

## Neurophysiological changes in COPD patients with chronic respiratory insufficiency

O. KAYACAN<sup>1</sup>, S. BEDER<sup>1</sup>, G. DEDA<sup>2</sup>, D. KARNAK<sup>1</sup>

<sup>1</sup>Ankara University Medical Faculty Department of Chest Diseases and Tuberculosis, Ankara, Turkey

<sup>2</sup>Department of Pediatric Neurology, Ankara, Turkey

### Abstract

Chronic hypoxemia is known to cause peripheral neuropathy (PNP) in chronic obstructive pulmonary disease (COPD) patients. We aimed to know how often PNP is encountered in such patients and the changes in the central nervous system (CNS) if any.

We enrolled 32 patients (30M, 2F; mean age  $\pm$  SD :  $61.5 \pm 8.8$  years) with COPD into the study.  $PaO_2 \geq 55$ mmHg was considered as the cut-off value designating tissue hypoxia. According to this cut-off value the subjects were divided into two groups : Group I, n :19,  $PaO_2 < 55$ mmHg and Group II, n :13,  $PaO_2 \geq 55$ mmHg. All subjects were evaluated with motor and sensory nerve conduction studies (MNCV and SNCV, respectively), electromyography, visual and brainstem evoked potentials (VER and BAER, respectively).

We detected PNP in 93.8% of the study subjects. Distal latency of sural nerve correlated significantly with cigarette consumption and reduction in PEFR. SNCV of median nerve was reduced as  $PaCO_2$  was elevated and pH was lowered. BAER wave III latency showed significant inverse correlation with PEFR,  $FEF_{25}$  and  $FEF_{25-75}$ . Interpeak latency (IPL) of BAER I-III was also significantly and inversely correlated with  $FEV_1/FVC$  and  $FEF_{25-75}$ . IPL of BAER III-V too showed significant correlations with  $PaCO_2$ ,  $HCO_3^-$  and pH of the arterial blood.

As BAER III and IPLs of it represent the pontomedullary portion of the brain, cigarette smoking and airways obstruction may not only cause peripheral neuropathy but also a delay in evoked responses of the brain stem by inducing chronic hypercapnia and respiratory acidosis in patients with COPD.

**Key words :** brainstem auditory evoked potentials (BAER) ; COPD ; Peripheral neuropathy ; Respiratory insufficiency ; visual evoked potentials (VER).

### Introduction

COPD and chronic hypoxia have been known to cause PNP for a long time. Appenzeller *et al.*, (1968) were the first to report the presence of PNP in seven out of eight patients with COPD and malnutrition. Several authors have reported PNP in patients with COPD at an incidence of 28 to 95% (Faden *et al.*, 1981 ; Friss *et al.*, 1994 ; Gunn *et al.*, 1991 ; Jarratt *et al.*, 1992 ; Kajimoto *et al.*, 1994).

Smoking, long-lasting hypoxia and age have been the contributing factors for the development of PNP in patients with chronic pulmonary disease (Friss *et al.*, 1994 ; Gunn *et al.*, 1991 ; Jarratt *et al.*, 1992 ; Malik *et al.*, 1990 ; Nakano *et al.*, 1997). We observed many patients with COPD complaining of paresthesia especially affecting the feet. Our aim was to investigate the neurophysiological changes in the peripheral and central nervous system in patients with COPD moderate to severe hypoxemia.

### Methods and materials

#### Study subjects and clinical evaluations :

Thirty-two patients (M/F : 30/2, mean age  $\pm$  SD :  $61.5 \pm 8.8$  years) with clinically stable COPD were enrolled in the study.  $PaO_2 < 55$ mmHg was considered as the cut-off value for tissue hypoxia. According to this cut-off value the subjects were divided into two groups. Nineteen subjects with tissue hypoxia ( $PaO_2 < 55$ mmHg) constituted Group I and 13 with moderate hypoxemia ( $PaO_2 \geq 55$ mmHg) Group II. Any subject with a history of alcohol abuse, use of neurotoxic drugs or agents, diabetes mellitus, renal failure or malignancy was excluded. The study subjects were studied when they were in a clinically stable state. They were interrogated for the duration of the symptoms of COPD (cough, sputum production, dyspnea, wheezing) and cigarette consumption (pack-years).

