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Event-related evoked potentials in chronic respiratory encephalopathy

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Background: Cognitive event-related potential (P_{300}) is an index of cognitive processing time. It was found to be prolonged in dementia, renal, and hepatic encephalopathies, but was not extensively assessed in respiratory failure.

Objective: To evaluate P_{300} changes in patients with respiratory failure, and especially those with mild or subclinical hypoxic–hypercapnic encephalopathy.

Methods: Auditory event-related evoked potential P_{300} latency was measured using an oddball paradigm in patients with respiratory failure due to any cause (partial pressure of oxygen in arterial blood (PO_2) should be 75 mm/Hg or less). Apart from blood gases measurement, patients underwent the Mini-Mental State Examination (MMSE). Patient performances were compared with that of matched normal control. Patients were admitted into the study from outpatient clinics and wards at King Khalid University Hospital and Sahara Hospital.

Results: Thirty-four patients (12 women, 22 men) were admitted to the study. Ages ranged from 19–67 years with a mean of 46.1 years. Respiratory failure was severe or very severe in 11 patients (33%), and mild or moderate in the rest (66%). Mean value for PO_2 and partial pressure of carbon dioxide in arterial blood (PCO_2) were 63.7 and 45.2 mm/Hg, respectively. pH mean was 7.4 and O_2 saturation was 90.7%. P_{300} latency ranged from 218 to 393 milliseconds, with a mean of 338.4 milliseconds. In comparison with control (309.9 milliseconds), there was a significant difference ($P = 0.007$). P_{300} amplitude differences were not significant. No significant difference in MMSE was noted between mild and severe respiratory failure. Results of detailed neuropsychological assessment were clearly abnormal but were limited by the small number of tested patients. P_{300} latency changes correlated significantly with age as well as severity of respiratory failure. P_{300} was also significantly delayed whether hypoxia occurred with or without hypercapnia.

Conclusion: Results show a significant delay of P_{300} latency in patients with severe and mild respiratory failure. This was associated with subclinical encephalopathy in most patients, evidenced by a near-normal MMSE score. Apart from confirming the importance of P_{300} latency measurement as a marker of respiratory encephalopathy, this study asserts the causal relationship between hypoxemia and cognitive derangement. Furthermore, it promotes the early use of oxygen therapy in a selected group of patients with mild or moderate respiratory failure, who have responsibilities which involve taking rapid critical decisions.

Keywords: event-related evoked potentials, hypoxic–hypercapnic encephalopathy, respiratory failure, chronic respiratory encephalopathy

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Introduction

Chronic hypoxic–hypercapnic states occur in many pulmonary and cardiac diseases. These states affect the central nervous system causing well-described nonspecific clinical

manifestations including headache, dullness of mentation and drowsiness, confusion progressing in severe cases to coma with papilledema, asterixis, action tremor, and muscular twitching.[1] When these features appear in the context of a severe respiratory failure, the association is clear, and electroencephalography (EEG) shows marked slowing of brain activity.[2,3] On the other hand, mild chronic hypoxic conditions cause subtle or subclinical changes including inattention, reduction in psychomotor activity, forgetfulness, slight decrease of intelligence, slowing of reaction time, and abnormalities in constructional drawings.[4–6] Grant and colleagues administered the Halstead–Reitan neuropsychological test battery to patients with chronic obstructive pulmonary disease (COPD), and found their scores to be significantly lower than controls in all tests.[5] COPD patient performance, particularly in tasks requiring sustained attention, was poor. In these instances, abnormalities of partial pressure of oxygen in arterial blood (PO_2) and partial pressure of carbon dioxide in arterial blood (PCO_2) can be easily confirmed by a simple blood test. On the contrary, there is no similar readily available objective tests for the assessment of associated cognitive derangement as structured neuropsychological tests are too complex and timely to be included in the clinical assessment of most patients. Heaton and Pendleton have strongly argued that many of these subtle cognitive impairment affects the quality of various daily activities.[7] It is expected that such subtle cognitive dysfunction may have serious consequences in situations where patients are involved in activities requiring rapid critical decisions such as operators of complex machines.

