European Journal of Clinical Pharmacy
Print ISSN: 2385-409X **Online ISSN**: 3105-0409
Website: https://farmclin.com/

Original Research Article

Comprehensive Evaluation of Cochlear and Brainstem Auditory Function in Patients with Chronic Obstructive Pulmonary Disease

Article History:

Received: 12-11-2025
Revised: 26-11-2025
Accepted: 09-12-2025
Published: 25-12-2025

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Abstract: Chronic obstructive pulmonary disease (COPD) is characterized by airflow limitation caused by smoking and air pollution. This study aimed to assess auditory status using Oto Acoustic Emissions (OAEs) and Brainstem Evoked Response Audiometry (BERA) in stable patients compared to controls. ***Methods:*** 60 subjects were included: stable COPD patients (n = 30) and controls were age- and sex-matched healthy adults (n = 30). DPOAE signal-to-noise ratios (SNRs) and absolute signal levels were recorded bilaterally at 1500–8000 Hz. BERA was assessed by the Latencies of waves I-V and interpeak latencies (IPLs) of I-III, I-V, and III-V, were compared in both groups. Then the results were correlated with patient characteristics. ***Results:*** In both the ears, COPD patients exhibited lower Sigal to Noise (SNR) values in OAE and signal amplitudes compared to controls, with the most pronounced decline in the mid-to-high frequency range (>3000 Hz). BERA results showed increased absolute latencies of waves I and III bilaterally. IPLs I–V and III–V were significantly increased on the right side and IPL III–V on the left side in COPD subjects. Wave I, III, and I-III were negatively correlated with FEV1%, while wave II, V, and III-V were positively correlated with Smoking pack years. ***Conclusion:*** High frequency cochlear dysfunction and delayed brainstem neural conduction, negative correlation with FEV1% and positive correlation with smoking pack years and disease duration suggest auditory dysfunction worsens with disease severity and chronic exposure. This highlight hearing impairment as a significant yet under-recognized comorbidity in COPD, warranting early evaluation and intervention. Trial REF/2024/11/094791

Keywords: Brainstem Auditory Evoked Potentials (BAEP), Chronic Obstructive Pulmonary Disease Patients (COPD), Forced Expiratory Volume (FEV1), Inter Peak Latency (IPL)

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a common, non-communicable disease, an umbrella term for progressive lung diseases that make it difficult to breathe for patients such as emphysema and chronic bronchitis. It primarily arises from prolonged exposure to harmful substances, such as tobacco smoke, and chronic exposure to air pollution, dust, and chemicals. Chronic bronchitis is characterized by inflamed bronchial tube linings, causing daily cough and mucus production, and emphysema, where air sacs at the end of small lung air passages deteriorate due to exposure to harmful substances such as cigarette smoke. It has a worldwide prevalence of 11% in people aged 40 years or older. It has emerged as a critical global public health challenge.1 As of 2023, COPD remains a leading cause of morbidity and mortality worldwide, with a staggering global prevalence of approximately 391 million people. This represents ~5% of the world's adult population, and the prevalence increases with age, affecting 10-15% of adults over 40 in high-risk regions. COPD caused 3.3 million deaths globally in 2021, making it the third leading cause of death after ischemic heart disease and stroke.2 Furthermore, WHO mortality and disease burden projections state that COPD will be the third leading cause of death worldwide by 2030. India is grappling with a dual burden of traditional and modern risk factors, with a reported prevalence of 7.4%.3 It is the leading cause of disability among chronic respiratory diseases and was the second leading contributor of Disability Adjusted Life Years (DALY) in 2016. Nearly 32% of global DALYs due to COPD occurred in India, and it is responsible for 75.6% of

