Evoked and event related potentials in chronic respiratory failure

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ABSTRACT

Objectives: To assess the value of brainstem auditory evoked potentials and event related evoked potential (3rd positive component of evoked related potentials with latency of 300 millisecond, in evaluating cognitive dysfunction in patients with chronic respiratory failure.

Methods: Thirty-two patients with chronic obstructive pulmonary disease and respiratory failure of mild to moderate severity, were assessed regarding their mental function, utilizing mini-mental state examination, arterial blood gases including PH, partial pressure of carbon dioxide, partial pressure of oxygen, and both brainstem auditory evoked potentials and event related evoked potential response. Twenty-five normal subjects, matched for age and sex, were also studied as a control group. The study was carried out during the year 1999 to 2000 in 3 hospitals; King Khalid University Hospital, King AbdulAziz University Hospital and Sahara Hospital, Riyadh, Kingdom of Saudi Arabia.

Results: There were significant delay of event related evoked potential response in patients compared with controls ($P<0.05$). No significant difference was noted for brainstem auditory evoked potentials and mini-mental state examination scores were within normal limits in 78% of patients. When event related evoked potential were analyzed in comparison with blood gases and mini-mental state examination, there was a clear moderate correlation with severity of hypoxemia ($r = -0.697$). Correlation was also noted, but to a lesser degree with partial pressure of carbon dioxide ($r = 0.52$) and PH ($r = 0.53$). There was no correlation with mini-mental state examination.

Conclusion: The significant delay of event related evoked potential, which is considered the neuro-physiological correlate of cognition, points clearly to the presence of a certain degree of mental dysfunction in many of these patients, namely sub-clinical encephalopathy. These subtle changes commonly evade detection by conventional bed side test (mini-mental state examination), while detailed neuropsychological assessment is cumbersome and time consuming. So, event related evoked potential measurement may be an objective and practical test of subtle cognitive dysfunction in mild respiratory failure. Unfortunately, absolute event related evoked potential values may not be useful in individual patients, in view of its wide range. However, it is probably very helpful in the assessment of a group of subjects, such as trials of a new therapeutic modality. A follow-up study utilizing a larger group of patients, and formal neuropsychological mental assessment, will be expected to confirm and expand the present study's conclusions.

Keywords: Evoked potentials, event related potential, P300, respiratory failure, respiratory encephalopathy.

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Chronic hypoxic-hypercapnic state may occur following many pulmonary and cardiac diseases. It affects the central nervous system causing well described, though non-specific complaints of headache, dullness of mentation, drowsiness and confusion progressing in severe cases to coma with

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papilledema, asterixes, action tremor, and muscular twitching.[1] Electroencephalography (EEG) in severe states shows non-specific generalized slowing of brain activity, which does not correlate with the severity of associated blood gases abnormalities.[2,3] Milder states on the other hand, may be associated with subtle (sub-clinical) symptoms, of inattention, reduction in psychomotor activity, forgetfulness, slowing of reaction time, and abnormalities in constructional drawings.[4-6] In these instances, abnormalities of partial pressure of oxygen (pO_2) and partial pressure of carbon dioxide (pCO_2) can be readily confirmed by a simple and quick test, while there is not yet an established objective method for the assessment of the associated mental derangement. Heaton and Pendleton[7] have forcefully argued that in such situations although neuropsychological tests do not show severe abnormalities, the subtle cognitive impairment affects the quality of patients daily activities. This can have grave consequences in situations where some of these patients are involved in operating machines, driving, or making critical decisions.