Visual-, auditory-, and somatosensory-evoked potentials are well established neurophysiological tests and are widely used in investigating various neurological disorders.[8–11] Although its value in assessing acute hypoxic states is well established,[12,13] its benefit in assessing the effect of chronic hypoxic–hypercapnic states on the nervous system was doubtful.[14–19] Cognitive event-related evoked potentials (EREPs) are long-latency potentials obtained during information processing tasks which involve attention, stimulus discrimination, memory, and related processes.[20] Among the many EREP components, the P_{300} potential is the most widely studied and used. It is a positive-going potential with a modal latency of 300 ms and centroparietal scalp distribution, obtained usually by the oddball paradigm.[21] P_{300} latency is an index of cognitive processing time and was shown to be prolonged in normal aging, confusional states, and dementia.[22–24] P_{300} latency has been found also to be a sensitive marker of subclinical encephalopathy in hepatic and renal failure.[25–28] The effect of acute hypoxia on EREP was studied in an experiment that utilized a simulated high altitude environment, and P_{300} latency was found to be delayed.[29] So far, few studies have described P_{300} latency abnormalities in chronic respiratory insufficiency.[16,17,30] A group of 19 patients with mild or moderate respiratory failure (RF) of different etiologies were studied by Barbieri and colleagues[16] and another group of 17 patients with variable severity chronic RF by Nakano and colleagues.[17] Although their results show a tendency for P_{300} changes, these were not significant. Umahara and colleagues, on the other hand, in a selected group of 14 patients with post pulmonary tuberculosis RF, were able to detect a significant delay in P_{300}.[30] Taking into account the large variability of P_{300} latency, these studies are limited by the relatively small number of studied subjects, besides the insignificant results in the first two. This study is designed to examine cognitive EREP in RF in a large group of patients and compare it with mental assessment results and measurement of blood gases. In particular, we aim to determine the sensitivity of P_{300} changes in detecting mild or subclinical cognitive impairment (ie, subclinical respiratory encephalopathy).

Patients and methods

Thirty-four patients, 12 females (35.3%) and 22 males (64.7%) were admitted to the study from both King Khalid University Hospital and Sahara Hospital out- and inpatient services. All had chronic RF with PCO_2 of 75 mm/Hg or less, which could be either type I in the presence of hypoxia alone, or type II when combined with hypercapnia. All patients should be able to conduct all required assessments and investigations. Patients with any cause of mental dysfunction apart from RF were excluded. The severity of RF was defined according to PO_2 as mild (75–65 mm/Hg), moderate (64–60 mm/Hg), severe (59–50 mm/Hg), and very severe (<50 mm/Hg). Patients underwent the following assessments and investigations:

Clinical:

(a) Full neurological assessment

(b) Mini-Mental State Examination (MMSE)

Arterial blood gases:

PO_2, PCO_2, PH, and O_2 saturation.

Neurophysiological:

P_{300} in two-tone oddball paradigm (Figure 1).

Event-related potential recordings were performed using standard methods recommended by the International Federation of Clinical Neurophysiology (IFCN).[31]

Data analysis

The StatPac Gold (StatPac Inc., Bloomington, MN) statistical analysis package was utilized to analyze the results.