total DALYs among chronic respiratory diseases in India.4 As COPD advances, it leads to hypoxemia (low blood oxygen) because emphysema and alveolar destruction reduce the surface area for gas exchange. In contrast, chronic bronchitis causes airway inflammation and obstruction of mucus. This creates lung regions with poor ventilation (V) but maintained perfusion (Q) (low V/Q), leading to hypoxemia. When there is low tissue oxygen (PaO_2 < 60 mmHg), hypoxia occurs, which causes systemic effects, and hypoxia affects visual and auditory receptors.5 Risk factors such as smoking, occupational hazards, and air pollution exacerbate the burden of COPD, with aging populations and urbanization further amplifying prevalence. However, it is essential to note that many of these risk factors are preventable, offering hope for reducing the burden of COPD. In low and middle-income countries, indoor air pollution from biomass fuels remains a significant driver, particularly among women. Globally, smoking (46.0%), pollution from ambient particulate matter (20.7%), and occupational exposure to particulate matter, gases, and fumes (15.6%) had the highest contributions to DALYs due to COPD.6 In various studies, the most associated risk factors in India were active and passive smoking, as well as exposure to biomass fuel. Biomass fuel exposure, including the use of wood in the house, solid fuel, gas, kerosene, or cooking fuel, and coal, is considered the second most significant risk factor for COPD, encompassing chronic bronchitis and emphysema.7 Based on the GOLD criteria, a diagnosis of COPD is suspected if the patient presents with related symptoms (e.g., chronic cough, sputum, and shortness of breath) and risk factors (tobacco smoking and occupational exposures) but is confirmed by the presence of a post-bronchodilator forced expiratory volume in one second/forced vital capacity value of <0.7 done by spirometry method.8 Hypoxemia can disrupt the highly sensitive auditory system and inner ear's transduction process, which is particularly vulnerable to the effects of blood and oxygen deprivation. Therefore, any significant reduction in oxygen levels can disrupt the generation and transmission of auditory nerve impulses, leading to hearing impairment.9 The inner ear being a metabolically active organ in the body, requires oxygen for maintaining the ionic gradients and for bio mechanical process which is essential for hearing, The motility of outer hair cells (OHCs) of cochlea is an energy intensive process which depends majorly on oxygen; hence their functioning is highly susceptible to damage from hypoxia which can cause clinically significant hearing loss.10 Given the high metabolic demand of the cochlea, and dependency of OHC to oxygen a link exists between COPD and potential cochlear dysfunction. Hypoxemia in COPD patients may induce a state of "cochlear fatigue," progressively impairing OHC function. Kemp in 1970s defined OAEs as the release of sound produced in cochlea and its propagation to the middle ear and external acoustic meatus, and these sounds are produced by the movement of OHCs, so their presence indicates active OHC function so OAEs are a sensitive, and non-invasive tool for assessing the health of cochlea.11 Distortion product otoacoustic emissions (DPOAEs) reflect outer hair cell integrity and cochlear function essential for hearing sensitivity and are elicited by presenting two simultaneous pure tones (f1 & f2). Its application for screening of hearing loss has the advantage of being fast and require minimal behavioral response. DPOAE, which is an objective test, checks cochlear stress by measuring how the ear responds to different sound frequencies.12 Many studies have examined DPOAE in infants or new born but larger studies in Chronic COPD patients are less in this Signal to Noise ratio (SNR). In the literature review performed to evaluate the relationship between COPD and the affection of the auditory system, there were studies showing that the arterial transport mechanism in the inner ear was closely associated with the cochlear oxygen reserve and that the decrease in oxygen level greatly affected the inner ear cells.13 By evaluating outer hair cell (OHC) function, otoacoustic emissions (OAE) can identify cochlear damage in COPD patients even before it becomes apparent as a hearing impairment. Some studies have shown that auditory receptors are affected by hypoxia. Early detection of auditory impairment can be made possible by recording BAEP in patients with COPD.14,15 Brainstem Auditory Evoked Potentials (BAEPs), also known as Auditory Brainstem Responses (ABRs), are the auditory pathways that generate neurophysiological signals in response to sound. The signal travels along the auditory nerve and brainstem structures (e.g., the cochlear nucleus, superior olivary complex, lateral lemniscus, and inferior colliculus), which generate waves I to V. The latencies of these waves represent the speed of electrical sound signals transmitted through the different structures of the auditory pathway. BAEPs are used clinically to assess the integrity of the auditory pathway and diagnose disorders affecting the brainstem or auditory nerve 5. Eid et al., defined Oto Acoustic Emission (OAEs) as the release of sound energy produced in the cochlea and its propogation to the middle ear and external acoustic meatus. reported that Hypoxemia affects the cochlear area in the auditory pathway, resulting in increased absolute and interpeak latencies in BEAP, and smoking precipitates hearing loss at higher frequencies in a dose-dependent manner.16 Parlewar et al. concluded that chronic hypoxemia and smoking are causative factors in the development of tissue hypoxia and decreased cerebral perfusion, which eventually slows nerve conduction in auditory pathways, causing prolongation of latency. Therefore, smoking pack years and decreased FEV1% predicted value have an impact on BAEP.17

The link between hypoxemia and cochlear dysfunction in the past studies has been proved, but a critical question remains whether hearing can be affected in the patients with stable COPD who do not have resting hypoxemia. In stable COPD the auditory dysfunction may stem from the chronic systemic inflammation and oxidative stress that are hallmarks of the COPD disease. Hearing loss is problematic and represents a significant concern that should be seriously investigated as an important comorbidity in chronic obstructive pulmonary disease patients. Therefore, in this study we are attempting to assess the auditory system including the cochlear function, using DPOAEs, and the auditory pathway using BAEP in stable COPD patients and to analyse the changes with the patient characteristics, disease duration, smoking pack years, and FEV1%.

