Research Article

Quantitative Eeg Analysis in Patients With Severe Copd: Some Clues of Chronic Hypoxemic Degeneration

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Abstract

Objective: This cross-sectional clinical and electrophysiological study was performed in order to determine the electroencephalographic correlates of cognitive disturbances in patients with severe chronic obstructive pulmonary disease (COPD), using quantitative electroencephalographic (QEEG) measurements.

Materials and Methods: Electroencephalograms were obtained from 33 patients with severe or very severe COPD and from 20 age and sex matched controls.

Results: Patients showed mild cognitive impairment unrelated to depression, especially in the construction, language and memory areas. Electroencephalograms revealed fronto-temporal slow waves especially in the left hemispheres. QEEG revealed higher frequency slow wave-bands and lower frequency beta activity, predominantly in the bilateral fronto-temporal localizations, in addition to decreased global relative beta power in patients with COPD. Analysis of variance of QEEG parameters and clinical characteristics showed that age, PaO₂, PaCO₂ and FEV₁ had significant correlation with QEEG variables in different cerebral localizations.

Conclusion: It was concluded that cognitive impairment in COPD patients was far from being a coincidence and some important clues about its degenerative basis, especially in data processing areas, existed.

Keywords: Chronic obstructive pulmonary disease, cognitive impairment, quantitative EEG, slow wave asymmetry, chronic hypoxemia

Ağır Koah’lî Hastalarda Kantitatif Eeg Analizi: Kronik Hipoksemik Dejenerasyona Ait İpuçları

Özet

Amaç: Bu kesitsel klinik ve elektrofizyolojik çalışma ağır KOAH’lî hastalarda kognitif bozulmanın elektrofizyolojik göstergilerini kantitatif EEG (KEEG) yardımı ile belirlemek amacı ile yapıldı.

Gereç ve yöntem: 33 ağır veya çok ağır KOAH tanılı hasta ve yaş-cins uyumlu 20 sağlıklı kontrolden EEG kayıtları alındı.

Bulgular: Hastalarda depresyondan bağımsız olarak yapılandırılma, lisan ve bellek alanlarının ön planda etkilendiği hafif kognitif bozulma saptandi. EEG kayıtlarında sol hemisfere daha belirgin olmak üzere fronto-temporal yavaşlama görüldü. KEEG analizinde KOAH’lî hastalarda global kısmi beta-power’da düşmeye ilaveten her iki fronto-temporal bölgede hakim olmak üzere yavaş dalga aktivitesinde artma ve beta aktivitesinde azalma saptandi. KEEG analizi bulguları ve klinik
değişkenlerin kıyaslandığı varyans analizinde yaş, PaO₂, PaCO₂ ve FEV₁ ile farklı serebral lokalizasyonlardaki KEEG bulguları arasında anlamlı ilişki saptandı.

Sonuç: KOAH’lı hastalarda saptanan kognitif bozulmanın bir tesadüften daha fazla bir anlamı olduğu ve veri işleme süreçleri başta olmak üzere dejenерatif etkilenmeyi destekleyecek bazı ipuçları olduğunu sonucuna varılmıştı.

Anahtar Kelimeler: Kronik obstrüktif akciğer hastalığı, kognitif bozulma, kantitatif EEG, yavaş dalga asimetrisi, kronik hipoksemi

INTRODUCTION

The most common basis of chronic obstructive pulmonary disease (COPD) is an obstruction of air flow into the lungs, which leads to hypoxemia and hypercapnia due to poor ratio of ventilation to perfusion in the lung parenchyma. The ineffective exchange of gases leads to a decrease in arterial oxygen partial pressure (PaO₂) and to an increase in arterial carbon dioxide partial pressure (PaCO₂) in the blood as COPD progresses (26).

