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CORRELATION OF DISEASE DURATION, SMOKING PACK YEARS AND FEV1% PREDICTED WITH BAEP PARAMETERS IN PATIENTS OF COPD

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ABSTRACT

COPD is a progressive disease associated with an amplified chronic inflammatory response to noxious particles or gases in the airways and lungs. It is characterized by airflow limitation that is not fully reversible. Long term exposure to lung irritants that damages the lungs and airways usually is the cause of COPD. Worldwide, the most commonly encountered risk factor for COPD is tobacco smoking. The early detection of auditory impairment can be possible by recording of *BAEP* in patients of COPD. Study includes 100 individual, all males with the age group of 40-60 yrs. were divided in two groups, study group (n=50) and controls (n=50). Study group includes patients of COPD, as per gold criteria and those had a duration of COPD for more than 5 years with stable course of disease. Controls are age & sex matched normal healthy adults. Spirometry was done in patients to confirm the diagnosis of COPD and the severity of airflow limitation. And *BAEP* recording was done. *Latencies* of wave I, II, III, IV, V and *Interpeak latencies* I-III, III-V, I-V of right ear had a statistically non-significant positive correlation with disease duration. There were increase in right ear *latencies* of wave I, II, III, IV, V and *Interpeak latencies* of I-III, III-V, I-V along with increase in *smoking pack years* indicating a positive correlation with p value <0.05 showing a statistical significance. Also statistical significant (p value <0.05) negative correlation between post-bronchodilator *FEV1%* predicted value and right ear latencies of wave I, II, III, IV, V &*Interpeak latencies* of I-III, III-V, I-V ; indicating prolongation of latencies of *BAEP* with reduction in *FEV1%* predicted. The progressive chronic hypoxemia leads to development of tissue hypoxia and decreases the cerebral perfusion; also it slows the nerve conduction in auditory pathways which causes prolongation of *latency*. The contents of tobacco smoke in addition to hypoxemia lead to *hypoxia*. Therefore *smoking pack years* and decreased *FEV1%* predicted value definitely have impact on *BAEP*.

Key Words: BAEP, Latencies, Interpeak latencies, FEV1 % predicted value, Smoking pack years, Disease duration, Hypoxia

INTRODUCTION

Chronic Obstructive Pulmonary Disease (COPD), a common preventable and treatable disease, is characterised by persistent airflow limitation that is usually progressive and associated with an enhanced chronic inflammatory response in the airways and the lung to noxious particles or gases. Exacerbations and comorbidities contribute to the overall severity in individual patients [(1)].

The term COPD is commonly used to refer the related conditions emphysema and chronic bronchitis [(2)].The recently published GOLD report (2014) used the term emphysema and chronic bronchitis for diagnosis of COPD, but they are not included in definition. Because chronic bronchitis defined as the presence of cough and sputum production for at least 3 months in each of 2 consecutive years, is not necessarily associated with airflow limitation. Emphysema, defined as destruction of the alveoli, is a pathological term that is sometimes (incorrectly) used clinically and describes only one of several structural abnormalities present in patients with COPD and can also be found in subjects with normal lung function [(1)].

Long term exposure to lung irritants that damages the lungs and airways usually is the cause of COPD. Worldwide, the most commonly encountered risk factor for COPD is tobacco smoking[(3,4,5)]. Studies show that approximately 80-90% of

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patients with COPD have been smoking and approximately 15% of all smokers will develop COPD [6]. Non-smokers may also be at risk for developing COPD as a consequence of passive smoking, indoor and outdoor air pollution or occupational dusts and chemicals[7,8]. COPD risk is related to the total burden of inhaled particles a person encounters over their lifetime [9].

1) Tobacco smoke includes cigarette, bidi, pipe, cigar and other types of tobacco smoking.
2) Indoor air pollution from the burning of biomass fuel used for cooking and heating in poorly vented dwellings, a risk factor that particularly affects women in developing countries [10].
3) Occupational dusts and chemicals are risk factors when the exposures to them are sufficiently intense and prolonged [7,11].
4) Outdoor air pollution also contributes to the lungs' total burden of inhaled particles, although it appears to have a relatively small effect in causing COPD [1].
5) Genetic factors- The genetic risk factor that is best documented is a severe hereditary deficiency of alpha-1 antitrypsin [12].

These indicators are not diagnostic themselves, but the presence of multiple key indicators increases the probability of a diagnosis of COPD. Spirometry is required to make a clinical diagnosis of COPD; the presence of a post-bronchodilator $FEV_1/FVC < 0.70$confirms the presence of persistent airflow limitation and thus of COPD. Spirometry (meaning measuring of breath) is the most common of the pulmonary function tests measures how much air can breathe out (volume) and how fast can blow air out (flow)[13].