Methods

The present study was conducted in the Neurophysiology lab, Physiology Department at the Rajasthan University of Health Sciences and the College of Medical Sciences, Jaipur, Rajasthan. The subjects were recruited from the Pulmonary Medicine OPD at the RUHS hospital, Jaipur. Ethical committee approval was taken from the Institutional Ethical Committee, RUHS Medical College, Jaipur. The participants involved 60 subjects, who were divided into two groups. In the first group, patients who were on regular medications and had clinical stability were recruited from the Pulmonary Medicine Department. These patients were selected based on their stable condition and regular medication use to ensure the study's results were not influenced by acute exacerbations or irregular treatment. (n=30) and in the second group, control groups who had no history of COPD or smoking (n=30). The subjects in both groups had no history of hearing loss, ear pathology, or any other medical condition that might affect their hearing (e.g., diabetes mellitus, hypertension, noise exposure, or ototoxic drug therapy), if yes then they were excluded. The patients' age group was between 30 and 50, as this age range is more likely to be affected by COPD and its comorbidities, and it also minimizes the potential confounding effects of age-related hearing loss. Clinical evaluation, medical history, all sociodemographic data, and smoking pack years will be calculated from the mode of smoking (bidi, cigarette, or hookah), daily consumption, and the total number of years the patient has been smoking.) In addition, spirometry was done, and cases with COPD were defined as patients with an FEV1/FVC ratio <70% after bronchodilator therapy, according to the GOLD definition for COPD.18 The participant information sheet explained the nature and purpose of the study to all subjects who fulfilled the inclusion criteria, and written informed consent was obtained from all participants. Then, a complete ear examination was done for both ears, and any wax was removed. All the subjects underwent Distortion product otoacoustic emissions (DPOAE) test. The DPOAE was measured using Otoport Flexi, OTODYNAMICS test device. Before OAE testing the probe fit was checked by using a broadband stimulus like click and the corresponding check graph. Probes were of different sizes to fit according to the size of the ear canal. They are used to send the audio frequencies from the outer ear to the tympanic membrane, then the probe received the reflected sounds. Subject was made to sit in a silent room during the test. DPOAEs were measured in response to two primary tones, presented simultaneously, at frequencies f1 and f2 and levels L1 and L2. The stimulus levels of the primary tones were set at L1=65dB and L2= 55dB sound pressure level (SPL). Signal-to-noise ratio (SNR) is an index that compares the level of a desired signal to the level of background noise and is defined as the ratio of signal power to the noise power, often expressed in decibel. Signal to noise ratio (SNR) was measured at 1500,2000,3000,4000,6000 and 8000 Hz in the subjects' right and left ears separately. DPOAE responses were analyzed using raw signal-to-noise ratio (SNR) values. Clinically, an SNR $\geq$ 6 dB is considered a detectable emission,19 however, for statistical comparison, all measured SNR values—including negative values—were included. Negative SNR values represent responses where the emission amplitude fell below the noise floor, indicating absent or markedly reduced outer hair cell activity, which is expected in patients with cochlear dysfunction such as COPD. The DPOAE amplitude at each frequency is the primary measure of the cochlear health and Outer hair cell (OHC) function. The higher value, healthier OHC activity. The BERA recording was done in the Neurophysiology Lab in the Department of Physiology. The left and right ears were tested separately. The recording (active) electrodes were placed on both ears using the electrode paste. The skin was prepared by mild abrading and degreasing with Nu-Prep gel. The electrodes were placed at their respective sites using electrode paste according to the 10-20 international electrode placement system. The reference electrode was placed on the vertex, and the active electrode was placed on both sides of the mastoid. The click stimuli, at an intensity of 100 dB SPL, were presented to the stimulated ear (ipsilateral). The masking sound (white noise) of 60 dB SPL was given to the non-stimulated, contralateral ear through the headphones. The click stimuli were presented at a rate of 20 clicks per second. Responses to 2000 click stimuli were averaged for 10 milliseconds. The signals will be picked up by electrodes, filtered, amplified, averaged, displayed on the screen of the Octopus NCV/EMG/EP-4 Channel machine, and recorded. Subsequently, interpeak latencies (IPLs)

will be calculated. Classical BAEP consists of 5-8 vertex-positive peaks, which are labelled as I, II, III, IV, and V using Roman numerals.
The initial five peaks are of clinical interest as shown in Fig I20
The wave peaks have been postulated to arise from:
1. Cochlear nerves – Waves I and II
2. Cochlear nucleus – wave III
3. Superior olivary complex – wave IV
4. Nucleus of lateral lemniscus – wave V
5. Inferior colliculus – wave VI and VII

BAEP waveforms from each ear, including absolute latencies of the I, II, III, IV, and V waves, as well as interpeak latencies (IPLs) of I-III, III-V, and I-V, were analyzed for comparison between COPD patients and controls.