Posteroanterior and left lateral chest x-rays were obtained. Spirometric tests were done by using Vitalograph alpha and the best of three consecutive tests was taken into consideration. Forced vital capacity (FVC), forced expiratory volume in one second ( $FEV_1$ ), the ratio of  $FEV_1$  to FVC ( $FEV_1/FVC$ ), peak expiratory flow rate (PEFR), forced expiratory flow after 25% of FVC has been exhaled ( $FEF_{25}$ ), forced expiratory flow after 50% of FVC has been exhaled ( $FEF_{50}$ ), forced expiratory flow after 75% of FVC has been exhaled ( $FEF_{75}$ ), forced expiratory flow during the middle half of FVC ( $FEF_{25-75}$ ) were measured. Arterial blood gas analysis was performed by using ABL 330, and  $PaO_2$ ,  $O_2$

saturation, PaCO<sub>2</sub>, pH and HCO<sub>3</sub><sup>-</sup> were evaluated.

The ECG, hemogram, serum electrolytes, fasting serum glucose, renal functions, CPK, vitamin B<sub>12</sub> and folic acid levels of the patients were also recorded in order to exclude concurrent risk factors for PNP.

The control group consisted of 20 age-matched healthy adults without any sign or symptom of PNP. The exclusion criteria of the patient group were also used for the controls.

*Electrophysiological studies :*

Every patient underwent a neurological examination. They were further evaluated for PNP via Motor nerve conduction velocity (MNCV), sensory nerve conduction velocity (SNCV), electromyography (EMG), visual evoked response (VER) and brainstem auditory evoked response (BAER). The results were compared with age matched controls.

For VER, Flash -VER (F-VER) was used because of the lack of subjects' cooperation for pattern-VER. F-VERs were recorded by an electrode placed at theinion that was referred to linked ears. The light stimulus was from the Led-Goggles that is attached to Nihon Kohden Neuropack device. The duration of stimulus was 10 msec with an intensity of 10. The stimuli were given to each eye separately and each trial 200 flashes were averaged. The results were printed and the N2 latencies were measured.

BAERs were recorded in a quiet room with the patient in a quiet state, with the use of Nihon Kohden Neuropack device. The recordings were done monaurally through an earphone taped over the ear at a repetition rate of ten cycles per second and an intensity of 90 dB. The contralateral ear was masked by white noise to optimize unilateral stimulation. The biopotentials were recorded from left and right ear using vertex electrodes as reference. For each ear 2000 clicks were averaged and the results were printed. Excessively noisy activity was automatically rejected. The latencies were measured with a cursor from a screen.

This study was approved by the ethical committee of Ankara Medical School.

*Statistics :*

The statistical examinations were done by using the SPSS program, version 8.0 on a personal computer. Results were given as mean ± SD. The groups were compared by using ANOVA and Student's t test. Bonferonni's correction was used to establish the exact significance at the level of p<0.05. The correlation between the parameters was examined by using Pearson's Moment Product Correlation Analysis. Any p value <0.05 was considered significant.

**Results**

The characteristics, spirometric tests and the arterial blood gas analysis findings of the study subjects are shown in Tables 1, 2 and 3. Two groups were similar with regard to age, cigarette consumption and duration of the symptoms of COPD. However, spirometric tests showed significantly more severe obstruction on the airways of Group I when compared with Group II. They were also significantly more hypoxemic and hypercapnic than Group II.