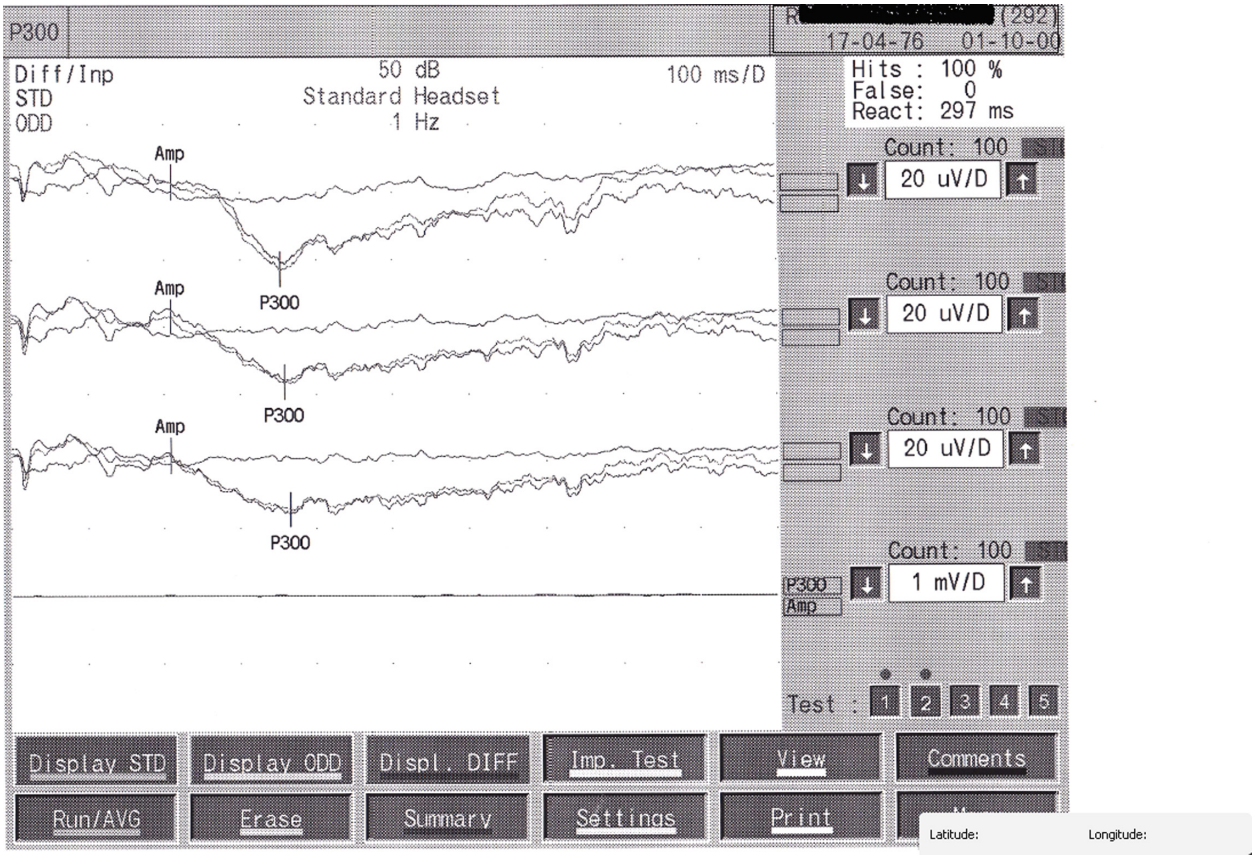

Figure 1 P_{300} in two-tone oddball paradigm.

Results

Patient ages ranged from 19 to 67 years with a mean of 46.4 ± 11.6 years. Eight were below the age of 40 years (25.8%), 22 (61.3%) were aged 40–59 years, and four (12.9%) were older than 60 years. Biodata, P_{300} latency and amplitude, blood gases results, and MMSE scores are included in Table 1.

Thirty-six controls matched for age, sex, and education level were included. Their demographic data and results of P_{300} latency and amplitude measurements are included in Table 2.

Fourteen patients (40%) had severe or very severe RF, and 60% had mild to moderate severity RF.

The mean value for PO_2 and PCO_2 were 63.7 ± 14.3 mm/Hg (range from 32–90.7 mm/Hg), and 45.26 ± 10.68 mm/Hg (range from 30–79.8 mm/Hg) respectively. Mean value for pH was 7.4 ± 0.34 and 90.7% ± 7.2% for O_2 saturation. MMSE scores ranged from 22–30 with a mean of 26.1 ± 2.02. Table 3 summarizes these results. No significant difference in MMSE could be found between different subtypes of RF.

P_{300} (C_z) latencies in patients ranged from 268 to 393 ms, with a mean of 339.29 ± 54.26 ms. P_{300} amplitude was extremely variable at 13.52 ± 11.3 μv. The mean P_{300} latency in controls was 309.96 ± 29.15 ms, ranging from 220–372 ms, and P_{300} amplitude mean was 15.08 ± 6.43 μv. EREP results for patients and controls are summarized in Table 4.

