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P50 sensory gating in hypoxemic chronic obstructive pulmonary disease patients

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Abstract. – PURPOSE: Chronic obstructive pulmonary disease (COPD) is a condition characterized by progressive airway obstruction and recurrent attacks. Multisystem involvement with extrapulmonary manifestations has been seen in COPD patients. Numerous neurological involvement like cerebrovascular diseases, polyneuropathies, motor neuron diseases and cognitive impairement has been reported in COPD patients. Cognitive dysfunction is usually associated with hypoxia or hypercapnia in COPD patients. To our knowledge there is no study about sensory gating in COPD patients. We performed p50 test to COPD patients and we investigate sensory gating in COPD patients.

PATIENTS AND METHODS: 25 male patients with COPD and 17 healthy male subjects for controls included to this study. The patients were diagnosed with COPD according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) criteria. p50 amplitude and latency, percentage of P50 suppression, N100 amplitude and latency and the N100 suppression percentage of the COPD patients and controls presented were measured and compared.

RESULTS: We found that the conditioning amplitudes (S1) did not differ between COPD patients and controls ($p > 0.05$) but (S2) amplitude was significantly increased in COPD patients ($p < 0.05$). COPD patients showed significantly lower P50 and N100 suppression percentage than controls ($p < 0.05$).

CONCLUSIONS: COPD patients showed a disturbance cognitive function such as attention with p50 suppression rate decrease. P50 sensory gating test can be useful to analyze the pre-attention period of cognitive impairment in the early phase of COPD patients.

Key Words:

Hypoxemic chronic obstructive pulmonary disease, chronic obstructive pulmonary disease, COPD, Sensory gating test, p50 amplitude and latency.

Introduction

Chronic obstructive pulmonary disease (COPD) is a common preventable and treatable disease characterized by persistant airflow limitation in the airway. It is one of the major cause of morbidity and mortality throughout the world. It is well known that COPD is associated with significant systemic abnormalities[1]. Multisystem involvement with extrapulmonary manifestations has been seen in COPD patients[2]. Hypoxaemia, hypercapnia, systemic inflammation and neurohormonal activation are the main mechanisms of the pathophysiology in systemic involvement[3].

Numerous neurological involvement like cerebrovascular diseases, polyneuropathies, motor neuron diseases and cognitive impairment has been reported in COPD patients[4-7]. Cognitive dysfunction is usually associated with hypoxia or hypercapnia in COPD patients. Previous studies investigate the cognitive functions by psychological or neurophysiological tests in these patients[7,8].

Respiratory sensations can dominate cognitive awareness; so there might be a cognitive neural basis for respiratory somatosensation. Respiratory related evoked potentials and neuroimaging studies have shown that respiratory chemostimulation, mechanostimulation, and motor drive can change the brain neural activity[9-11]. Respiratory related evoked potential studies have also provided some information about neural gating process[10,11].

Sensory gating is the ability of the brain to inhibit irrelevant sensory input[12]. It is usually measured in evoked potential paradigm as p50 paradigm. The sensory gating paradigm has been analyzed mostly in psychiatric diseases such as schizophrenia[13]. But in further studies it has been showed that not only psychotic diseases but also other systemic and neurological diseases like migraine, Alzheimer disease influence the p50 sensory gating[14,15].

To our knowledge there is no study about sensory gating in COPD patients. In this study we performed p50 sensory gating test to hypoxemic COPD patients and we investigate the sensory gating ability in COPD patients.

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Patients and Methods

This work is a cross-sectional clinical study and conducted between January and December 2011. We included 25 hypoxemic male patients aged ≥ 40 years with COPD and 17 healthy male subjects for controls. All patients provided written informed consent form. The patients were diagnosed with COPD according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) criteria in the Chest Department of the Medical Faculty of Inonu University. All patients were previous cigarette smokers with a smoking history of ≥10 pack-years. COPD patients gave up smoking at least 6 months ago. Control group were selected from healthy volunteers. They also had no additional problem as detected by detailed history and neurological examination. There was no neurological deficit in COPD patients and controls. Patients having history of diabetes mellitus, trauma, malignancy, dementia, uremia, cerebrovasculer or cardiovascular disease, hepatic failure, psychiatric disorders and usage of some drugs which may effect the cognitive ability were excluded from the study. All COPD patients were also evaluated by a neurologist. Patients without a history of neurological disorder but had signs of nervous system involvement were also excluded. All subjects hearing status was examined and normal subjects were included into the study.