Neuropsychological assessment provides an objective method for delineating changes in higher cortical functions and is an accepted as the diagnostic procedure for the assessment of cerebral dysfunction (23). Advanced COPD may lead to encephalopathy or intellectual impairment secondary to hypoxemia and hypercapnia (22) and changes in cognitive function occur in patients with COPD who are still able to function on an ambulatory basis (21). Some important studies have shown that 27% of patients with mild hypoxemia demonstrate neuropsychological deficit and this ratio rises to 61% in patients with severe hypoxemia (8).

Electroencephalogram (EEG) is a record of the electric activity from the scalp, obtained with the aid of an array of electrodes. After amplification, the signal is usually saved in graphic or digital format. Since Berger, who first defined human EEG in 1931, one of the most significant issues of EEG implementation is to evaluate and quantify the waves. The development of quantitative EEG (QEEG) was motivated by the need to study the mental state and disease diagnosis. Before brain imaging techniques became available, EEG was the main tool in this area (28). Digital EEG has been recommended by the American Academy of Neurology and the American Association for Clinical Neurophysiology. Proposed indications for QEEG include epilepsy, cerebrovascular diseases, dementia, postconcussion syndrome, cranial trauma, learning disorders, attention deficit hyperactivity disorder, schizophrenia, depression, alcoholism, drug dependence, and criminal psychiatry (17,25,29).

Although it is widely accepted that chronic severe hypoxemia causes generalized electroencephalographic slowing, few studies have reported details of quantitative EEG analysis (22) in severe COPD patients and none of them have included the relation with the cognitive changes.

We performed this clinical and electrophysiological study to determine electroencephalographic correlates of cognitive disturbances in patients with severe COPD using quantitative electroencephalographic (QEEG) measurements. We also aimed to investigate the relation between clinical and electroencephalographic parameters.

METHODS

Subjects

The study population included 33 patients with severe COPD and 20 age and sex matched controls. Written informed consent for each step of the trial was asked from all subjects according to the Helsinki convention. All participants were right-handed as indicated by positive laterality quotients on the Edinburgh Handedness Inventory (18). The mean score was 19.4 ± 2.0 in the COPD and 17.9 ± 1.9 in the controls, revealing no statistical difference between the two groups (p>0.05). Both study and control subjects underwent ophthalmologic and audiological examinations to exclude hearing or visual deficits, which might compromise the reliability and validity of the
neuropsychological testing. Each subject underwent pulmonary function tests (PFT), arterialized blood sample analysis, neuropsychological screening, EEG and cranial computed tomography (CT).

Inclusion criteria for the study were as follows: 1) strict diagnosis of COPD according to GOLD criteria (6), 2) absence of symptoms of memory or language deficit, 3) being free of any psychotropic drugs for at least 2 weeks prior to the study, 4) being neurologically intact (no epilepsy, stroke, head injury, dementia, sleep disorder, toxic chemical exposure, etc), 5) no history of concomitant severe or chronic medical illnesses (hepatic failure, chronic renal failure, decompensate diabetes mellitus, etc.), 6) no history of depression or other major psychiatric disorder (other anxiety disorders, schizophrenia, drugs or alcohol abuse) according to DSM-IV (2), and 7) no history of psychosurgery or any other neurosurgical procedure.

At the time of the study, patients were receiving a standardized daily therapy including the following medications: long action β2-agonist (14 patients-42.4%), long action β2-agonist and long-action anti-cholinergic drugs (12 patients- 36.3%), long action β2-agonist combined with long-action anti-cholinergic drugs and Theophylline (7 patients- 21.2%). None of them was receiving inhaled or systemic corticosteroid therapy. Blood levels of Theophylline were in the therapeutic ranges in all patients receiving the drug. Continuous oxygen therapy was being administered to nine patients by a Venti mask at concentrations ranging from 24 to 40% according to the individual needs (41.6%). All patients had stable COPD according to GOLD criteria (11) and none of them had carbon dioxide narcosis or encephalopathy according to the clinical or EEG data.