Statistical Analysis

Statistical data analysis was performed using SPSS software, version 17 (SPSS Inc., Chicago, IL, USA). The normality of data distribution was assessed using the Shapiro-Wilk test. Independent t-Test for normally distributed data and Mann-Whitney U test for non-normally distributed data was used for group comparisons. A p value of <0.05 was considered statistically significant.

RESULTS

The study included 30 COPD patients with COPD and 30 Healthy control subjects. The COPD patients had a post-bronchodilator FEV1 less than 80% of the predicted value, and the ratio of FEV1/FVC% % <70%. The average duration of symptoms in all patients with COPD was 4.1 □ 0.844. (Table 1). All the healthy subjects were nonsmokers and had no history of chronic illness. The severity of COPD, according to GOLD criteria, was grade I in 3 cases (10%), grade II in 10 cases (33.3%), grade III in 7 cases (23.3%), and grade IV in 10 cases (33.3%). In both the ears, COPD patients exhibited lower DPOAE SNR values and signal amplitudes compared to controls, with the most pronounced decline in the mid-to-high frequency range (>3000 Hz). (Table 2) In the right ear, COPD patients had negative mean SNR values at 3000 Hz, 4000 Hz, and 6000 Hz, while controls showed greater SNR values, resulting in significant p-values ($p < 0.001$ for 3000 and 4000 Hz; $p = 0.02310$ for 6000 Hz). In the left ear significantly reduced SNR was also there at 2000 Hz in COPD subjects. Even at 8000 Hz, where variability was higher, the left ear continued to show a significant group difference ($p = 0.00760$). Patients showed gradually diminishing or absent SNR values in the mid to high frequency regions. Across both ears, the mean DPOAE absolute signal levels (in dB SPL) for the COPD group were lower than the control group at all frequencies, and these differences were statistically significant ($p < 0.01$) In the Left ear, COPD group mean signal levels declined from –2.39 ± 9.89 dB at 1500 Hz to –19.94 ± 12.02 dB at 8000 Hz; controls ranged from +9.96 ± 4.84 dB at 1500 Hz to –8.68 ± 12.92 dB at 8000 Hz. And talking about the right ear COPD group values fell from +0.42 ± 11.52 dB at 1500 Hz to –21.79 ± 12.06 dB at 8000 Hz; controls ranged from +7.50 ± 5.61 dB at 1500 Hz to –11.65 ± 16.12 dB at 8000 Hz. As the frequency increases from 1500 Hz to 8000 Hz, COPD patients' signal levels decrease, while controls show higher values. In the high frequency band from 6000 to 8000 Hz patients showed the lowest SNR and DPOAE signal levels in both the ear. Regarding the BERA test results, the absolute latencies of waves I and III in both ears were increased in COPD subjects, with a significant prolongation of the latencies in patients compared to controls. The interpeak latencies (IPLs) showed a significant increase in I-V and III-V on the right side and in III-V on the left side in the COPD group compared to the control group. (Table 3) The correlations of variables of BERA wave patterns recorded in both left ear and right ear with the characteristics of COPD patients (Table 4, 5) The correlation between smoking pack years with wave V and inter-peak latency of wave III-V of the left ear was a positive one (Fig. II). In the right ear also, the latency of wave II correlated significantly positively with smoking pack years Disease duration correlated positively with wave III and with inter-peak latency of wave III-V of left ear, and the correlation in right ear of wave IV and wave I-V with disease duration was a positive one. The correlation between the characteristics of COPD patients with the BERA waves in the left ear showed that FEV1 % has a negative correlation with wave I and III. (Fig. III) Similarly, the latencies of wave III and interpeak latency of wave I-III correlated significantly negative with FEV1.