Routine laboratory tests (erythrocyte sedimentation rate, hemogram, glucose, AST, ALT, urea, creatinine, vitamin B12, thyroid function tests) were performed to all subjects. Respiratory function tests and arterial blood gas analysis were performed for all patients. The respiratory function tests were performed using a spirometry device (SensorMedics Vmax 22, Yorba Linda, CA, USA). Forced expiratory volume in one second (FEV_1), forced vital capacity (FVC), FEV_1/FVC, peak expiratory flow rate (PEF), forced expiratory flow (FEF 25-75%) were measured and the severity of COPD was staged according to the GOLD guidelines. pH, arterial oxygen tension (PaO_2), arterial carbon dioxide tension ($PaCO_2$), and arterial oxygen saturation (SaO_2) were analyzed in blood samples drawn from the radial artery.

P50 Measurements

The electrophysiological examinations performed at the same time of the day for all subjects at the Laboratory of Clinical Neurophysiology of the Inonu University Department of Neurology. The subjects were seated in a sound-and light-attenuated, electrically shielded room. Patients eyes were open and they pointed straight ahead to avoid eye motion artifacts.

The electroencephalogram (EEG) was recorded with a MEM-4200K evoked potential recorder (Nihon Kohden, Tokyo, Japan) system in four channels for recording of evoked responses, integrated with an auditory stimulator. The test stimulus, a click sound of 0.1 sec duration set 60 dB above the auditory threshold with a rarefaction output phase, was presented biaurally through earphones. The auditory threshold of each subject was measured 15 min before recording through the earphones. The interval between the first and second clicks (interstimulus interval = ISI) was 500 ms, and the interval between two pairs of clicks was 10 sec. Electroencephalographic activity was recorded from a disk electrode from vertex (Cz) and referenced to the left mastoid. The mean signal was registered in two channels, and amplified 20,000 times with a bandpass filter between 1 and 100 Hz. EEG data were collected for 1000 ms. for each paired stimulus presented. Additional channels were used to record the electrooculogram (EOG) between the superior orbita and lateral canthus. Trials were rejected automatically by the device if they contained artifacts indicated by a response of ±100 ÌV over the area of P50 for evoked potentials or the EOG recordings. Thirty non-rejected waves were added together to give an average signal, which was used for analysis. EEG data were collected for 1000 ms. for each paired stimulus presented. The averages of S1 waves and of S2 waves were collected in sequence. The S1 and S2 wave averages were then considered separately for analysis. The wave peaks were determined visually and the latencies and amplitudes were marked manually. The most positive peak between 40 and 90 ms after the conditioning stimulus was selected as the P50 final latency and the wave amplitude (S1) was measured from baseline to peak. The second wave (S2 = test) was determined using the corresponding peak between S1±10 ms. away from the latency of the first wave form (conditioning) and its amplitude was also measured from baseline to peak.

The data were collected by one investigator and analyzed by an independent trained evaluator blind to the of the subjects. Averages with no discernible conditioning P50 and N100 waves were excluded from the analysis. The percentage of P50 and N100 suppression was calculated by us-

ing the following formula: (1-[second click amplitude / first click amplitude]) × 100[16].

Statistical Analysis

Results were expressed as mean values and standard deviation. P50 and N100 variables of the COPD patients and control groups were compared. The Kolmogorov-Smirnov test showed that there was not normal distribution of the variables. Comparisons between the groups were performed using the χ^2 test (for gender) and the Mann-Whitney *U* tests for means. The criteria for significance were $p < 0.05$ for all tests. Statistical analysis was carried out with SPSS 16.0 for Windows (SPSS Inc., Chicago, IL, USA).

Results

The age, p50 amplitude and latency, percentage of P50 suppression, N100 amplitude and latency and the N100 suppression percentage of the COPD patients and controls are presented in Table I. COPD patients were in stage 3 or 4 according to the GOLD criteria.

The conditioning amplitudes (S1) did not differ between COPD patients and controls ($p = 0.17$), where as test (S2) amplitude was significantly increased in COPD patients ($p = 0.016$). COPD patients showed significantly lower P50 suppression percentage than controls ($p = 0.012$) (Figure 1 shows the boxplot of p50 suppresion percentage).

