Electrophysiological assessment in patients with long term hypoxia

Faik Ilik, MD, Ahmet C. Pazarli, MD, Fatih Kayhan, MD, Harun Karamanlı, MD, Hatice K. Ozlece, MD.

ABSTRACT

الأهداف : لتقييم أنماط الجُهْدُ البَصَرِيُّ المُحَرّض (VEP) في مرضى السدة الرئوية المزمن (COPD) الذين كانوا متوافقين مع العلاج بالأكسجين التكميلي بالنسبة للمرضى غير متوافقين COPD .

الطريقة : تم استعراض بروتوكول الدراسة الاستباقية والموافقة عليها من قبل اللجنة الأخلاقية المحلية للجامعة سلجوق وتم إجراء الأبحاث في Elbistan State Hospita ، قسم علم الأعصاب كهرمان ، مارس ، تركيا من مايو إلى أكتوبر 2014م . وأجريت قياسات غاز الدم والاختبارات ووظائف الرئة في المرضى الذين يعانون من المرحلة متقدمة COPD . تم تقييم VEP في كلا العينين للمرضى المتوافقين وغير المتوافقين .

النتائج : شملت الدراسة 43 مريضاً 24 (55.8%) من المرضى لم تكونوا متوافقين مع العلاج بالأكسجين ، في حين 19 مريضاً (44.2%) كانوا يتلقون العلاج كافية من الأوكسجين . لم يكن هناك فروق ذات دلالة إحصائية بين المرضى الذين يعانون من الاهتمام بالنتائج اختبار وظيفة الرئة وقياسات غاز الدم . كان كُمُون VEP أكبر بكثير في كلتا العينين عند المرضى غير متوافقين .

الخاتمة : أفادت الدراسات السابقة كُمُون VEP لفترات طويلة عند وجود التهاب الجهاز العصبي المركزي . وقد لوحظ النتائج الكهربية الفسيولوجية مماثلة لدراستنا ونرجع ذلك بسبب الإجهاد التأكسدي والالتهاب الذي ينتج ثانويا لنقص التروية المزمن .

Objective: To evaluate visual evoked potentials (VEP) patterns in chronic obstructive pulmonary disease (COPD) patients who were compliant with supplemental oxygen treatment relative to non-compliant COPD patients.

Methods: This prospective study protocol was reviewed and approved by the local ethical committee of Selcuk University and the research was performed in the Department of Neurology, Elbistan State Hospital, Kahramanmaras, Turkey from May to October 2014. Blood gas measurements and pulmonary function tests were carried out in patients with advanced stage COPD. The VEP was assessed in both eyes in both compliant and non-compliant patients.

Results: The study included 43 patients; 24 (55.8%) of the patients were not in compliance with their supplemental oxygen treatment, while 19 patients (44.2%) received adequate oxygen treatment. There was no statistically significant difference between patients with regards to pulmonary function test results and blood gas measurements. The VEP latency was significantly greater in both eyes of the non-compliant patients.

Conclusion: Previous studies have reported prolonged VEP latencies in inflammatory diseases of the central nervous system. Similar electrophysiological findings were observed in our study and we propose that this may be due to oxidative stress, and inflammation that occurs secondary to chronic ischemia.

Neurosciences 2016; Vol. 21 (1): 26-29
doi: 10.17712/nsj.2016.1.20150333

From the Department of Neurology (Ilik), Baskent University, the Department of Pulmonary Medicine (Karamanli), Mevlana University, Konya, the Department of Pulmonary Medicine (Pazarli), Elbistan State Hospital, Elbistan, the Department of Psychiatry (Kayhan), Selcuk University, Department of Neurology (Ozlece), Edirne State Hospital, Edirne, Turkey.

Received 12th May 2015. Accepted 19th August 2015.

Address correspondence and reprint request to: Dr. Faik Ilik, Department of Neurology, Baskent University, Konya, Turkey. E-mail: faikilik@hotmail.com

Chronic obstructive pulmonary disease (COPD) is an irreversible disease characterized by airflow limitation. Airflow limitation is generally progressive and is associated with an abnormal pulmonary inflammatory response to harmful particles and gases.[1] Some COPD patients become oxygen-dependent over time.[2] However, prior studies indicate that patient compliance with long term oxygen treatment (LTOT) and the average daily duration of oxygen concentrator use is quite low.[3] Visual evoked potentials (VEP) are electrical impulses originating from the occipital cortex in response to stimulation of the retina with light.[4] In

the present study, we evaluated VEP patterns in COPD patients who were compliant with supplemental oxygen treatment relative to non-compliant COPD patients. We aimed to determine the effects of reduced oxygenation on signal transduction in the optical nerve and brain using electrophysiological methods.