Fig I: Figure representing a normal BERA waveform

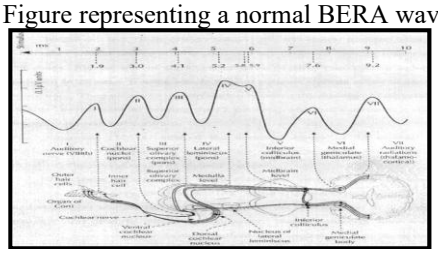

Fig II: Scattered plot diagram showing a positive correlation between Smoking Pack Years and Latency of Wave V over left ear in COPD patients

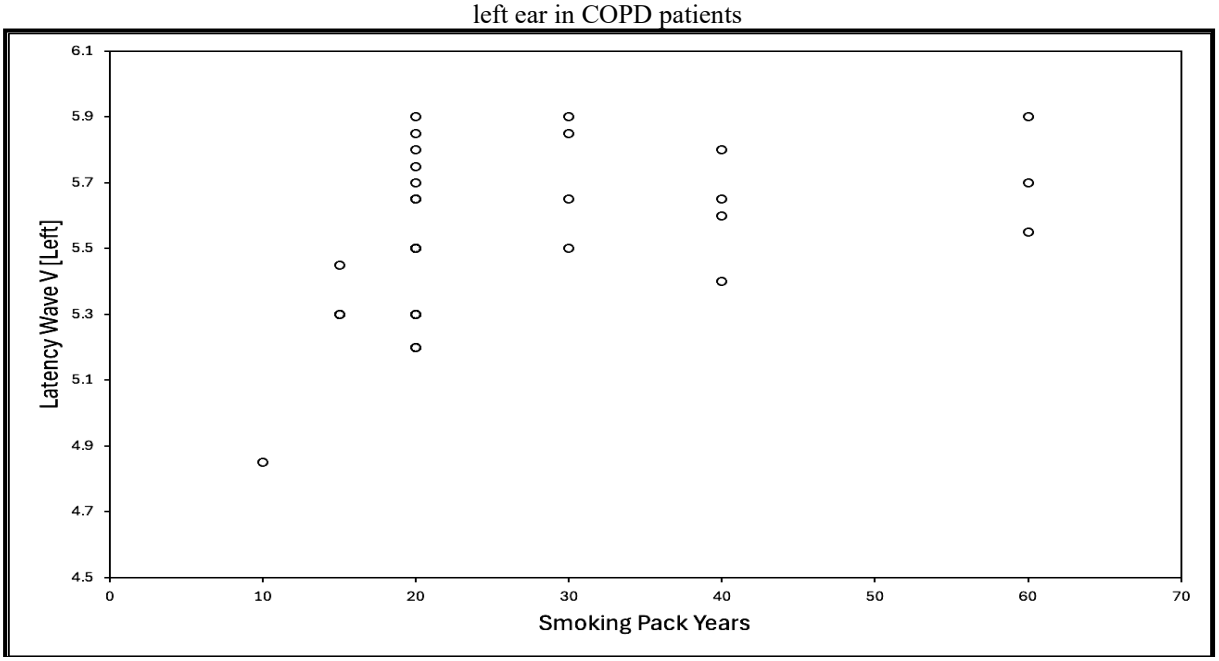

Fig III: Scattered plot diagram showing a negative correlation between FEV1 and Latency of Wave I over left ear in COPD patients