P_{300} latency (C_z) was higher among patients than controls (339.29 ± 54.26 ms, vs 309.97 ± 27.08 ms), and was also higher for P_z measurements (339.06 ± 54.88 ms, vs 310.49 ± 31.11 ms). The differences were statistically significant for both measurements ($P = 0.005$ and 0.008, respectively).

The mean P_{300} latency from all measurements was also significantly higher in patients than controls (338.44 ± 53.99 ms vs 309.96 ± 29.15 ms; $P = 0.007$).

P_{300} amplitude at C_z and P_z were lower in patients than controls (16.68 ± 7.39 μv vs 13.52 ± 11.3 μv and 13.48 ± 6.05 μv vs 11.41 ± 9.14 μv, respectively), but were not statistically significant. Also the mean P_{300} amplitude difference was not statistically significant (13.42 ± 12.2 μv vs 15.08 ± 6.43 μv, respectively) between both groups. The mean P_{300} latency in patients changed from 324.2 ms in mild RF to 367.3 ms in very severe RF.

There is a moderate correlation between age and the mean P_{300} (latency) in cases ($r = 0.54$, $P = 0.001$), but not in controls

Table 1 Biodata and results of blood gases, EREP, and MMSE in 34 patients

Serial no	File no	Sex	Age	PO_2	PCO_2	PH	O_2 Sat %	$F_z C_z P_z$ Latency ms			$F_z C_z P_z$ Amplitude μv			MMSE
1	466650	F	43	47.2	71.4	7.360	80.9	327	328	329	1.17	0.10	0.85	24
2	508904	M	53	39.7	35.3	7.464	78.2	326	332	344	10.40	8.05	7.11	25
3	596577	F	31	51.2	49.2	7.401	86.0	304	302	306	5.57	8.99	9.27	24
4	346571	M	62	75.2	44.5	7.400	95.0	359	358	358	9.27	8.93	11.00	23
5	596731	M	39	56.9	40.6	7.442	91.8	322	326	329	11.40	19.40	18.20	24
6	055464	M	45	32.0	64.2	7.353	63.2	332	332	332	4.97	4.36	6.69	26
7	543238	M	54	64.6	46.5	7.378	93.2	362	368	368	15.50	11.40	9.48	25
8	460117	M	53	47.2	49.7	7.362	84.2	392	393	397	52.80	20.80	11.60	24
9	416512	M	65	52.2	43.7	7.424	88.2	383	382	382	9.88	6.06	7.77	27
10	147927	M	67	49.6	52.2	7.379	83.6	549	558	554	20.30	12.10	7.36	28
11	414386	M	55	69.9	34.6	7.443	93.7	299	302		10.60	15.90		30
12	159095	M	30	52.1	49.3	7.378	84.1	304	283	282	16.20	13.50	7.71	27
13	206853	M	36	40.8	49.2	7.373	81.5	251	268	268	3.98	9.64	14.50	24
14	606009	M	46	62.5	40.6	7.450	92.5	294	295	306	7.89	15.60	12.80	27
15	611416	M	36	74.5	41.2	7.397	97.6		202	208	11.30	9.80	3.35	25
16	096204	M	57	65.5	43.1	7.398	93.0	352	352	352	23.60	18.30	14.90	29
17	111112	F	37	57.7	48.3	7.349	88.4	340	329	320	8.62	7.86	5.79	26
18	618472	F	50	54.0	65.5	7.398	86.8	368	372	367	9.23	16.70	10.80	25
19	612457	M	46	68.5	38.9	7.413	93.0	329	332	338	15.80	16.40	15.40	27
20	005619	F	40	67.4	39.8	7.431	96.6	311	308	312	15.60	20.40	17.00	28
21	345696	F	50	75.7	37.9	7.409	96.0	387	391	398	10.40	8.05	7.16	26
22	229859	M	38	57.9	39.5	7.423	92.6	378	374	374	4.99	9.01	10.40	25
23	055464	M	45	75.7	79.8	7.338	95.0	378	362	245	14.00	10.40	13.20	28
24	252915	M	38	58.5	47.1	7.407	90.3	351	332	331	6.59	3.10	2.54	24
25	344947	F	65	75.9	37.4	7.449	95.0	355	358	358	3.29	3.10	1.18	25
26	393969	F	50	75.2	44.0	7.394	96.8	336	336	338	18.10	16.70	17.40	26
27	535671	F	52	75.2	44.1	7.400	96.1	345	341	338	16.00	11.20	7.99	30
28	591569	M	19	73.7	38.2	7.374	94.5	309	308	305	8.05	16.40	20.60	27
29	596133	M	46	66.1	35.1	7.443	94.0	327	336	348	21.10	18.30	16.80	28
30	472146	M	58	72.8	30.9	7.463	95.5	330	334	334	101.60	68.50	53.60	29
31	568092	F	40	65.6	44.2	7.351	91.9	318	318	319	22.20	25.30	14.60	24
32	016557	F	58	70.3	40.7	7.396	94.1	311	312	312	0.73	6.76	10.10	22
33	514339	F	40	75.9	33.6	7.394	96.6	390	395	395	21.90	10.70	5.65	28
34	550413	M	26	64.8	38.7	7.421	93.0	319	309	309	6.49	7.86	3.59	27