Table 1

Characteristics of the study subjects :  
Subjects of the two study groups were comparable with respect to age, cigarette smoking and duration of the COPD symptoms

	Group I (n : 19)	Group II (n :13)	p
M/F	17/2	13/0	
Age (years)	61.5 ± 8.6	61.4 ± 9.4	ns
Cigarette consumption (pack-years)	37.4 ± 28.5	38.3 ± 25.9	ns
Duration of COPD (years)	11.9 ± 6.6	7.9 ± 5.4	ns

ns : not significant

Table 2

Spirometric findings of the study subjects :  
Significant airways obstruction was detected in Group I when compared to Group II

	Group I	Group II	p
FVC (% of predicted)	43.7 ± 11.9	58.3 ± 23.1	< 0.05
FEV1 (% of predicted)	31.1 ± 6.7	49.8 ± 22.2	< 0.05
FEV1/FVC (%)	59.2 ± 15.1	66.6 ± 13.4	ns
PEFR (% of predicted)	31.0 ± 19.2	48.0 ± 20.1	<0.05
FEF <sub>25-75</sub> (% of predicted)	15.9 ± 6.2	30.0 ± 16.6	=0.005
FEF <sub>25</sub> (% of predicted)	16.4 ± 9.6	30.3 ± 22.5	< 0.05
FEF <sub>50</sub> (% of predicted)	11.2 ± 4.8	26.6 ± 17.1	<0.01
FEF <sub>75</sub> (% of predicted)	13.3 ± 4.3	23.0 ± 10.2	<0.01

ns : not significant

Table 3

Arterial blood gas analysis findings of the study subjects :  
Group I had significant hypoxemia and hypercapnia when compared with Group II

	Group I	Group II	p
PaO <sub>2</sub> (mmHg)	45.2 ± 7.8	65.5 ± 8.7	<0.0001
O <sub>2</sub> saturation (%)	75.4 ± 10.2	91.4 ± 2.9	<0.0001
P(A-a)O <sub>2</sub>	23.6 ± 13.4	15.4 ± 5.7	<0.05
PaCO <sub>2</sub> (mmHg)	54.6 ± 12.5	44.6 ± 7.3	<0.05
HCO <sub>3</sub> <sup>-</sup> (mEq/L)	30.5 ± 5.0	26.7 ± 2.5	<0.05
pH	7.36 ± 0.05	7.39 ± 0.04	ns

ns : not significant

On EMG, we detected PNP in 93.8% of the study subjects. Eighteen subjects in Group I (94.7%) and 12 in Group II (92.3%) had PNP. Motor and sensory involvement in the upper and motor involvement in the lower extremities was prominent. When compared with the control group,

Table 4

Peripheral nerve conduction velocities of the study groups vs. controls : MNCV of the median and peroneal nerves were slightly but significantly slower in Group I when compared with controls

	Group I	Group II	Control	p (Group I vs. Control)	p (Group II vs. Control)
Median MNCV (m/sec)	53.7 ± 3.8	49.8 ± 16.6	57.8 ± 2.6	<0.05	ns
Median SNCV (m/sec)	36.8 ± 27.3	40.4 ± 26.7	54.5 ± 2.5	ns	ns
Peroneal MNCV (m/sec)	41.2 ± 14.0	46.2 ± 3.3	50 ± 3.5	<0.05	ns
Sural nerve distal latency (msec)	2.9 ± 2.2	3.3 ± 1.8	2.7 ± 2.0	ns	ns