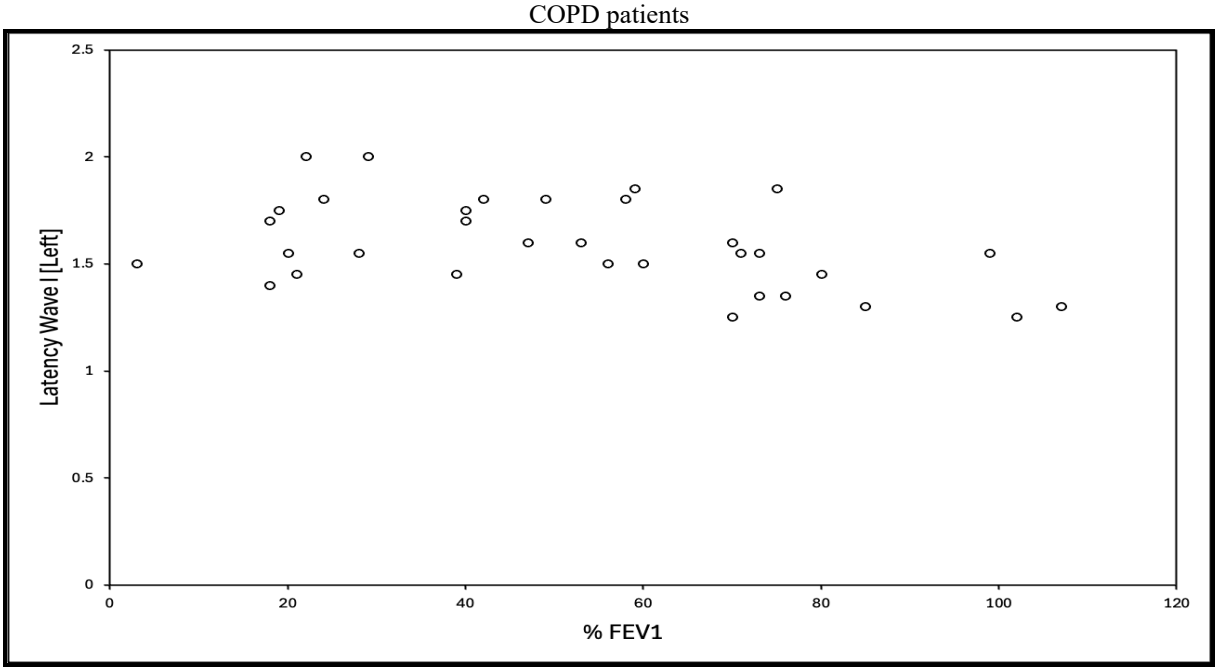

Table 1: Details of study variables (disease duration, smoking pack years, Spirometry findings)

	Cases (Mean ± SD)	Controls (Mean± SD)
Age (years)	62.95 ± 8.58	60.77 ± 6.69
Disease Duration (years)	4.1 ± 0.844	**Not Applicable**
Smoking pack years	30.09 ± 18.86	-
FEV1% predicted	49.62 ± 27.23	

Table 2: DPOAE amplitude and SNRs for both COPD and control group for both left and right ear

SNR (dB) comparison between groups (Right Ear)			
Frequency (Hz)	COPD (Mean ± SD)	Control (Mean ± SD)	p-value
1500	2.71 ± 9.91	6.44 ± 7.02	0.09910
2000	1.46 ± 12.32	8.20 ± 5.37	0.24550
3000	-1.37 ± 11.69	9.39 ± 9.89	0.00030*
4000	-4.41 ± 11.55	12.56 ± 6.36	0.00000*
6000	-6.50 ± 11.56	2.87 ± 14.73	0.02310*
8000	-8.99 ± 11.50	-1.03 ± 14.26	0.14500

SNR (dB) comparison between groups (Left Ear)			
Frequency (Hz)	COPD (Mean ± SD)	Control (Mean ± SD)	p-value
1500	2.90 ± 8.38	4.58 ± 5.79	0.94270
2000	-0.04 ± 13.39	5.71 ± 5.72	0.01070*
3000	-4.29 ± 13.35	11.35 ± 3.77	0.00000*
4000	-8.12 ± 12.01	15.03 ± 5.95	0.00000*
6000	-8.47 ± 11.95	8.66 ± 12.01	0.00000*
8000	-6.90 ± 12.19	2.31 ± 12.32	0.00760*

DPOAE AMPLITUDE (dB SPL) comparison between groups (Left ear)			
Frequency (Hz)	COPD (Mean ± SD)	Control (Mean ± SD)	p-value
1500	-2.39 ± 9.89	9.96 ± 4.84	0.00000*
2000	-5.73 ± 15.06	5.46 ± 6.19	0.00060*
3000	-14.80 ± 14.02	5.15 ± 3.66	0.00000*
4000	-18.87 ± 13.20	6.03 ± 5.04	0.00000*
6000	-19.95 ± 12.74	-0.91 ± 12.62	0.00000*
8000	-19.84 ± 12.02	-8.68 ± 12.92	0.00060*
DPOAE AMPLITUDE (dB SPL) comparison between groups (Right ear)			
Frequency (Hz)	COPD (Mean ± SD)	Control (Mean ± SD)	p-value
1500	0.42 ± 11.52	7.50 ± 5.61	0.00150*
2000	-5.63 ± 15.76	5.24 ± 6.61	0.00970*
3000	-11.54 ± 13.74	1.11 ± 11.16	0.00020*
4000	-15.60 ± 13.08	3.54 ± 5.78	0.00000*
6000	-18.91 ± 12.21	-6.96 ± 16.56	0.00180*
8000	-21.79 ± 12.06	-11.65 ± 16.12	0.00830*

Table 3: Comparison of Brainstem Auditory Evoked Potentials wave patterns (Absolute latencies and Inter peak

latency) in study and control groups, *Significant (p- value<0.05)