With a structured interview, detailed history of COPD and any history of memory deficit were inquired and recorded. Standardized Mini Mental State Examination (MMSE) Test (16) was used to evaluate the cognitive status. A score less than 24 indicated a generic cognitive dysfunction as a general rule. Those subjects were also evaluated by Cornell Depression scale (1) in order to determine co-morbid depression. Patients, who scored more than 8 in the latter test, were not included.

Chest x-rays were obtained in all subjects. Standardized PFTs were done using dry spirometer device (Sensor Medics MPM, Yorba Linda, CA). We calculated the forced expiratory volume in 1 second (FEV1), the forced vital capacity (FVC) and FEV1/FVC ratio from maximal expiratory maneuvers. Data were expressed as a percentage of the predicted standardized values according to European Respiratory Society (ERS) criteria (20). The acceptable recordings were obtained from each maneuver and the highest values were used for further analysis (5,24).

Arterial blood gas analysis was performed by using ABL 330. PaO2, O2 saturation, pH and HCO3 were evaluated for each patient. Patients with FEV1 levels lower than 50% were included in this study as having severe or very severe COPD according to GOLD criteria (6).

Electroencephalographic analysis

Each subject was seated in a soundproof, light-controlled, well ventilated recording room, while 30 minutes of resting EEG data were being collected from the 14 monopolar electrode sites of the International 10/20 system, referred to Cz. Computerized EEG recordings were obtained using Medelec Profile 40-channel digital EEG equipment (Oxford, England). The following 12-channel and Ag-AgCl disk electrodes (Medelec, Oxford, England) were used for the data collection: O1-P3, P3-T5, T5-T3, T3-F7, F7-F3, F3-Fz, Fz-F4, F4-F8, F8-T4, T4-T6, T6-P4, and P4-O2. The electrode impedance was carefully kept below 5 k Omega. Hyperventilation was employed as standardized activation method. The filtering interval, frequency and amplitude of the device were adjusted to 10 to 59 Hz, 30 mm/sec, and 100 mV, respectively. The EEG results were evaluated visually, and analyzed quantitatively by the same neurologist (AO) and biophysicist (UC), who were blinded to the clinical diagnosis of the subjects.

Baseline activity and hyperventilation responses were quantitatively evaluated. Data were subsequently segmented into the
consecutive 2-second epochs. Epochs contaminated by blinks, eye movements, and movement related artifacts were excluded from the analysis using a rejection criterion of ± 100 mV on any channel. These criteria produced an artifact free data, as verified by direct visual inspection of the raw data. Each epoch was then baseline corrected and tapered over the entire 2 seconds using a Hannig window. Channel by channel calibrations were performed prior to the testing of each patient. Distributions of basic EEG waves by frequency (i.e. delta [0.5-3 Hz], theta [3.5-8 Hz], alpha [8.5-12 Hz], and beta [12.5-30 Hz]) were recorded. For each montage, distributions obtained at two different states (baseline and hyperventilation response) were compared between the patient and control groups. Additionally, general distribution patterns and hemispheric asymmetries of each waveform were determined irrespective of the montage distributions. To examine these regional differences directly, data were pooled across electrode sites within anterior (right=F8/F4, left=F7/F3) and posterior (right=T6/P4, left T5/P3) regions.

Statistical Analyses
Data were first evaluated using descriptive statistics. For the analysis of quantitative data, a variance analysis model using six factors (montage, procedure, waveforms, groups, hemispheres and regions) was employed. After comparative statistics, in order to determine the relative ratio of slow waves, we performed theta/alpha and theta/beta ratios for each region. The effects of age, gender, duration of illness and PFT scores on QEEG were analyzed in the same regression analysis model. In order to evaluate correlation between clinical variables and electrophysiological data, we performed Pearson correlation analysis. Values of p<0.05 were considered statistically significant.

RESULTS
Subjects
Of the 33 subjects in the COPD group, 7 were female (21.2%) and 26 were male (78.8%). Their mean age was 63.2±7.6 years (range 46 to 76 years). Of the 20 volunteers, 5 were female (25%) and 15 were male (75%). Their mean age was 59.7±6.5 years (range 45 to 70 years). COPD and control subjects were identical (p>0.05) with respect to gender and age.