COPD is often associated with clinical manifestations that include metabolic abnormalities, weight loss, muscle weakness and wasting, anxiety, depression[14], Osteoporosis, Cardiovascular diseases like Corpulmonale[15], Atherosclerosis, ischemic heart disease and stroke[16]. Many of the systemic co-morbidities associated with COPD have been related to systemic inflammation [17]. There is rapidly growing body of evidence indicating that the pulmonary disease observed in patients with COPD is also associated with systemic inflammation[18]. COPD is associated with systemic inflammation, recognized as a risk factor for its systemic complications. Hypoxemia triggers oxidative stress and inflammation in COPD patients [19].

The existing medical literature suggests that hypoxemia results in peripheral nerve damage by harming the vasonervosum. In the early stages of ischemia, mechanisms to reduce peripheral neuropathy are activated, but these become insufficient over time and obvious neuropathy is inevitable in chronic hypoxemia [20].

There are some studies showing that auditory receptors are affected from hypoxia [21,22]. The early detection of auditory impairment can be possible by recording of BAEP in patients of COPD. Brainstem auditory evoked potentials (BAEPs) are the potentials recorded from the ear and vertex in response to a brief auditory stimulation to assess the conduction through the auditory pathway up to the midbrain [23]. BAEP is a far field recording of the synchronized response of a large number of neurons in auditory pathway. The use of the BAEP has been well documented both from a neurological and audio logical stand point [24]. BAEP is a simple, non-invasive procedure to detect early impairment of acoustic nerve and CNS pathway, even in the absence of specific symptoms. Therefore Correlation of disease duration, smoking pack years and FEV_1% predicted with BAEP parameters done in patients of COPD.

MATERIALS AND METHODS

The present study was conducted in the Department of Physiology and Department of Pulmonary Medicine in Grant Government Medical College & J.J Hospital, Mumbai. Before commencement of study, approval was taken from the Institutional Ethical Committee.

The study design involved 100 individuals which can be divided in two groups.

Group I –Diagnosed patients of COPD as per GOLD criteria, after applying inclusion and exclusion criteria were accepted for study (n=50)

Group II –Age & sex matched normal healthy adults (n=50).

In addition, spirometry was done to confirm the diagnosis of COPD and the severity of airflow limitation was determined by GOLD gradation criteria (post-bronchodilator FEV_1/FVC ratio less than 70%, consistent with airflow limitation that is not fully reversible,GOLD criteria).

GOLD gradation of COPD:[25]

Severity of Airflow limitation based on Post-Bronchodilator FEV_1 in patients of FEV_1/FVC <0.70		
Severity		**FEV_1 % predicted**
GOLD 1	Mild	$FEV_1 \geq$ 80% predicted
GOLD 2	Moderate	$FEV_1$50–79% predicted
GOLD 3	Severe	FEV_1 30-49% predicted
GOLD 4	Very severe	FEV_1< 30% predicted

The evaluation was done in following stages -

1) A written informed consent was taken from all participants of this study.
2) A detailed history-taking and thorough clinical exami-

nation was done.
3) Spirometric test was performed in both groups and diagnosis of COPD was confirmed in cases
4) BAEP recording was done.

Among COPD patients, those had a duration of COPD for more than 5 years with stable course of disease, having a regular follow up for 1 year with no hospitalization for COPD related illness in preceding 6 months were included in study group. All COPD patients in study were males and had smoking history. They were having moderate to severe airflow limitation. The subjects who met the criteria were selected for the study. The study and control group were selected as per inclusion and exclusion criteria. Spirometry test was done in study group with the help of ***MEDGRAPHICS Body Plethysmograph***machine.

Inclusion criteria for selection of COPD patient -

1. Males with age group of 40-60 years.
2. On spirometric test, patients having post-Bronchodilator FEV_1% predicted valueless than 80% with FEV_1/ FVC ratio <0.70.
3. Patients with normal auditory function tests.

Inclusion criteria for controls

1. Normal healthy male individuals with age group of 40-60 years.
2. Subjects having no addiction (Non-smokers).
3. Subjects having normal hearing.