Methods. This prospective comparative study was conducted in the Department of Neurology, Elbistan State Hospital, Kahramanmaras, Turkey, from May 2014 to October 2014. The study protocol was reviewed and approved by the local ethical committee of Selcuk University. Forty-three oxygen dependent COPD patients who were being followed in the thoracic disease clinic were included. In all patients included in the study, partial pressure of oxygen in blood (PaO_2) was <55 mmHg or arterial oxygen saturation (SaO_2) was <88% despite optimal treatment for 3-4 weeks. As a result, all study participants met the absolute criteria for LTOT prescription. The VEP was performed in all patients. Exclusion criteria were as follows: patients who are not candidates for continuous supplemental oxygen despite a diagnosis of COPD, previous history of cerebrovascular disease, history of demyelinating disease, or history of optic neuritis and other eye diseases. The demographic characteristics of all patients were recorded. Patients were questioned regarding the duration of daily supplemental oxygen use. The COPD status was evaluated using pulmonary function tests and forced expiratory volume in 1 second (FEV1), forced vital capacity (FVC), FEV1/FVC were recorded along with blood gas measurements pH, partial pressure of oxygen (pO_2) and partial pressure of carbon dioxide (pCO_2). Pattern reversal (PR) and VEP examination were performed in the electrophysiology laboratory in a dim, silent environment after positioning the patient for comfort. Hairy skin was cleaned with a cleansing gel. Using silver disc electrodes, the active electrode was placed on the Oz point according to the international 10-20 electroencephalography (EEG) electrode placement system. A reference electrode was placed on the Fz point, and the ground electrode was placed on the A1 (left ear) point. Electrode impedances were maintained below 5 KOhm. Electrodes were connected to a Key Point 2012 EMG evoked system, Alpine Biomed Aps, Denmark. Stimuli were presented in a checkerboard pattern alternating in a frequency approximately once per second (black-white contrast) using a 27×35 VD-40IA video monitor. Pupil-screen distance was adjusted to approximately one meter. Patients were asked to fixate on a white, small, and unchanging square in the middle of the screen using a single eye. The left eye was stimulated first, followed by the right eye. Monocular two sided VEP responses were recorded. The average of 200 cortical responses recorded from the Oz point were recorded as the VEP response. The first major negative peak in potential observed during the PR VEP examination was marked as N75 (N1), the second major negative peak was marked as N135 (major N2) and positive P100 (P1) wave peaks were also marked. Latency values were recorded and reported by the same neurologist. Differences in VEP latencies between patients who were oxygen compliant and those who were non-compliant with LTOT were evaluated statistically.

Statistics. Statistical analysis was performed using the the Statistical Package for Social Sciences (version 16.0, SPSS Inc., Chicago, IL, USA). Values were expressed as means±SD or as percentages. Means were compared by the student's t-test, or one-way analysis of variance test. The percentage was calculated in presence and absence group by Pearson's Chi-square test. The limit of statistical significance was set at $p<0.05$.

Results. The study included 43 patients; 27 males and 16 females. The mean age of the patients was 68.8±12.28 years. Twenty-four (55.8%) of the patients were not in compliance with their supplemental oxygen treatment, while 19 patients (44.2%) were receiving adequate oxygen treatment (defined as at least 15 hours per day) (**Table 1**). The Mean FEV1 was 32.2 and the mean FEV1/FVC was 92.8. There was no statistically significant difference in pulmonary function test parameters between compliant and non-compliant patients (*p*-values: FEV1 0.677, FVC 0.147, FEV1/FVC 0.397). In addition, there was no significant difference in blood gas measurements (pO_2, pCO_2, pH) between the 2 groups. The VEP was recorded in both eyes in all patients. According to the evaluation of VEP latencies in compliant and non-compliant patients, there was a significant difference in VEP latency measurements in the right eye ($p=0.03$) and an even larger difference in the left eye ($p=0.00$). Bilateral VEP prolongations were

Disclosure. The authors disclose no affiliation or financial involvement with organizations or entities with a direct financial interest in the subject matter or materials discussed in the manuscript. No funding was received for this work from any organization.