The mean duration of COPD was 8.7±5.6 years (3 to 30 years, median: 6 years). COPD patients with arterial oxygen partial pressure (PaO2) less than 60 mmHg for at least 6 months were classified as severely hypoxic. Mean FEV1 % value was 36.2±8.2 (16% to 48%), FEV1 (L) value was 1.0±0.3, mean PaO2 was 54.7±4.9 mmHg (41 to 59.7 mmHg) and mean PaCO2 was 45.0±6.0 mmHg (39 to 67 mmHg) in COPD group. These values were corresponding to severe or very severe airflow limitation according to GOLD criteria. Co-morbid medical conditions of COPD patients were cor-pulmonale (41.6%) and hypertension (20.8%).

All of the subjects were right handed and none of the patients had any important neurological deficit, except some subjective memory complaints. The mean score of MMSE was 24.6±3.7 (13 to 30). They had some problems in the areas of orientation, attention, recent memory, language and construction. Except for decreased deep tendon reflexes (21.2%) and positive palmo-mental reflexes (12.1%), none of the patients had neurological abnormality. None of the patients showed important cranial CT abnormality, except for non-specific ischemic changes especially in the periventricular regions. None of the neuroimaging examination suggested degenerative (e.g. Alzheimer disease) or multi-infarct dementia, either.

Electroencephalographic evaluation
Five patients of the COPD group and one of the control subjects had specific EEG characteristics of fronto-temporal slow waves, especially in left hemispheres, although none of the subjects had epileptiform EEG abnormalities and important amplitude asymmetry. One patient showed low amplitude changes especially in the frontal areas. None of the subjects revealed encephalopathic or sleep changes during resting EEG scans.

Analyzing the general distribution of the waveforms irrespective of the montage, the
The most prevalent waveform was alpha (43.8±22.7%) at the background activity. This was followed by beta (22.6±15.4%), delta (19.5±17.0%) and theta (14.4±10.1%) frequencies. As shown in Table 1, the frequency of theta waves significantly increased and the frequency of alpha and beta waves significantly decreased during hyperventilation in patients with COPD compared to the controls.

**Table 1. The comparison of the frequencies of basic wave forms between COPD group and the controls during resting state and hyperventilation**

<table>
<thead>
<tr>
<th>EEG Waves</th>
<th>COPD (n=33)</th>
<th>Controls (n=20)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Delta-BA</td>
<td>19.5±17.0</td>
<td>17.1±11.5</td>
<td>0.050</td>
</tr>
<tr>
<td>Delta-HV</td>
<td>28.5±23.5</td>
<td>29.2±20.1</td>
<td>0.705</td>
</tr>
<tr>
<td>Theta-BA</td>
<td>14.4±10.1</td>
<td>12.7±8.0</td>
<td><strong>0.047</strong></td>
</tr>
<tr>
<td>Theta</td>
<td>12.5±10.1</td>
<td>10.7±7.6</td>
<td><strong>0.028</strong></td>
</tr>
<tr>
<td>Alpha-BA</td>
<td>43.8±22.7</td>
<td>43.7±23.3</td>
<td>0.927</td>
</tr>
<tr>
<td>Alpha-HV</td>
<td>38.1±25.3</td>
<td>34.6±23.0</td>
<td><strong>0.050</strong></td>
</tr>
<tr>
<td>Beta-BA</td>
<td>22.6±15.4</td>
<td>26.2±16.9</td>
<td><strong>0.009</strong></td>
</tr>
<tr>
<td>Beta-HV</td>
<td>19.2±15.2</td>
<td>26.0±22.5</td>
<td><strong>0.000</strong></td>
</tr>
<tr>
<td>Mean frequency-BA</td>
<td>9.0±4.7</td>
<td>9.7±5.1</td>
<td>0.127</td>
</tr>
<tr>
<td>Mean frequency-HV</td>
<td>8.7±6.8</td>
<td>7.5±5.8</td>
<td><strong>0.033</strong></td>
</tr>
</tbody>
</table>

Note: Data are represented as mean±standard deviation; BA: Background activity; HV: Hyperventilation response; **highlights**: statistically significant differences.