Exclusion criteria for both

1. Patients of COPD in acute exacerbation.
2. Subjects having any clinical neuropathy.
3. Subjects having hearing loss.
4. Subjects suffering from another acute/ chronic medical disorder like hypertension, diabetes mellitus, malignancy, leprosy, tuberculosis.
5. Subjects with history of addiction to alcohol, drug abuse.
6. Subjects with history of drug intake known to cause central neuropathy e.g. Reserpine, Phenytoin, Alphamethyldopa, Nitrofurantoin.
7. Subjects who had history of taking ototoxic drugs e.g. Gentamycin, Amikacin, Streptomycin, Kanamycin and Quinine.

Evoked Potential study[26]

Pre-test preparation –

The skin was prepared by mild abrading and degreasing by *Nu-Prep* gel. Standard cup electrodes were used. The electrodes were placed on their respective sites using electrode paste as per 10-20 international system of electrode placement. The tests were carried out in a quiet room. ***EMGand EP digital neurophysiological system software, Neuro-ME-Pw*** version 3.0, 64.0 was used to conduct evoked potential tests.

Brain stem auditory evoked potential Recording –

All the techniques of recording, machine settings and instruments were maintained uniformly throughout the study. Patients were made to lie down comfortably on couch and were asked to close their eyes and relax. BAEPs are obtained using monaural (one ear at a time) stimulation.

Electrode placement –

Active electrodes (M_i, M_c) - over mastoid processes

Reference electrode (C_z) – at vertex

Ground electrode (F_z) – at forehead in midline

Montage consisting of the following derivations was used for BAEP recording-

Channel 1: Vertex – ipsilateral mastoid process ($C_z - M_i$)

Channel 2: Vertex – contralateral mastoid process ($C_z - M_c$)

The following machine setting was used throughout the study.

1) **Stimulus** – Monaural auditory stimulus in the form of clicks were delivered through *TDH-39P* headphone at a rate of 10 per second (10 Hz) with the alternating polarity. The click stimuli at an intensity 100 dB SPL was given to the stimulated ear (ipsilateral) and masking sound (white noise) of 60 dB SPL to non-stimulated, contralateral ear through the headphone. Stimulus duration was 0.1 milliseconds. Responses to 2000 click stimuli were averaged for 10 milliseconds.
2) **Filter**– Low and High band pass filter was set at 100 Hz and at 3000 Hz respectively.
3) **Impedance** – The electrode impedance was kept below 5 kΩ

The signals picked up by these electrodes were filtered, averaged, amplified and displayed on the computer monitor. Two trials of recording were done and wave forms were super imposed to check for reproducibility.

Parameter studied: BAEP waveforms from each ear with absolute latencies of I, II, III, IV, V waves and Inter peak latencies (IPLs) of I-III, III-V, I-V were considered for comparison among COPD patients and controls.

Statistical analysis:

The results were expressed as mean and standard deviation for each variable, separately for right and left side. **Unpaired**

(independent) t- test was used for intergroup comparisons in the healthy volunteers group and the COPD group, **p-value of 0.05 or less** has been considered as statistically significant.

Correlation between disease duration, smoking pack years and FEV_1% predicted with BAEP and VEP parameters were done. All statistical analyses were carried out with the help of SPSS version 20.0 software.

OBSERVATIONS AND RESULTS

Table 1: Table showing the patients characteristics (Disease duration, Smoking pack years), Age distribution and Spirometric findings in study group.

	Cases (Mean ± S.D.)	Controls (Mean± S.D.)	p value	
Age (years)	52.92 ± 3.93	51.48 ± 5.4	0.1312	ns
Disease duration (years)	10.82 ± 2.89			
Smoking pack years	31.04 ± 6.6			
FEV_1 % predicted	47.73 ± 8.13	90.71 ± 4.62	< 0.0001	s

p value ≤ 0.05 = Statistically significant
p value > 0.05 = Statistically non-significant

There was no statistical significant difference (p value > 0.05) in age distribution among cases and controls.

FEV_1 % predicted spirometric value was statistical significantly less in cases compared to controls (p value < 0.05).

Bar diagram no. 1: Showing the comparison of post-bronchodilator FEV_1% predicted value in study group.

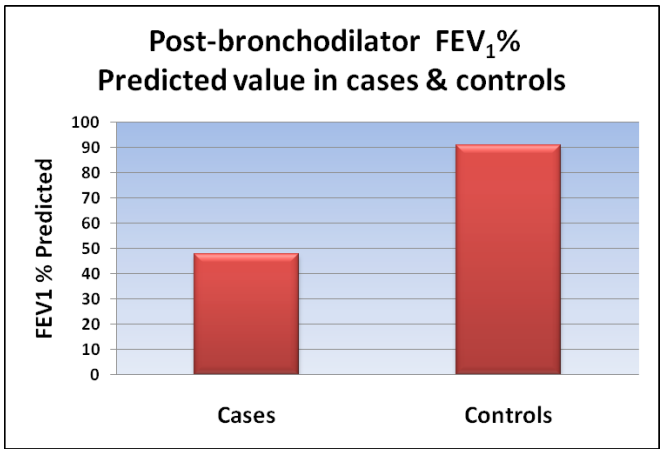


Table 2: Table showing BAEP parameters of Right ear in case group compared to control group.