There was no significant difference in N100 latencies between COPD patients and controls ($p = 0.83$). However, we found a significant difference in N100 amplitudes ($p = 0.01$) and N100 suppression percentage ($p = 0.042$) between COPD patients and controls (Figure 2 shows the boxplot of N100 suppresion percentage), (Figures 3 and 4 are records of P50 test in COPD patients).

Discussion

Cognitive damage is one of the important extra-pulmonary findings that can develop in COPD patients. Various studies have investigated the relationship between COPD and cognitive functions[6,8,17]. Hypoxia, hypercapnia, acidosis and the hypoxia-related hyperventilation have been shown to play an important role in the decrease of cognitive function[17-19]. Chronic hypoxia leads to cerebral neuron loss and increases free radical production while also causing an inflammatory reaction and glial activation that decrease cerebral blood flow[20]. We evaluated sensory gating in COPD stage 3 or 4 patients with the p50 and N100 parameters and compared the results with a healthy age-matched group. We found statistically decreased p50 suppression percentage and N100 suppression percentage in COPD patients.

Sensory gating shows the pre-attention early period in information processing and is accepted to be the result of the integration of multistep procedures. It is the basic physiological mechanism in the filtration of unnecessary stimulants, in selecting and throwing the stimulants evaluated unimportant by the nervous system and protecting the

Table I. Demographic datas, p50 values and N100 values of COPD patients and controls.

	Control (n=17)	COPD patients (n=25)	p
Age	61.52 ± 6.33	65.16 ± 9.95	0.19
P50 response to first click			
Latency (ms)	58.06 ± 10.73	52.92 ± 12.42	0.17
Amplitude (μV) (baseline to peak)	2.76 ± 1.05	3.53 ± 2.60	0.25
P50 response to second click			
Latency (ms)	55.88 ± 10.06	50.52 ± 12.27	0.014
Amplitude (μV) (baseline to peak)	0.93 ± 0.48	1.97 ± 1.63	0.016
P50 supression percentage	65.21 ± 15.77	43.82 ± 30.23	0.012
N100 response to first click			
Latency (ms)	102.00 ± 22.23	97.24 ± 22.22	0.5
Amplitude (μV) (baseline to peak)	6.76 ± 3.57	7.26 ± 4.18	0.88
N100 response to second click			
Latency (ms)	84.82 ± 14.62	83.42 ± 20.99	0.83
Amplitude (μV) (baseline to peak)	2.48 ± 1.31	4.38 ± 2.66	0.010
N100 supression percentage	55.63 ± 31.66	35.56 ± 28.95	0.042

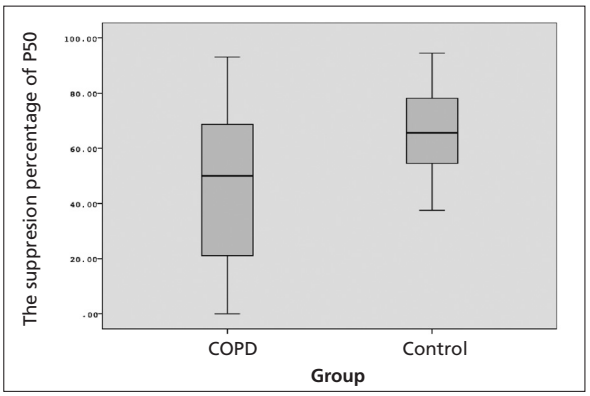

Figure 1. The boxplot of p50 suppresion percentages of patients and controls.

brain from the chaos from stimulant excess. Sensory gating has been studied in many neuropsychiatric disorders especially schizophrenia. It is evaluated as the ratio of the second P50 response amplitude to the first response as a percentage[21]. The P50 inhibition mechanism is complex. However, it is believed that cholinergic stimulation of the inhibitor interneuron through α7 nicotinic acetylcholine receptors are important[22]. It is well known that the cortical cholinergic system is necessary to mediate attention control.

Dyspnea is one of the major symptom of COPD and a combination of central neural, chemical, and mechanical modalities[9]. Modality-specific activation of cortical neural processing centers makes change in neural activity that gates-in this information to the brain information processing centers[9-23]. This activation leads cognitive awareness for modality. Gating-in and gating-out sensory modalities are important and need for these physiological functions[9].