The study of evoked potentials is a well-established neurophysiological method in the investigation of various neurological disorders.[8-11] Visual evoked potentials (VEP) was found to be more sensitive than both EEG and psychometry in detecting the pre-clinical stage of hepatic encephalopathy.[9] Brainstem auditory evoked potential (BAEP) study detects the brainstem dysfunction secondary to structural and metabolic causes,[10] and somatosensory evoked potentials (SSEP) were found to be of importance in detecting sub-clinical encephalopathy.[9] The value of evoked potentials in assessing acute hypoxic states is well established.[12,13] However, its value in assessing the effect of chronic hypoxic-hypercapnic states on mental function is not similarly well defined and the results of different studies were inconsistent.[14-18] Cognitive event-related potentials (ERP) are long-latency potentials that are obtained during performance of information processing tasks involving attention, stimulus discrimination, memory, and related processes.[19] Among the many ERP components, the event related evoked potential (P300) component is the most widely studied.[20] Event related evoked potential latency which is considered to be an index of cognitive processing time (stimulus evaluation), is prolonged in normal aging, confusional states, and dementia.[21-23] It was found also to be a sensitive marker of sub-clinical encephalopathy in hepatic and renal failure.[24-27] So far, few studies have described P300 abnormalities in chronic respiratory failure (CRF).[17,18,28] Results of these studies were persistent and non controversial, however, number of tested patients were generally small.[11-19] This study was set up to assess objectively the value of BEAP and P300 response in assessing cognitive function respiratory failure.

Methods. Thirty-two patients with chronic respiratory failure were admitted to the study, from King Khalid University Hospital (KKUH), King Abdul-Aziz University Hospital (KAAUH) and Sahara Hospital. Respiratory failure was defined as the fall of arterial pO_2 to 70 mmHg or less. It was labeled as mild between 70 and 65 mmHg, as moderate between 64 and 60, and severe when it drop to 59 or less. All patients satisfied the inclusion criteria of having pO_2 value of 70 mmHg or less, and being able to undergo neuro-physiological tests. Patients suffering from any other disease that may affect their mental function were excluded. Also those utilizing medications known to affect mental function were excluded. None were using portable oxygen. All patients had detailed clinical neurological assessment and a formal (modified) mini-mental state examination. Arterial blood gases (pO_2, pCO_2, log of hydrogen ion concentration [PH] and O_2 blood saturation), were measured at the same time of recording VEP, BAEP and auditory ERP, which was carried out in 2-tone oddball paradigm, using a Nicolett-Viking machine at KAAUH. All evoked potentials and ERP recordings were carried out utilizing standard methods recommended by the International Federation of Clinical Neurophysiology (IFCN).[29-31] Twenty-five controls, matched for age and sex, were selected from primary care and orthopedic clinics as well as from hospital staff. Any one with an illness that may affect mental function was excluded. All had EP and ERP, utilizing the same protocol used for patients. Stat Pac Gold statistical analysis package, was utilized to analyze the results.

Results. Thirty-two patients were admitted to the study (15 females, 17 males), ages range from 32 to 61 years with a mean of 44.6 years. There were 25 controls (13 female and 12 males), ages range from 21 to 65 years with a mean of 38.1 years. All patients had respiratory failure due to chronic obstructive pulmonary disease (COPD), with or without cor pulmonale. Visual evoked potentials were found to be within normal limits in the first 10 patients, and they were dropped from further assessment. Twenty-seven patients (88%) underwent all intended tests. The mean values for pO_2, pCO_2, PH, mini-mental state examination (MMSE), and duration of the disease were 51.1 mm.Hg, 57.6 mm.Hg, 7.3, 24.6, and 8.5 years. Mini-mental state examination score was mildly abnormal (20-23) in 6 patients (22%) only. Event related evoked potential mean latency for controls was 366.18 ± 62.1 ms, and for patients 435.28 ± 64.6 ms. Results are summarized in **Table**

1. On comparison of both groups using Student t-test, P300 latency was significantly prolonged in patients (P=0.001) **Table 2**. On the other hand, there was no significant differences between both groups regarding absolute and inter-peak waves latencies, of waves I-V BAEP complex. There was no significant difference with respect to both age and sex. Correlation and regression analysis was carried out within patients group, between P300 latency and each of the following variables: PH, pCO_2, pO_2 and MMSE. It showed significant correlation with all blood constitutes, being specially marked for *p*O2 (r = 0.697), less so for PH (r = 0.52), and for *p*CO2 (r = 0.53). Correlation for MMSE was however weak, with a correlation coefficient of 0.26.