Table 1 - Oxygen therapy and demographic characteristics of the patients (N=43).

Variable	n (%)
Age	68.8±12.28
Gender	
Male	27 (62.8)
Female	16 (37.2)
LTOT	
Compliant	19 (44.2)
Non-compliant	24 (55.8)

LTOT - long term oxygen treatment

significantly different between compliant and non-compliant patients (p=0.04). Multivariate regression analysis identified oxygen use as an independent risk factor for bilateral VEP prolongation.

Discussion. Long term oxygen treatment is one of the few treatment options demonstrated to prolong life expectancy among patients with respiratory insufficiency. More than 2 million people worldwide benefit from LTOT.[5] For optimal effectiveness, LTOT should be used at least 15 hours a day, including during sleep.[6] However, studies indicate that in practice daily oxygen concentrator utilization time is far lower in many patients.[3] Oxygen-dependent COPD patients were included in the present study. Twenty-four (55.8%) of the study subjects were non compliant with LTOT, whereas 19 (44.2%) patients were adhered to their treatment (>15 h/day). We observed no difference in pulmonary function tests and blood gas measurements when patients were examined according to COPD stage. We aimed to investigate the effect of chronic hypoxemia on signal transduction in the brain by comparing VEP latency in compliant and non-compliant patients. The VEP is an indicator of signal transduction in the visual pathway from the retina and occipital area.[7] There was significant difference in VEP latencies between patients who were compliant and non-compliant with LTOT measured from the right eye (p=0.03) and a highly significant difference in VEP latency in the left eye (p=0.00). Singh et al[8] measured VEP latencies at sea level and at 4300 m above sea level, determining that VEP latency is prolonged at high altitude. They reported that acute clinical hypoxia had an adverse effect on VEP latency.[8] In the present study, we observed a statistically significant difference in bilateral VEP latencies when patients adhering to LTOT were compared with to non-compliant patients (p=0.04). In addition, chronic hypoxia was identified as an independent risk factor for bilateral VEP prolongation.

A previous study reported that COPD patients had a greater risk for mild cognitive impairment, potentially associated with long term hypoxia.[9] Kırmemiş et al[10] showed that S100B levels are elevated in sub-clinical hypoxia. The S100B protein is an acidic calcium binding protein that is highly specific to brain tissue.[11] The VEP latencies are also prolonged in multiple sclerosis (MS), an inflammatory demyelinating disease. Optic neuritis is commonly observed in MS patients. The VEP latency prolongation is an important finding in the McDonald diagnostic criteria.[12] Although the etiology of MS is not yet clear, inflammation plays an important role.[13] Other studies indicate that oxidative stress has a major role in the etiology of MS.[14] In addition, ischemia modified albumin, a highly sensitive marker for ischemia, is elevated in MS patients.[15] In another study, correction of chronic hypoxia with full CBAP treatment resulted in a reduction in inflammation and decreased expression of some inflammatory markers.[16] In the present study, VEP latencies were found to be prolonged in both eyes among patients who were not adhering to LTOT guidelines. In accordance with other findings reported in the literature, we propose that this may be due to oxidative stress and inflammation that occurs secondary to chronic ischemia. Perhaps similar to what has been reported in MS patients, in the present study, chronic ischemia significantly influenced VEP latency.

Previous studies have investigated the effects of chronic hypoxia on cognitive function and biochemical parameters.[9,10] In this study, the effect of chronic hypoxia on signal transduction in the brain was shown using electrophysiologic methods by comparison of similar patient groups. This study had a limitation that should be taken into consideration. Relatively small number of patients were included the study. In conclusion, chronic hypoxia because of unsteady usage of oxygen in oxygen-dependent patients can result brain signal transduction delay.