ns : not significant

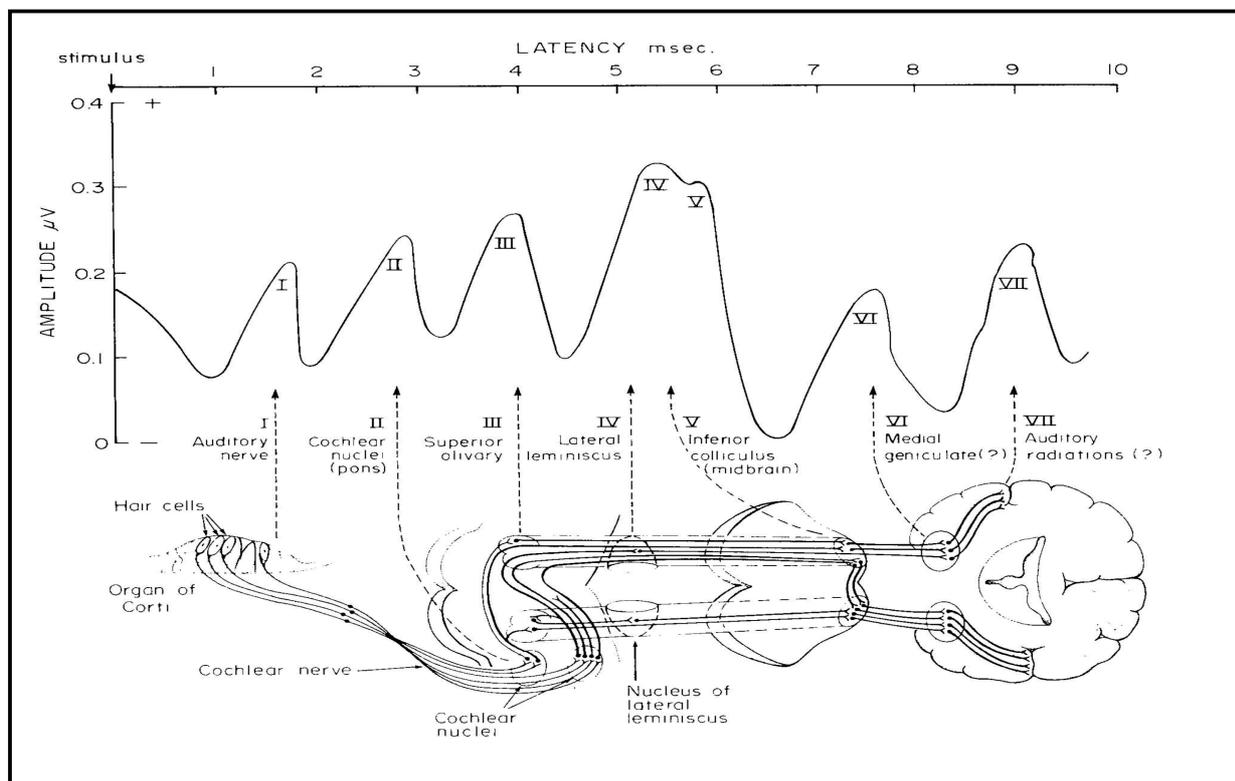


FIG. 1.— BAER reflects the electrical activities in the pathway from the auditory nerve to the brain. BAER wave I and IPL of BAER I-III shows the peripheral part of the pathway, BAER III and IPL of BAER III-V the central part .

significant slowing of the MNCV of the median and peroneal nerves in Group I were detected (Table 4). SNCV of the median nerve showed weak but significant correlations with PaCO<sub>2</sub> ( $r = -0.5$ ,  $p < 0.05$ ) and pH ( $r = 0.5$ ,  $p < 0.005$ ) of the arterial blood. Although sural nerve distal latency was not changed in comparison with the control group, it showed significant correlations with cigarette consumption ( $r = -0.4$ ,  $p < 0.05$ ) and reductions in FEV<sub>1</sub>/FVC and PEF (r = 0.4,  $p < 0.05$ ).

VER latencies of the study subjects were not different from that of the control group.

The normal pattern of interpeak latency (IPL) of BAER waves can be seen on Figure 1. When the nerve conduction is slows down, IPL of BAERs are pathologically prolonged. BAER wave III and its IPLs show the nerve function of brain-stem i.e. the ponto-medullary portion of the brain. IPL of BAER III-V of the study subjects was slightly prolonged without showing significance when compared with controls (Table 5).

We found weak but significant correlations between BAERs and spirometric test and blood gas

Table 5

BAER and VER latencies of patients with COPD : BAER III-V IPL of the study subjects were slightly prolonged without showing significance in comparison with the control group.