		COPD			Control		P
		Mean	SD		Mean	SD	
I-Latency (ms)	Right	1.57	0.22		1.44	0.19	0.02
	Left	1.61	0.21		1.44	0.23	0.01*
II-Latency (ms)	Right	2.60	0.21		2.58	0.26	0.67
	Left	2.63	0.22		2.53	0.23	0.08
III-Latency (ms)	Right	3.40	0.31		3.10	0.26	0.00*
	Left	3.51	0.27		3.13	0.30	0.00*
IV-Latency (ms)	Right	4.30	0.40		4.46	0.38	0.11
	Left	4.48	0.43		4.49	0.23	0.96
V-Latency (ms)	Right	5.43	0.39		5.42	0.31	0.84
	Left	5.49	0.46		5.47	0.22	0.82
IPLs	Right	1.83	0.41		2.05	0.64	0.12
I-III (ms)	Left	1.96	0.36		2.04	0.39	0.41
IPLs	Right	3.80	0.66		3.15	0.73	0.00*
I-V (ms)	Left	3.89	0.44		4.03	0.53	0.29
IPLs	Right	2.21	0.63		3.49	0.92	0.00*
III-V (ms)	Left	1.98	0.36		2.27	0.56	0.02*

Table 4: Correlation of variables of BAEP wave patterns recorded over right ear with disease duration, FEV1 % predicted, smoking pack years

BAEP (right ear)		Disease Duration	FEV1 % Predicted	Smoking Pack Years
I	r	-0.09	-0.48	0.11
	p	0.63	0.00*	0.56
II	r	-0.08	-0.15	0.66
	p	0.66	0.41	0.01*
III	r	0.00	-0.43	0.25
	p	0.99	0.01*	0.80
IV	r	0.47	0.08	0.16
	p	0.01*	0.65	0.75
V	r	0.04	0.01	0.13
	p	0.84	0.97	0.97
I-III	r	-0.06	0.37	-0.11
	p	0.77	0.04*	0.56
I-V	r	0.52	-0.03	-0.08
	p	0.00*	0.87	0.67
III-V	r	-0.34	-0.12	-0.05
	p	0.06	0.54	0.78

Table 5: Correlation of variables of BAEP wave patterns recorded over left ear with disease duration, FEV1 % predicted, smoking pack years

BAEP (left ear)		Disease Duration	FEV1 % Predicted	Smoking Pack Years
I	r	-0.14	-0.44	0.17
	p	0.45	0.01*	0.36
II	r	-0.05	0.16	0.03
	p	0.79	0.40	0.86
III	r	0.42	-0.39	0.23
	p	0.02*	0.02*	0.21
IV	r	0.30	-0.22	0.10
	p	0.11	0.24	0.60
V	r	0.02	0.01	0.41
	p	0.92	0.96	0.02*
I-III	r	-0.19	0.05	0.18
	p	0.31	0.80	0.80
I-V	r	0.23	0.08	0.27
	p	0.22	0.66	0.66
III-V	r	0.38	-0.03	0.51
	p	0.04*	0.87	0.01*

DISCUSSION

The present study aimed to assess the relationship between COPD and the affection of the auditory system, with the use of Oto Acoustic Emissions (OAE) and Brainstem Auditory Evoked Potentials (BAEP) in COPD patients and to identify any possible correlations with smoking index, disease duration, and spirometric findings. All the study group patients were significant smokers, and the smoking pack years were more than 30 years; they had irreversible/partially reversible airflow limitation. In this study both COPD patients and controls were matched for age, sex, and BMI. This study depicts a clear pattern of cochlear outer hair cell dysfunction in stable COPD patients, reflected by significantly reduced DPOAE SNR and signal amplitudes at mid to high frequency regions (3000-8000 Hz) across both ears. These findings are indicative of absent or diminished OHC activity. Our findings are in line with previous studies showing that patients with hypoxemia reported that OAE abnormalities are more pronounced in patients with hypoxemia compared to controls.16, 21, 22. Many studies have generally reported pass/fail outcomes but not the frequency profile of both SNR and DPOAE amplitude in stable COPD. In our study the presence of negative SNR values at 3000–4000 Hz in COPD, compared to positive SNRs in controls at the same frequencies, depicts that outer hair cell dysfunction is not limited to the extreme basal region but begins in the mid-high frequencies and progressively worsens toward 8000 Hz. As this study is in stable COPD patients the results indicate that cochlear dysfunction is present even as a result of oxidative stress, or chronic smoking exposure on OHCs, and not only because of acute exacerbations. Together, our results authenticate previous evidence that COPD is associated with cochlear dysfunction but also provide novel detail by mapping a bilateral, frequency-dependent decline in DPOAE SNR and amplitude across 1500–8000 Hz in stable COPD patients. There was no significant difference in noise floor levels between the COPD and control groups across frequencies ($p > 0.05$), which shows that the lower amplitudes in SNR in the COPD are attributable to diminished DPOAE signals rather than elevated background noise. The latencies of Brainstem auditory Evoked Potentials waves (BAEPs) indicate the speed of sound signals as they travel through different parts of the auditory pathway. So, if the latencies are prolonged, then it indicates slower conduction of hearing signals.23 In the current study (Table 2), the ABR test results reported marked prolongation of absolute latencies of BERA wave I and III in both ears of COPD patients compared to controls, indicating central nervous system involvement, along with auditory impairment of the eighth cranial nerve. Atis et al. also had

