

The mean amplitudes of P100 wave in both the eyes of COPD patients were significantly decreased ($p<0.0001$) as compared to the corresponding eye of the healthy volunteer.

Statistically Significant difference in amplitude was seen with increasing severity of COPD

No significant difference in P100 latency was seen with severity of disease

Significant decrease in P100 amplitude identifies axonal involvement. In 38.3% patients axonal loss was observed in right eye and in 33.3% patients in left eyes.

In majority of the cases (Right eye-48.3%; left eye-51.6%) prolonged P100 latency suggested nerve demyelination along with characteristics of axonal involvement

Table 4: Correlation of Spirometric Indices with VEP variables

VEP variables		FEV1	FEV1/FVC	PEFR	PACK YEARS
P100 LATENCY RIGHT	r	-0.08	0.04	0.07	-0.17
	P	NS	NS	NS	NS
P100 LATENCY LEFT	r	-0.05	0.05	0.08	-0.02
	P	NS	NS	NS	NS
P100 AMPLITUDE RIGHT	r	**0.43**	**0.38**	**0.37**	**-0.27**
	p	**0.001**	**0.01**	**0.01**	**0.02**
P100 AMPLITUDE LEFT	r	**0.30**	**0.35**	**0.34**	**-0.26**
	p	**0.02**	**0.01**	**0.01**	**0.02**

Statistical analysis showed amplitude of P100 wave on both the sides having a significant positive correlation with FEV1, FEV1/FVC and PEFR.

Inverse correlation was observed between smoking pack years and P100 amplitude. No significant correlation was seen with P100 latency

Discussion:

COPD and chronic hypoxia have been known to affect the functional integrity of visual pathways [11, 12.] Many authors have reported VEP abnormalities in these patients[2,3,13]. In the present study we detected VEP abnormality in 86.6% in right eye and 84.7% in left eye of COPD patients who had mild to severe hypoxemia.

In the present study out of 60 stable COPD patients, 52 patients were observed to have significant VEP abnormalities. None of these subjects had any concomitant visual impairment and any evidence of peripheral neuropathy clinically. The COPD patients and healthy control subjects were assessed using Pattern Shift VEP evaluation. VEP was considered abnormal when either P100 wave latency was prolonged suggesting nerve demyelination and decrease in P100 amplitude suggesting axonal degeneration[14]. P100 wave latency and amplitude were interpreted as abnormal when the differences exceed 3 standard deviation above and below the mean of age matched control respectively.[15]

In right eyes axonal degeneration was electro physiologically diagnosed in 23 patients and evidence of both demyelination and axonal degeneration in 29 patients. Electrophysiological study of left eye showed evidence of axonal degeneration in 20 patients and both demyelination and axonal degeneration was seen in 31 patients.

The study of Gupta et al also reported visual impairment in 22 out of 40 COPD patients. They observed prolonged P100 latency and decreased amplitude in both the eyes. They suggested that chronicity of illness and heavy smoking might be the possible cause of VEP abnormalities[2.] Similar observations were reported by Murat Sezar et al (2007). [8]

Ozge et al (2005) in their study of cranial optic nerve involvement reported VEP abnormality in 82.1% cases with COPD and explained the involvement of optic nerve as a part of neuropathy.[13]

Animal experiments have established severe hypoxemia as a cause of derangement in brainstem evoked response and VEP[16].

On statistical analysis positive correlation between the P100 amplitude and spirometric variables (FEV1%, FEV1/FVC and PEFR %) and inverse correlation with pack years was observed.

No correlation between P100 latency and reported inverse correlation between P100 latency and FEV1/FVC.[2]

Helin D[17] et al (2012) evaluated visual field parameters in patients with COPD. 38 COPD patients and 29 healthy controls were included in the study.

COPD patients were smokers (pack years 37.92 ± 20.98) and with normal visual acuity. Visual field

analysis was done and VEP parameters were recorded from all the subjects.

Mean deviation, Pattern standard deviation and corrected pattern standard deviation were significantly different between COPD patients and control group for both standard achromatic perimetry (SAP) and short wavelength automated perimetry (SWAP). They also reported prolonged VEP P100 latencies in COPD patients.

Kergout et al (2006)[18] studied retinal ganglion cell sensitivity to mild hypoxemia and showed that ganglion cell function is reduced with decreased blood arterial oxygen.

Helin D et al[17] (2012) also concluded from their study that COPD related vascular changes, low oxygen saturation might contribute to reduction in retinal sensitivity.

Wimpissinger et al (2004)[19] and Akarsu et al (2004)[20] studied the effect of smoking on eye and emphasized the role of decreased blood flow in ocular and retinal blood vessels.

Early identification of the existence of sub clinical VEP abnormalities in COPD patients with no clinically detected visual impairment may help in planning and management of the COPD patients.

Conclusion

Our data suggests that hypoxemia caused by airway obstruction in COPD and smoking may cause abnormality in visual evoked responses in the striate and peristriate occipital cortex. P100 latency reflects the functional integrity of visual pathway, an increase in P100 latency with increasing severity of COPD indicates a progressive degeneration in visual quality.

Study limitation: No investigation of the blood gas levels in COPD patients is the limitation of the study.

Acknowledgment:

We are thankful to Dr Nishant Shrivastava, Assistant Professor, Department of Pulmonary Medicine for clinical diagnosis of COPD patients.

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Disclosure: No conflicts of interest, financial, or otherwise are declared by authors