Abbreviations: EREP, event-related evoked potentials; MMSE, Mini-Mental State Examination; PO_2, partial pressure of oxygen in arterial blood; PCO_2, partial pressure of carbon dioxide in arterial blood.

(r = 0.06, $P = 0.71$). The correlation between age and mean P_{300} amplitude was weak for cases and controls (r = 0.17, $P = 0.32$ and r = 0.07, $P = 0.67$, respectively).

Discussion

This study clearly confirm the occurrence of P_{300} latency delay in association with RF. This is consistent with results obtained by Umahara and colleagues in their selected group of 14 patients with postpulmonary tuberculosis RF.[30] P_{300} latency is already experimentally proven as marker of cognitive function (central processing time), and its delay has already been documented in other metabolic encephalopathies. Of special importance is the fact that significant P_{300} latency changes were observed in association with various degrees of RF, including the mild or subclinical states. Most patients with mild RF in this study had no or some nonspecific complaints, such as headache, concentration, and memory difficulties, which usually do not raise significant clinical concern. Furthermore MMSE was

Table 2 Biodata and results of P300 in 36 normal controls

Serial no	Hospital no	Age	Sex	Education/Work	P_{300} Latency ms	P_{300} Amplitude μv
1	111111	44	M	College level	372	18.1
2	580776	41	F	College level	313	13.2
3	068562	68	F	College level	328	14.9
4	170476	57	F	College level	356	19.3
5	155210	38	F	College level	308	16.3
6	224721	57	F	College level	309	28.2
7	382234	42	M	College level	288	26.3
8	103774	49	F	College level	334	20.0
9	050455	58	F	College level	290	23.3
10	312645	55	M	College level	220	14.5
11	149844	53	F	College level	283	24.9
12	339360	45	F	College level	361	11.0
13	123784	51	F	College level	295	19.6
14	219041	56	F	College level	344	5.83
15	469789	43	M	Secondary level	316	10.7
16	338830	50	F	College level	258	10.3
17	344239	53	F	College level	301	26.9
18	123456	54	F	Secondary level	305	21.1
19	041768	45	F	Secondary level	312	9.05
20	001020	63	M	Secondary level	333	16.2
21	015408	55	M	Secondary level	290	23.9
22	035526	62	M	Secondary level	306	10.1
23	002477	58	M	Secondary level	302	22.4
24	028034	48	M	Secondary level	274	5.98
25	070112	48	M	Secondary level	308	33.8
26	018549	57	M	College level	309	7.06
27	396058	46	M	College level	328	15.3
28	712658	62	M	College level	355	22.8
29	851708	56	M	College level	308	38.3
30	417765	55	M	Secondary level	301	13.1
31	123456	52	M	Secodary level	333	21.1
32	026199	50	M	Secondary level	338	8.9
33	123456	44	M	College level	274	20.7
34	000440	47	M	College level	319	15.1
35	000112	47	M	College level	323	15.4
36	000000	40	F	Secondary level	308	13.1