consistent results, they studied BERA in COPD patients and reported significant ABR abnormalities (76.1%), and concluded that the functions of the eighth cranial nerve were highly affected.24 Gupta et al. also had consistent results with our research; the common abnormalities they observed were in wave I and III, and they found in wave V too, and interpeak latencies I-III and III-V on both sides.9 Eid et al., also summarized that hypoxia due to smoking habits aggravates hearing loss; they suggested that any reduction in oxygen supply can lead to significant changes in ABR waves, as the transduction functions of nerve impulses along the auditory pathway are affected by oxygen availability.16 Although Nakano et al. and Barbieri et al. results were in disagreement with our study, as they found nonsignificant differences in ABR tests between COPD patients and control subjects.25,26 Smoking elevates the carboxyhaemoglobin levels, and nicotine and carbon monoxide are the contributing factors to abnormal BERA waves, as it eventually decreases the perfusion of the hearing organs.27 Rabhu et al. and Pezzoli et al. both concluded that hearing loss becomes more prominent with increased smoking frequency.28,29 Our results also support this hypothesis. This research suggests that the irregularities observed in BERA waves may be linked to chronic smoking, as it leads to brainstem hypoxia and decelerates the processing of information along the auditory pathway. Previous literature suggests that hypoxemia may contribute to peripheral nerve injury through ischemic mechanisms, but there were very less studies which reported abnormal OAE and BERA results in stable COPD patients. Although none of the subjects in this study had significant hypoxemia, the longer duration of disease and more smoking pack years raise important questions regarding the underlying mechanisms contributing to peripheral neuropathy. Unlike previous studies that evaluated either cochlear function (OAE) or brainstem conduction (BERA) individually, the present study integrates both to provide a comprehensive assessment of auditory pathway involvement in COPD. We found significant reduction in DPOAE amplitudes and increased latencies of waves in stable COPD patients without hypoxemia conditions. This suggests that not only hypoxemia is a prerequisite for auditory dysfunction, the chronic inflammation and increased oxidative stress in stable patients could be one of the factors, as they can promote the apoptosis of the outer hair cells, this indicates that auditory dysfunction is one of the underappreciated extra-pulmonary manifestations of COPD. Moreover, given that our study comprised of chronic smokers, the potential impact of cigarette smoke on OAEs and brainstem auditory evoked potentials (BAEPs) cannot be overlooked and warrants further investigation in future studies. A major limitation of the present study was that the sample size was not large enough.

Conclusion

Our study showed that COPD patients with chronic smoking habits, oxidative stress and microvascular compromise are at a higher risk of developing auditory pathway impairments which was evidenced by prolonged BERA/ABR wave latencies and frequency-dependent reductions in DPOAE SNR and signal amplitude, most prominently in the high-frequency regions of the cochlea. These findings indicate bilateral outer hair cell dysfunction and both central auditory pathway dysfunction and eighth cranial nerve involvement. Therefore, DPOAEs serve as a sensitive marker for early cochlear involvement in COPD and BAEPs may serve as an important tool for early detection of subclinical auditory dysfunction, highlighting the need for monitoring and preventive strategies to reduce further neurological complications.

The authors declare that they have no conflicts of interest. This research was supported by Multidisciplinary Research Unit (MRU), Department of Health Research, New Delhi, India This research was reviewed and approved by the institutional review board of Rajasthan University of Health Sciences, Jaipur [(DCG(I) Registration No. ECR/762/Inst/RJ/2015)]. Informed consent was obtained from all participants. The Ethics approval number is “Letter No. RUHS-CMS/Ethics Comm./2024/306”. The data that support the findings of this study are available from the corresponding author upon reasonable request. The authors would like to express their deepest appreciation to the Multi-Disciplinary Research Unit (MRU, DHR) of Rajasthan University of Health Sciences and College of Medical Sciences (RUHS-CMS), Jaipur, Rajasthan, for giving financial support to this project, and to the members of the research team, lab technicians, for their invaluable contributions throughout the project.

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