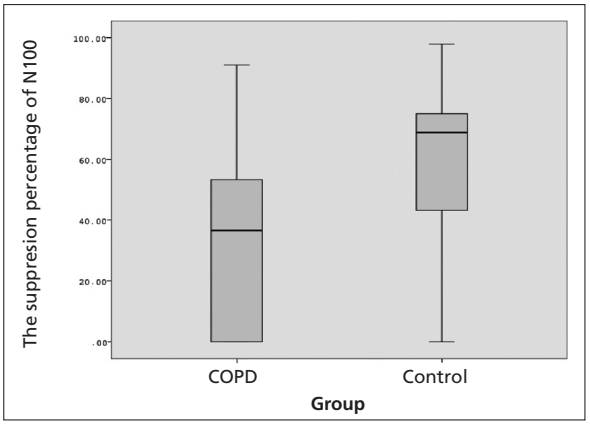

Figure 2. The boxplot of N100 suppresion percentages of patients and controls.

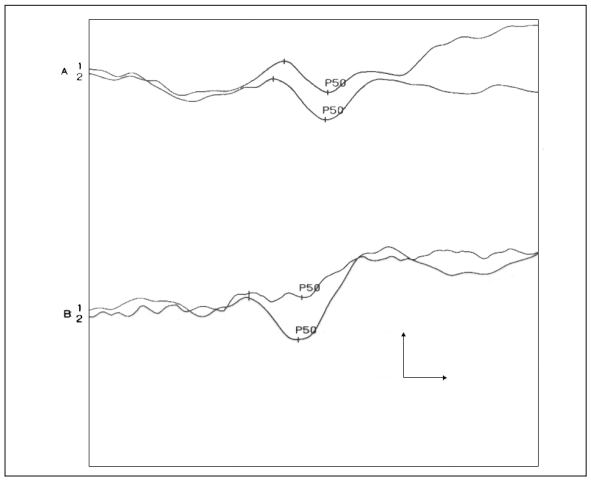

Figure 3. An example for p50 record of COPD patient.

The prefrontal cortex, Heschl gyrus and hippocampus are the anatomical structures that play role in the sensory gating process. Frontal cortex is one of the key areas for p50 suppression and is closely associated with the maturation of the p50 pattern. Frontal cortex involvement may, therefore, influence p50 suppression[24,25]. Cognitive studies in COPD patients have shown frontal lobe functions to be affected predominantly[26,27]. Also some studies showed that the afferent stimulus for air hunger is effecting the sensory areas of the forebrain[9,28], and it also has an important role for direct projection of chemoreceptors to the forebrain[9]. The lower p50 suppression rate in COPD patients compared to controls in our study may again be explained by involvement of this region and, therefore, a disturbance in sensory gating.

Von Leupold et al[29] demonstrated that anxiety and depression are significantly associated with increased dyspnea and reduced functional performance in COPD patients. In another study Von Leopold et al[30] showed that anxiety is associated with greater neural processing of respiratory sensations during an unpleasant affective context. These results are also suggesting a neural mechanism that underlies the increased perception of respiratory sensations in individuals.

The negative effect of age on cognitive functions is well known[31]. Increased age in healthy individuals may disturb cognitive functions and it may, therefore, be difficult to differentiate the cognitive function decline due to COPD and age in elderly COPD patients. Thus, we compared our cases with age-matched healthy individuals and found P50 suppression percentage to be lower in COPD patients.

Smoking is also known to decrease cognitive functions in a way that correlates with the number of cigarettes smoked; cognitive functions are known to get better when the patient quits smoking[32,33]. It has been postulated that smoking decreases cognitive functions by causing subcortical hypoperfusion[33]. A p50 study in smokers in the normal population found the p50 suppression rate to be lower in heavy smokers than mild smokers and non-smokers[34]. Our patient group had smoked years ago but had stopped active smoking following the diagnosis of COPD (at least 6 months ago). Our control group, therefore, also included healthy volunteers who had quit smoking at least 3 months ago.

Some studies have evaluated the relationship between cognitive functions and P300 latency in COPD patients. Disturbed respiratory function tests accompanied by a P300 latency increase have been reported[6,35]. Mavioglu et al[35] have also found increased P300 latency as the vital capacity decreases.

Conclusions

We found that COPD patients showed a disturbance cognitive function such as attention with p50 suppression rate decrease. To our knowledge this is the first study to investigate p50 suppression in COPD patients. This should, therefore, be considered a preliminary analysis and further studies with a larger number of cases should be undertaken.

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