The mean frequency was significantly decreased in the left temporal (8.6±4.1% versus 12.8±7.9%, p=0.019) and increased in the right frontal (8.6±5.7% versus 5.3±4.3%, p=0.045) regions during basic state analysis in COPD patients when compared with the controls. Also, basic state recordings revealed an evident decrease in beta activities on the right frontal (23.1±13.3% versus 31.5±19.6%, p=0.050), temporal (16.0±11.5% versus 25.6±18.9%, p=0.034) and occipital regions (15.4±9.9% versus 22.4±16.7%, p=0.050).

They also revealed significantly increased theta activity (15.1±14.1% versus 9.1±5.4%, p=0.038) on the right temporal region. On the other hand, hyperventilation recordings showed significantly decreased delta (11.9±10.2% versus 23.1±19.8%, p=0.012) and beta activities (16.0±11.4% versus 22.8±13.7%, p=0.050) in the left occipital region, evident increase of theta activity (12.2±12.5 versus 7.3±4.9%, p=0.050) in the left temporal and right frontal regions (10.1±8.9% versus 6.6±3.5%, p=0.050) and decrease in beta activity (12.3±8.5% versus 24.8±19.4%, p=0.003) in the right temporal region (Figures 1 and Table 2).
The COPD patients showed high delta activity in the left anterior region (p=0.002), high alpha activity in both of the posterior regions (p=0.000 for left and p=0.000 for right) and high beta activity (p=0.003) in right anterior regions during basic state. Similarly high alpha activity in both of the posterior regions (p=0.000 for left and p=0.000 for right) was shown during hyperventilation, in addition to high delta activity in the right frontal region (p=0.000).

Theta/alpha and theta/beta ratios were calculated for each montage both for the basic and the hyperventilation states. Significantly decreased theta/beta ratios of right frontal region (0.9±0.9 versus 0.3±0.4, p=0.035) was shown in COPD patients.
**Table 2.** Correlation analysis results between clinical and QEEG variables during basic state and hyperventilation*.
(First figures in brackets represent r values and seconds represent p values)

<table>
<thead>
<tr>
<th>Delta</th>
<th>Theta</th>
<th>Alpha</th>
<th>Beta</th>
<th>MF</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
<td></td>
<td></td>
<td>Left frontal*</td>
<td>Left parietal</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(r=.42,0.014)</td>
<td>(r=.40,0.020)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Right temporal*</td>
<td>(r=.40,0.019)</td>
</tr>
<tr>
<td><strong>PaO₂</strong></td>
<td>Right frontal</td>
<td></td>
<td>Right frontal</td>
<td>Left frontal</td>
</tr>
<tr>
<td></td>
<td>(r=-44,0.009)</td>
<td></td>
<td>(r=.34,0.049)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Right frontal*</td>
<td></td>
<td>Right frontal*</td>
<td>(r=.36,0.035)</td>
</tr>
<tr>
<td><strong>PaCO₂</strong></td>
<td>Right frontal</td>
<td>Left frontal</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>(r=.36,0.036)</td>
<td>(r=.38,0.024)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Left parietal</td>
<td>Right frontal*</td>
<td>(r=.42,0.014)</td>
<td>(r=.55,0.001)</td>
</tr>
<tr>
<td><strong>FEV₁ (lt)</strong></td>
<td>Left occipital</td>
<td>Left temporal</td>
<td>Left occipital</td>
<td>Left parietal</td>
</tr>
<tr>
<td></td>
<td>(r=.34,0.048)</td>
<td>(r=.38,0.026)</td>
<td>(r=.39,0.024)</td>
<td>(r=.48,0.005)</td>
</tr>
<tr>
<td></td>
<td>Left parietal</td>
<td>Left frontal</td>
<td>Left parietal</td>
<td>Left temporal</td>
</tr>
<tr>
<td></td>
<td>(r=.39,0.022)</td>
<td>(r=.38,0.027)</td>
<td>(r=.60,0.000)</td>
<td>(r=.38,0.028)</td>
</tr>
<tr>
<td></td>
<td>Right temporal</td>
<td>Right frontal</td>
<td>Left frontal</td>
<td>Left frontal</td>
</tr>
<tr>
<td></td>
<td>(r=.34,0.052)</td>
<td>(r=.46,0.007)</td>
<td>(r=.37,0.031)</td>
<td>Right frontal*</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(r=.42,0.014)</td>
</tr>
<tr>
<td><strong>FEV₁ (%)</strong></td>
<td>Left parietal</td>
<td></td>
<td>Left occipital</td>
<td>Left parietal*</td>
</tr>
<tr>
<td></td>
<td>(r=-.40,0.020)</td>
<td></td>
<td>(r=.42,0.020)</td>
<td>(r=.38,0.025)</td>
</tr>
<tr>
<td></td>
<td>Left parietal</td>
<td></td>
<td>(r=.45,0.009)</td>
<td>Right frontal*</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(r=.37,0.030)</td>
<td>Right temporal*</td>
</tr>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>(r=.38,0.026)</td>
</tr>
</tbody>
</table>