Right BAEP parameters	Cases (Mean ± S.D.)	Controls (Mean± S.D.)	p value	
Latency (ms)				
Wave I	1.62 ± 0.1	1.56 ± 0.12	0.0249	s
Wave II	2.79 ± 0.14	2.75 ± 0.12	0.0847	ns
Wave III	3.73 ± 0.19	3.65 ± 0.17	0.026	s
Wave IV	4.89 ± 0.21	4.78 ± 0.21	0.0164	s
Wave V	5.78 ± 0.33	5.61 ± 0.3	0.0091	s
Inter peak Latency (IPLs) (ms)				
I – III	2.11 ± 0.09	2.08 ± 0.05	0.0466	s
III – V	2.05 ± 0.15	1.96 ± 0.19	0.0139	s
I - V	4.16 ± 0.24	4.04 ± 0.2	0.0092	s

p value ≤ 0.05 = Statistically significant
p value > 0.05 = Statistically non-significant

Table 3: Table showing the correlation of disease duration with BAEP parameters in COPD patients.

Correlation of Disease duration (yrs) with BAEP parameters			
Right BAEP parameters	**r value**	**p value**	
Latency (ms)			
Wave I	0.21	0.1324	ns
Wave II	0.19	0.1817	ns
Wave III	0.23	0.1088	ns
Wave IV	0.21	0.1329	ns
Wave V	0.21	0.1329	ns
Inter peak latencies (IPLs) (ms)			
I- III	0.23	0.0978	ns
III- V	0.18	0.1912	ns
I - V	0.21	0.1398	ns

p value ≤ 0.05 = Statistically significant
p value > 0.05 = Statistically non-significant

There was statistically non-significant (p value >0.05), Latencies of wave I, II, III, IV, V and Inter peak latencies I-III, III-V, I-V of right ear had a statistically non-significant positive correlation with disease duration.

Table 4: Table showing the correlation of smoking pack years with BAEP parameters in COPD patients.

Correlation of smoking pack years with BAEP parameters			
Right BAEP parameters	**r value**	**p value**	
Latency (ms)			
Wave I	0.41	0.0025	s
Wave II	0.43	0.0017	s
Wave III	0.43	0.0017	s
Wave IV	0.42	0.002	s
Wave V	0.4	0.0037	s
Inter peak latencies (IPLs) (ms)			
I- III	0.43	0.0015	s
III- V	0.34	0.0136	s
I - V	0.39	0.005	s

p value ≤ 0.05 = Statistically significant
p value > 0.05 = Statistically non-significant

It was observed that there were increase in right ear latencies of wave I, II, III, IV, V and Inter peak latencies of I-III, III-V, I-V along with increase in smoking pack years indicating a positive correlation with p value <0.05 showing a statistical significance.

Scatter diagram no. 1: Showing positive correlation between smoking pack years with wave I latency of Right ear in cases.