References

1. World Health Organization. The GOLD global strategy for the management and prevention of COPD. Geneva (CH): WHO; 2001. [Accessed April 1998; Updated August 2005]. Available from: http://www.goldcopd.org/uploads/users/files/GOLDWkshp05Clean.pdf
2. Ahmadi Z, Bornefalk-Hermansson A, Franklin AK, Midgren B, Ekström MP. Hypo- and hypercapnia predict mortality in oxygen-dependent chronic obstructive pulmonary disease: a population-based prospective study. ***Respiratory Research*** 2014; 15: 30.
3. Katsenos S, Constantopoulos SH. Long-Term Oxygen Therapy in COPD: Factors Affecting and Ways of Improving Patient Compliance. ***Pulm Med*** 2011; 2011: 325362.

4. Weinstein GW. Clinical aspects of the visually evoked potential. ***Ophthalmic Surg*** 1978; 9: 56-65.
5. Nasilowski J, Przybylowski T, Zielinski J, Chazan R. Comparing supplementary oxygen benefits from a portable oxygen concentrator and a liquid oxygen portable device during a walk test in COPD patients on long-term oxygen therapy. ***Respir Med*** 2008; 102: 1021-1025.
6. Kim KH, Park TY, Kim ES, Chung KB, Lee SM, Yim JJ, et al. Clinical features of patients on home oxygen therapy due to chronic respiratory failure at one university hospital. ***Korean J Intern Med*** 2012; 27: 311-316.
7. Tandon OP. Average evoked potentials--clinical applications of short latency responses. ***Indian J Physiol Pharmacol*** 1998; 42: 172-188.
8. Singh SB, Thakur L, Anand JP, Yadav D, Amitabh PK, Banerjee PK, et al. Changes in visual evoked potentials on acute induction to high altitude. ***Indian J Med Res*** 2004; 120 :472-477.
9. Singh B, Mielke MM, Parsaik AK, Cha RH, Roberts RO, Scanlon PD, et al. A prospective study of chronic obstructive pulmonary disease and the risk for mild cognitive impairment. ***JAMA Neurol*** 2014; 71: 581-588.
10. Kırmemiş O, Tatlı MM, Tayman C, Koca C, Karadağ A, Uras N, et al. Subclinical hypoxia of infants with intrauterine growth retardation determined by increased serum S100B protein levels. ***Turk J Med Sci*** 2011; 41: 795-800.
11. Florio P, Marinoni E, Di Iorio R, Bashir M, Ciotti S, Sacchi R, et al. Urinary S100B protein concentrations are increased in intrauterine growth-retarded newborns. ***Pediatrics*** 2006; 118: 747-754.
12. Polman CH, Reingold SC, Banwell B, Clanet M, Cohen JA, Filippi M, et al. Diagnostic criteria for multiple sclerosis: 2010 revisions to the McDonald criteria. ***Ann Neurol*** 2011; 69: 292-302.
13. Frischer JM, Bramow S, Dal-Bianco A, Lucchinetti CF, Rauschka H, Schmidbauer M, et al. The relation between inflammation and neurodegeneration in multiple sclerosis brains. ***Brain*** 2009; 132: 1175-1189.
14. Cakmak A, Soker M, Koc A, Erel O. Paraoxonase and arylesterase activity with oxidative status in children with thalassemia major. ***J Pediatr Hematol Oncol*** 2009; 31: 583-587.
15. Aydin O, Ellidag HY, Eren E, Kurtulus F, Yaman A, Yılmaz N. Ischemia modified albumin is an indicator of oxidative stress in multiple sclerosis. ***Biochem Med (Zagreb)*** 2014; 24: 383-389.
16. Nural S, Günay E, Halici B, Celik S, Ünlü M. Inflammatory processes and effects of continuous positive airway pressure (CPAP) in overlap syndrome. ***Inflammation*** 2013; 36: 66-74.

Authorship entitlement

Excerpts from the Uniform Requirements for Manuscripts Submitted to Biomedical Journals updated November 2003.
Available from www.icmje.org

The International Committee of Medical Journal Editors has recommended the following criteria for authorship; these criteria are still appropriate for those journals that distinguish authors from other contributors.

Authorship credit should be based on 1) substantial contributions to conception and design, or acquisition of data, or analysis and interpretation of data; 2) intellectual content; and 3) final approval of the version to be published. Authors should meet conditions 1, 2, and 3.

Acquisition of funding, collection of data, or general supervision of the research group, alone, does not justify authorship.

An author should be prepared to explain the order in which authors are listed.