**DISCUSSION**

Hypoxemia affects mainly the neuronal metabolism supporting the neurotransmission rather than the energetic metabolism (3). Thus, cognitive functions, which hypothetically rely on more complex neuronal circuits, such as abstract thinking and constructive functions are expected to be more vulnerable to hypoxemia and as a result more severely compromised in COPD. Additionally, generation of free radicals, neuronal damage, inflammatory reaction and glial activation are well known effects of hypoxemia. However, there are some supportive data of anterior
cerebral hypoperfusion and selected neuropsychological dysfunctions in hypoxemic COPD patients, which can herald frontal-type cognitive decline with the worsening of the hypoxemia (12).

In the current study, we aimed to evaluate the cognitive and QEEG changes, which could only be attributed to chronic hypoxemia in COPD. Since, a close parallelism exists between cognitive decline and development of depressive symptoms in patients with chronic diseases, like COPD (11), we excluded patients with depression using Cornell Depression Scale and patients with a clinical diagnosis of dementia. As a result, unlike all the other studies in the literature, detected changes in the frontal and temporal areas, which also correlated with the MMSE results, were attributed to chronic hypoxemic changes.

In some comprehensive studies, cognitive impairment has been reported to affect a large number of patients with COPD (7,14,27). Some authors claimed that the cognitive disturbances were global or diffuse, while the others suggested only specific impairments, like memory and attention, or deficits in the areas of language and construction (4,7,9,12,19,27). Grant et al assessed the neuropsychological profile of patients with COPD and reported that the study population was characterized with diffuse mental deterioration, with particular impairment of higher cognitive functions. They thought that the possible mechanism was the accelerated aging of the brain (7). In Hjalmarson et al’s study, there was cognitive dysfunction within several cognitive domains. Verbal memory and conceptual function were the most affected, but impairment was also demonstrated in attention, visual memory and speed of information processing (9). In our study, we evaluated cognitive dysfunction by MMSE, an accepted screening test. Out of the total number of COPD patients, 66.6% showed some cognitive problems in some important higher cortical areas, like attention, recent memory, language, and construction, whereas only 3 patients (9%) showed general cognitive distribution. Thus, we observed both diffuse and more specific changes, though with varying frequencies. The detailed design of our study might be the reason of this result.