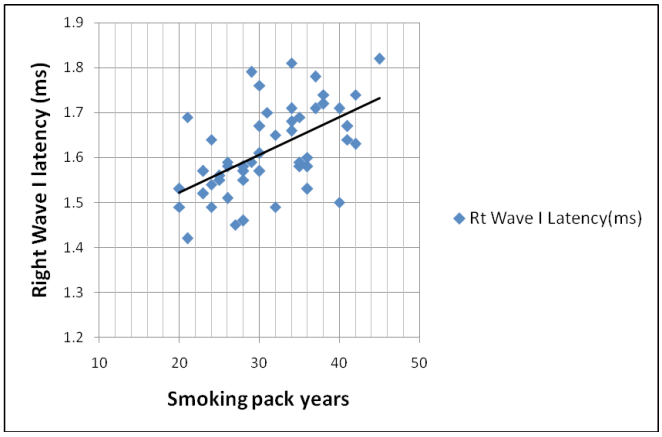


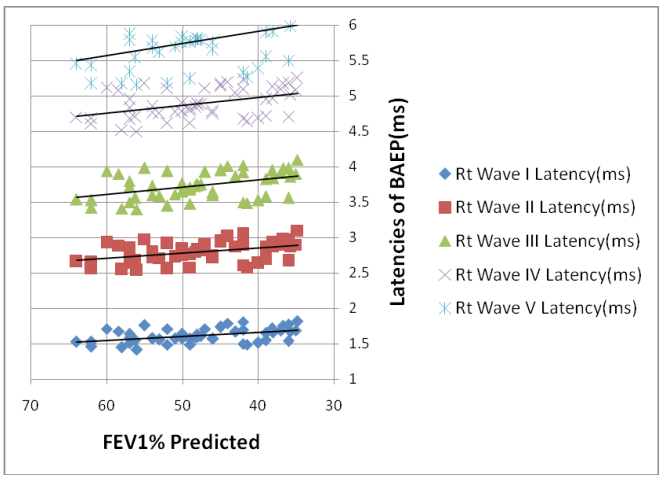
Table 5: Table showing the correlation of post-bronchodilator FEV_1% predicted value with BAEP parameters in COPD patients.

Correlation of FEV_1 % predicted with BAEP parameters			
Right BAEP parameters	**r value**	**p value**	
Latency (ms)			
Wave I	-0.44	0.0012	s
Wave II	-0.42	0.0024	s
Wave III	-0.43	0.0014	s
Wave IV	-0.43	0.0016	s
Wave V	-0.41	0.0029	s
Inter peak latencies (IPLs) (ms)			
I- III	-0.42	0.0024	s
III- V	-0.35	0.0105	s
I – V	-0.39	0.0049	s

p value ≤ 0.05 = Statistically significant
p value > 0.05 = Statistically non-significant

Table shows that there was statistical significant (p value <0.05) negative correlation between post-bronchodilator FEV_1% predicted value and right ear latencies of wave I, II, III, IV, V & Inter peak latencies of I-III, III-V, I-V ; indicating prolongation of latencies of BAEP with reduction in FEV1% predicted.

Scatter diagram no. 2: Showing negative correlation between FEV_1% predicted value and Right ear latencies of BAEP waves I, II, III, IV, V in cases.



DISCUSSION

In the present study, mean age group of COPD patients was 52.92 ± 3.93 years with disease duration of 10.82 ± 2.89. All were smokers with smoking pack year index 31.04 ± 6.6. On spirometric findings, all COPD patients were having post-bronchodilator FEV_1/FVC ratio less than 0.7, a GOLD diagnostic criteria of COPD. COPD patients were having moderate to severe airflow obstruction (grade 2 & 3) as per GOLD gradation of severity of airflow limitation with mean post-bronchodilator FEV_1 % predicted value 47.73 ± 8.13. There were no clinical signs and symptoms of peripheral neuropathy in study group.

Correlation of patient's characteristics with BAEP and VEP parameters was given in table no. 1-5. Present study found that there was non-significant correlation between disease duration and BAEP parameters while there was significant correlation of BAEP parameters with smoking pack years and severity of airflow obstruction. Similar findings are present in some studies *Vijay Kumar et al* [27] *(1996), Hafez et al* [28] *(2009), NesrienShalabietal*[29] *(2012).*

Vijay Kumar[27] (1996) studied BAEP in tobacco smokers and found latency of wave I and wave III were significantly prolonged. They concluded that abnormal BAEP findings were due to nicotine and toluene of smoke.

Hafez et al[28] (2009) found positive correlation of BAEP & VEP with disease duration, smoking pack years & $PaCO_2$. Their study showed negative correlation with spirometric indices.

NesrienShalabi[29] (2012) found latencies of wave I,III,V of BAEP had significant negative correlation with FEV_1, FEV_1/FVC and these latencies were positively correlated with smoking index.

Gupta et al [30] (2008) in their study found 65% of COPD patients had abnormalities in one or more BAEP variables. They hypothesized that the abnormal BAEP findings are due to brainstem hypoxia which increases with the severity of COPD. As COPD patients in their study were heavy smokers, they had given the possibility of the contents of cigarette smoke leading to BAEP abnormalities.

In addition to chronic hypoxemia and hypercapnia, other associated factors in patients with COPD, including tobacco smoking; malnutrition; and drugs used in COPD treatment, may be possibly associated with neuropathy seen in COPD patients.

CONCLUSION

The progressive chronic hypoxemia leads to development of tissue hypoxia and decreases the cerebral perfusion; also it slows the nerve conduction in auditory pathways which causes prolongation of latency. The contents of tobacco smoke in addition to hypoxemia lead to hypoxia. Therefore smoking pack years and decreased FEV1% predicted value definitely have impact on BAEP.

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