	Group I	Group II	Control
<b>BAER (Right ear)</b>			
I	1.6±0.2	1.7±0.2	1.5±0.5
II	2.8±0.4	2.8±0.2	2.7±0.6
III	3.9±0.4	3.9±0.4	3.7±0.6
IV	5.1±0.3	5.0±0.4	4.7±0.6
V	5.9±0.3	5.8±0.3	5.7±0.8
I-V	4.3±0.3	4.2±0.3	4.1±0.7
III-V	1.9±0.3	1.9±0.3	1.9±0.5
I-III	2.3±0.3	2.2±0.4	2.2±0.4
<b>BAER (Left ear)</b>			
I	1.6±0.2	1.6±0.2	1.7±0.4
II	2.7±0.3	2.6±0.4	2.7±0.5
III	3.8±0.4	3.9±0.4	3.9±0.4
IV	5.1±0.4	5.0±0.4	5.1±0.4
V	5.8±0.4	5.8±0.4	5.8±0.5
I-V	4.2±0.4	4.2±0.3	4.1±0.2
III-V	2.0±0.4	2.0±0.3	1.8±0.2
I-III	2.2±0.3	2.2±0.2	2.2±0.1
<b>VER (Right)</b>	102.4±16.1	105.7±14.9	102.3±13.7
<b>VER (Left)</b>	102.9±15.4	114.2±13.6	102.7±15.3

analysis results. BAER wave III correlated inversely with FEF<sub>25</sub>, PEFR and FEF<sub>25-75</sub> ( $r = -0.5, p < 0.05, < 0.01$  and  $< 0.01$ , respectively) (Figure 2). BAER wave V showed an inverse correlation with FVC and PEFR ( $r = -0.5, p < 0.05$ ). Although a slight and not significant prolongation of IPL of BAER I-III when compared with the controls was detected, it showed a significant inverse correlation with the reductions in FEV<sub>1</sub>/FVC and FEF<sub>25-75</sub> ( $r = -0.4, p < 0.01, r = -0.4, p < 0.05$ ). Similarly, the IPL of BAER III-V correlated significantly with an increase in PaCO<sub>2</sub> and HCO<sub>3</sub><sup>-</sup> ( $r = 0.5, p < 0.05$ ) and decrease in pH ( $r = -0.4, p < 0.05$ ) of the arterial blood (Figure 3).