COPD is clearly associated with brain dysfunction even in mild hypoxic levels. This finding is a validation and confirmation of many previous studies (7,19). Many factors have been claimed to affect the degree of impairment of cognitive functions. Some researchers (5, 23) found strong relationship between the neuropsychological impairment and PaO2, PaCO2 levels. On the other hand, Incalzi et al (10) showed positive correlation between cognitive impairment of COPD patients with their age and the duration of the disease. In the current study, we did not find any significant correlation between the mentioned parameters and the neuropsychological impairment. However, we evaluated the severity of the disease with FEV1/FVC ratios and found a statistically significant correlation, which was not described previously, between the severity of the disease and the neuropsychological impairment. We demonstrated that as the ratio decreased, the probability of the impairment increased (CC:0.35, p=0.042).

COPD may lead to a chronic encephalopathy, characterized by headache, papilledema, elevated cerebrospinal fluid pressure and twitching of extremities. The EEG shows considerable diffuse delta and theta activity; occasionally, anterior delta waves may show the configuration of triphasic waves (25). In our study, only five participants with COPD had fronto-temporal slow waves, although none of them had epileptiform discharge or triphasic waves by visual EEG analysis. On the other hand, QEEG showed background alpha activity predominance, as previously reported (22), and increased frequency of alpha and beta, as expected. Detailed QEEG analysis showed regional slow wave activity in bitemporal regions and increased frequency of activity in right frontal region during basic state analysis. These changes correlated well with the general MMSE results, especially in patients with memory, attention and construction problems, which were known to be functions of temporal and frontal regions (15). Kokodoko et al (13) found that more than 65% of the COPD patients, who had no clinically-
noticeable neurological sign and symptoms, showed an increase of slow activity together with a reduction of alpha activity, presumably secondary to respiratory pathology. General concept of this study was concordant with our study, although the authors used general EEG records instead QEEG.

Reeves et al (22) reported that impairment of pulmonary functions correlated significantly with the degree of alpha frequency slowing over the posterior cortical regions, and the slowest alpha frequencies occurred in those COPD patients with the lowest FEV1/FVC ratios. They concluded that the cognitive of impairment was an important clinical consideration, but might go unrecognized until late in the course of the disease. This was a unique study using QEEG analysis in these patients and had shown alpha asymmetry especially in severe COPD patients. Like Reeves et al we used QEEG, but made more detailed analysis. We added a broad montage system, hyperventilation analysis, brain mapping analysis and some extreme correlation analysis to our investigation. We not only compared the regions on the same hemisphere, but also made comparisons between regions on the right and the left hemisphere, and both in the basic and hyperventilation states. We showed important theta activity in the left temporal and the right frontal regions during hyperventilation. Hypocampal and anterior temporal damage of chronic hypoxemia, which in turn generate memory and attention deficit on cognitive tests, could be supported with this finding. In contrast to Reeves et al’s study (22), we showed important alpha asymmetry only in the right frontal region during basic state analysis. However, hyperventilation records showed increased slow wave activity, as delta, in the right occipital region as Reeves et al reported. These results supported a possible effect of respiratory alkalosis on EEG waves and might be correlated with some construction and perception abnormality of the COPD patients. Although, some QEEG results were corresponding with clinical and cognitive data, some of them could not been explained with the existing data base. At this point, we believed that correlation of QEEG analysis with SPECT and cognitive tasks might be of use.

We think that our study had some limitations. First of all, aging per se might partially account for the observed changes in cognitive and affective status. To avoid this handicap, we evaluated a control group by the same methods, and compared the results of COPD patients with those of the healthy controls. Secondly, we could not include functional imaging techniques to exclude perfusion disorders, which might result in cognitive dysfunction in this age group. Thirdly, we might have under evaluated the central nervous system effects of the COPD drugs. Anticholinergic side effects of these drugs hypothetically might cause some cognitive dysfunction. But, these side effects have been ignored in all the previous studies.

As a result, supported with the first detailed QEEG findings, we conclude that cognitive impairment in COPD patients is far from being a coincidence and important clues about its degenerative basis, especially in data processing areas, exist.

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