Discussion. Evoke related evoked potential latencies, particularly that of P300 were significantly delayed in our patients with chronic respiratory failure (CRF), inspite of having normal MMSE in most of them (78%). Considering the fact that P300 latency is an index of cognitive processing time,[19] this result indicates that subclinical or mild cognitive dysfunction (encephalopathy) is rather common in these patients. Which contrasts with results of the formal clinical mental assessment (MMSE), being within normal in more than 78% of patients. This implies that P300 can identify patients with

Table 1 - Bio-data and results of auditory event related potential, blood gases and mini-mental state examination measurements in 32 patients with respiratory failure due to chronic obstructive pulmonary disease.

N	Age	Gender	N1	P2	N2	P300L	PH	pCO_2	pO_2	MMSE
1	55 Y	F	49.50ms	91.50ms	210.00ms	430.50ms	7.32	69.1	52.2	24
2	42 Y	F	82.50ms	123.50ms	252.00ms	400.50ms	7.35	58	61.1	23
3	33 Y	M	94.50ms	120.00ms	250.50ms	297.50ms	7.37	46.5	63.3	26
4	37 Y	F	100.50ms	153.00ms	255.00ms	391.50ms	7.41	38.4	59.7	27
5	34 Y	F	117.00ms	148.50ms	255.00ms	393.00ms	7.39	41.5	62.5	24
6	49 Y	M	154.50ms	178.50ms	256.50ms	385.50ms	7.42	37	57.3	28
7	48 Y	F	72.00ms	117.00ms	148.50ms	499.00ms	7.33	43	60.8	23
8	45 Y	M	76.50ms	126.00ms	276.00ms	427.50ms	7.34	40	64.1	26
9	36 Y	F	61.50ms	96.00ms	193.50ms	564.00ms	7.28	73.9	44.3	24
10	39 Y	M	135.00ms	171.00ms	289.50ms	547.50ms	7.25	84.5	39.2	23
11	38 Y	F	85.50ms	114.00ms	225.00ms	399.00ms	7.36	41.7	63	25
12	38 Y	F	84.00ms	147.00ms	223.50ms	400.50ms	7.38	83.4	59	26
13	40 Y	F	70.50ms	105.00ms	148.50ms	334.50ms	7.35	35.1	60.8	26
14	52 Y	M	54.00ms	96.00ms	201.00ms	379.50ms	7.4	46.2	56.5	27
15	37 Y	M	85.50ms	115.50ms	352.50ms	493.50ms	7.32	72.8	48.1	25
16	60 Y	M	124.50ms	213.00ms	267.00ms	468.00ms	7.319	68	44.6	24
17	38 Y	F	78.00ms	99.00ms	156.00ms	460.50ms	7.31	70.5	45	22
18	50 Y	M	148.50ms	213.00ms	283.50ms	418.50ms	7.32	58.1	52.3	25
19	50 Y	F	64.50ms	126.00ms	241.50ms	427.50ms	7.4	42.1	49.7	28
20	50 Y	F	96.00ms	141.00ms	195.00ms	372.00ms	7.36	47	48.2	28
21	59 Y	M	81.00ms	151.50ms	240.00ms	490.00ms	7.31	68	44.6	20
22	53 Y	M	108.00ms	199.00ms	254.00ms	487.00ms	7.33	49.3	51.5	22
23	42 Y	M	76.00ms	133.50ms	228.00ms	448.00ms	7.3	67	41.8	26
24	35 Y	M	111.00ms	145.00ms	212.00ms	375.00ms	7.41	48	60.5	29
25	46 Y	F	96.00ms	123.00ms	209.00ms	393.00ms	7.44	41.9	55.8	25
26	48 Y	M	108.00ms	135.00ms	247.00ms	479.00ms	7.32	71	40.2	23
27	48 Y	M	91.00ms	140.00ms	223.00ms	528.00ms	7.3	74	39	21
28	40 Y	F	77.00ms	107.00ms	176.00ms	386.00ms	7.34	47.1	50.8	26
29	32 Y	M	86.00ms	129.00ms	200.00ms	443.00ms	7.28	73.8	33.7	24
30	50 Y	M	98.00ms	159.00ms	280.00ms	540.00ms	7.35	51.3	35.2	28
31	45 Y	M	84.00ms	130.00ms	192.00ms	367.00ms	7.24	80.1	52.5	23
32	61 Y	F	115.00ms	187.00ms	242.00ms	503.00ms	7.1	75	40.7	28