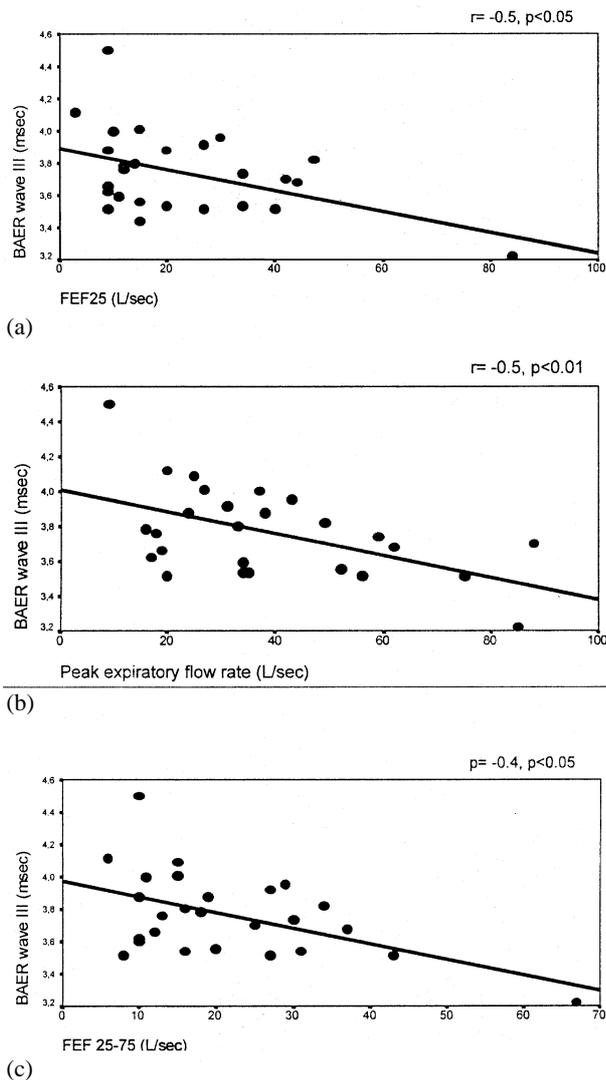


FIG. 2. — BAER wave III correlated weakly but significantly with (a) FEF<sub>25</sub>, (b) PEFR and (c) FEF<sub>25-75</sub>.

**Discussion**

Many authors reported clinically detectable or subclinical PNP at an incidence of 28-87% of patients with COPD (Friss *et al.*, 1994 ; Gunn *et al.*, 1991 ; Jarratt *et al.*, 1992). The prevalence of

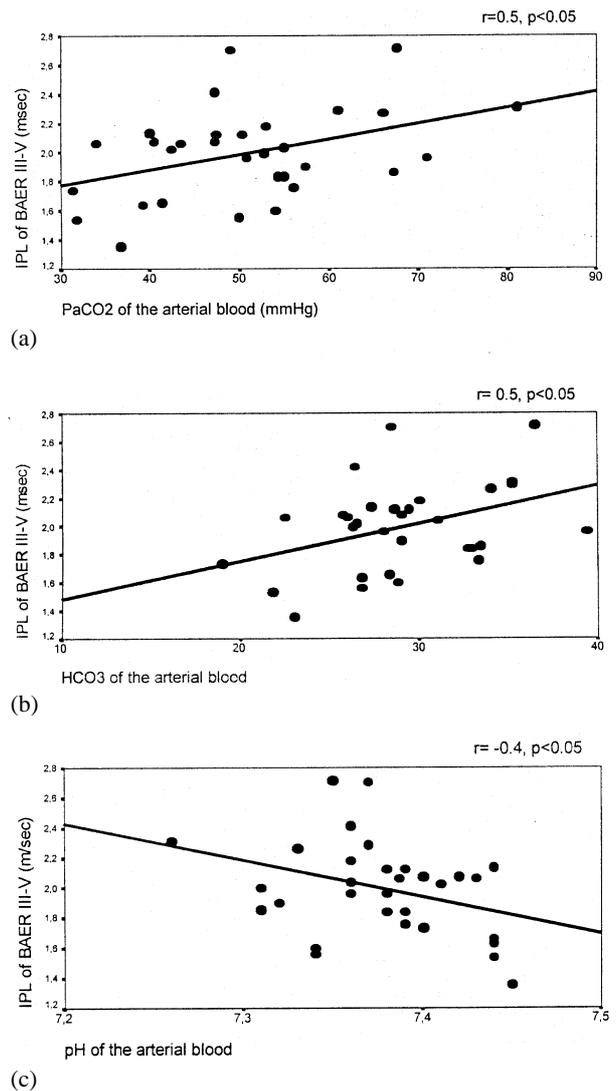


FIG. 3. — IPL of BAER III-V correlated positively with (a) PaCO<sub>2</sub>, (b) HCO<sub>3</sub><sup>-</sup> and negatively with (c) pH of the arterial blood.

the PNP increased with the severity of hypoxemia (Friss *et al.*, 1994). We detected PNP in 93.5% of our study subjects who had moderate to severe hypoxemia. This high incidence of PNP in our study group may be due to the severity of hypoxemia in our patients who were more severely hypoxemic than the study subjects in previous series. Although we were unable to establish a correlation between the NCVs and hypoxemia, the slowing of the NCVs of the peripheral nerves in Group I who were more hypoxemic than Group II, was more pronounced.