N - number, Y - year, F - female, M - male, N1 - first negative component of ERP, P2 -2nd positive component of ERP, N2- 2nd negative component of ERP, P300L -3rd positive component of ERP with latency about 300 ms, PH - log of hydrogen ions concentration pCO_2 - partial pressure of carbon dioxide, pO_2 - partial pressure of oxygen, MMSE - mini-mental state examination, ERP - event-related potential

Table 2 - Comparison of results of auditory event related potential in patients and controls.

ERP	Patients N=32	Controls N=25	P-value
N1	92.65 ± 24.99	73.4 ± 26.51	0.003
P2	138.55 ± 32.73	132.66 ± 27.28	0.006
N2	230.72 ± 44.06	198.22 ± 41.01	0.003
P300	435.28 ± 64.6	366.18 ± 62.1	0.001

N - number, ERP - event-related potential,
N1 - first negative component of ERP,
P2 - 2nd positive component of ERP
N2 - 2nd negative component of ERP,
P300 - 3rd positive component of ERP with latency about 300 ms

subclinical CRF, which evades detection by conventional bed-side tests. These results are consistent with those obtained by Umahara et al,[28] who assessed P300 in 14 patients with respiratory failure consequent to pulmonary tuberculosis. The fact that all our patients had COPD, should not make an important difference, apart from the fact that pCO_2 was probably higher in our group. Barbieri et al[17] studied 19 patients, and Nakano et al[18] studied patients with CRF due to various etiologies and of variable severity, and detected similar results. Barbieri et al[17] however, evaluated their patients with detailed neuropsychological tests which added more weight to the associated P300L changes. Abnormal neuropsychological tests has long been reported in patients with CRF.[4-7] Grant et al[5] administered the Halstead-Reitan test battery to COPD patients and found their scores to be significantly lower than controls in all tests, particularly in tasks requiring sustained attention. However, taking into account the fact that these tests are cumbersome and time consuming, while P300 measurement is relatively simple and quicker, the use of P300 in assessing cognitive dysfunction in such patients may be a promising practical alternative. In view of this data, P300 measurement is valuable in evaluating mental dysfunction in a large group of patients. So, it is expected to be an objective and practical test when a new therapeutic modality for example, needs to be evaluated. However, when it comes to the assessment of an individual patient, P300 latency value is so wide that a single measurement cannot be interpreted yet with enough certainty. Regarding VEP and BAEP, Mabin et al,[14] and Nakano et al,[18] reached a similar conclusion to ours, that the measurements of these potentials is not helpful in assessing respiratory encephalopathy, however Zeitelhofer et al[15] reported significant changes. It is possible that changes of VEP and BAEP occur in more severe states of CRF, while ERP's are affected earlier with milder alteration of blood gases. Furthermore, P300 latency appear to correlate with arterial blood gas derangement, which corresponds with the severity of respiratory failure. This reflects the deleterious effects exerted on the highly specialized neurons, by low pO_2, high pCO_2 and acidosis, individually or more likely together. Within available data, it is very difficult to speculate on whether changes in any of these parameters has a more important deleterious effect on the brain. The apparent higher correlation of hypoxemia with P300 latency delay is not enough to assume a dominant pO_2 effect.

In conclusion, mild or subclinical cognitive derangement, as reflected by P300 latency delay is a common complication of CRF. Event related evoked potential measurement is a practical and sensitive test of cognitive function, and is especially useful when a group of patients need to be assessed. It is recommended that these results be further confirmed, with larger studies aiming to standardize this test for use with individual as well as groups of patients.

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