Some authors did not find any correlation between the electrophysiological and spirometric findings or blood gas analysis results (Kajimoto *et al.*, 1994). However, some others have implicated chronic severe hypoxemia as the causative factor for PNP (Friss *et al.*, 1994 ; Nakano *et al.*, 1997). We detected weak but significant correlations with SNCV of the median nerve and PaCO<sub>2</sub> and pH of the arterial blood. Although the sural nerve distal

latency was not significantly impaired when compared with the controls, it correlated with cigarette consumption and reductions in FEV<sub>1</sub>/FVC and PEF<sub>R</sub>. Our data indicate that cigarette consumption and airways obstruction in COPD result in changes in blood gas values and these in turn cause slowing in the NCVs of the peripheral nerves.

Nakano *et al.* (1997) have recently studied BAERs in patients with chronic respiratory insufficiency. They studied a heterogeneous group of patients with chronic hypoxemia due either to obstructive or restrictive lung disease. The patients had mild to moderate hypoxemia. The authors did not find any change in BAER wave I and IPL of wave I-V. They did not mention the IPL of wave III-V which represents the central portion of the auditory pathway. To the best of our knowledge of the English literature, the present series is original as it is the largest in which BAERs of a homogeneous set of COPD patients have been studied. We found correlations between BAERs and spirometric test and blood gas analysis results in our subjects who had moderate to severe hypoxemia. BAER III and V correlated significantly with spirometric tests showing airways obstruction. IPL of BAER III-V was significantly correlated with PaCO<sub>2</sub> and HCO<sub>3</sub><sup>-</sup> and pH of the arterial blood gas. The correlation between the airways obstruction parameters and BAERs is most probably an indirect effect of COPD. Airways obstruction finally causes changes in arterial blood gases which should be implicated for the impairment in the nerve conduction in the brain stem causing prolongation in BAERs.

The effect of hypoxia and hypercapnia on BAERs have been mostly studied in animals. Kajimoto *et al.*, 1994 detected a transient increase in amplitude of all the BAERs which preceded the prolongation of latency, in response to hypoxia in dogs. Similarly, chronically hypoxemic and hypercapnic subjects of the present study showed slight prolongations in BAER wave IV and IPL of BAER III-V without statistical significance.

Sohmer *et al.* (1986) showed depressions in all BAERs in cats under severe hypoxemia. As the same depression was also observed when normal blood oxygenation was maintained and cerebral ischemia was induced, they speculated that the primary hypoxemia did not affect the ability of the brain tissue to generate evoked potentials but rather led to a secondary depression of the cardiovascular system, to cerebral ischemia and impaired the oxygen supply of the brain. Hence, they concluded that all these factors led to impairment in BAERs by showing additive effect. Our not investigating whether the patients had cerebral ischemia or not may be a limiting of this study. The present study subjects were middle aged people free from any neurological finding indicating ischemia. However, most of our subjects, especially the ones in Group

I had chronic cor pulmonale which may have impaired the cerebral blood flow too.

Gunn *et al.* (1991) studied *in utero* fetal sheep and concluded that acidosis might have contributed to the cerebral impairment caused by hypoxemia. In agreement with these findings, we found that hypercarbia and acidosis were important factors resulting in PNP and impairment in BAER.

Friss *et al.* (1994) detected prolongations in BAER wave V and IPL of BAER III-V in preterm infants under hypercarbic state. They speculated that hypercarbia had a deleterious effect on neuronal function. We also showed an relation between the IPL of BAER III-V and hypercarbia and acidosis. Our data suggest that hypercarbia and acidosis may contribute to the cerebral impairment caused by hypoxemia.

Our data suggest that smoking, airways obstruction and long lasting COPD may not only cause PNP, but also affect the ponto-medullary portion of the brain by altering blood gases resulting in hypoxemia, hypercapnia and respiratory acidosis. As the present data show weak correlations between the neurophysiological and blood gases parameters, further studies are needed in larger series of COPD patients.

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Oya KAYACAN,  
Ankara University, Medical Faculty,  
Chest Diseases and Tuberculosis Department  
Cebeci 06100 Ankara, Turkeyrkey  
E-mail : kayacan@medicine.ankara.edu.tr