Table 3a Summary of results blood gases and MMSE in 34 patients with respiratory failure

Blood gas N = 34	Minimum	Maximum	Mean	Median	Standard deviation
PO_2	32.0	90.7	63.72	65.15	14.34
PCO_2	30.0	79.8	45.26	43.4	10.78
pH	7.34	7.46	7.4	7.4	0.34
O_2 saturation	63.2	99.6	90.71	93.0	7.36
MMSE	22.0	30.0	26.09	26.0	2.02

Abbreviations: MMSE, Mini-Mental State Examination; PO_2, partial pressure of oxygen in arterial blood; PCO_2, partial pressure of carbon dioxide in arterial blood.

Table 3b Data of neuropsychological findings in five patients who underwent a full battery of neuropsychological assessments

Test	Mean	Standard deviation	Assessment
Digit span (forward)	3.2	1.78	Very poor
Verbal immediate recall	8	2.9	Acceptable, but slightly low
Verbal delayed recall	6.4	2.6	Poor
Verbal fluency	26.1	1.64	Good
Raven's test	19.0	6.44	Poor

found to be insensitive in most of these patients. P_{300} latency may be of special importance in this group of patients that demonstrate the presence of definite, though subtle, cognitive derangement. This is because patients at this stage may be executing or undertaking complicated or risky tasks unaware that their mental performance is compromised. Misjudgments or miscalculated decisions may have serious consequences, increase the burden of stress, precipitate work and home difficulties, and possibly emotional disturbances, including depression. Different studies has been able to document subtle cognitive derangements in subclinical respiratory encephalopathy using detailed neuropsychological assessments.[4–6] In such patients, P_{300} measurement will be an objective method in assessing cognitive derangement and confirming the presence of 'subclinical' respiratory encephalopathy.

On another front, P_{300} derangement occurs in both types of RF, and Its latency correlated well with severity of hypoxemia in both types. In type 2 RF, it may be partially responsible, however, in type 1 it is the only culprit. The question which arises here is whether correction of hypoxemia, however mild, may be of help in correcting the associated cognitive derangements. In cases of overt clinical respiratory encephalopathy associated with severe hypoxemia, the use of oxygen led to clear mental improvement, which formed the basis for portable oxygen therapy. Should portable oxygen be offered to patients with a milder degree of RF, especially those undertaking sophisticated, specialized professions? Results of the present study clearly goes in favor of such a decision, as the use of P_{300} latency as the marker of processing time was found to be prolonged in most of these patients. However a more definite answer to this question is expected from a prospective interventional study, where P_{300} latency is assessed before and after administering oxygen.

Finally, P_{300} latency varies widely in normal subjects, making measurements of individual patients of little use generally. Although we were able to establish a normal P_{300} latency value with a two standard-error range in this study, the practical use of these absolute values in individual patients will require prolonged experience. The main benefit of this potential will be in assessing the benefit of a therapeutic modality, ie, oxygen, in a group of patients with respiratory encephalopathy. Or conversely, assessing the effect of any medicine used for other reasons on exacerbating encephalopathy. Taking into account the fact that all patients in the group of mild encephalopathy do not use oxygen therapy, it is reasonable to suggest that at least some of those patients may benefit from an earlier introduction of such treatment, especially a subgroup of patients holding critical responsibilities, in whom cognitive dysfunction may affect their optimum performance.

Table 4 Summary of results of EREPs in 34 patients with chronic respiratory failure and their controls

EREP	Cases (X ± SD)	Controls (X ± SD)	t
F_z (latency)	339.29 ± 54.26 ms	309.97 ± 27.08	0.005*
C_z (latency)	339.06 ± 54.88 ms	310.49 ± 31.11	0.008*
P_z (latency)	338.06 ± 56.72 ms	309.43 ± 31.17	0.01*
F_z (amplitude)	15.28 ± 17.91 μv	15.08 ± 7.64	0.95
C_Z (amplitude)	13.52 ± 11.30 μv	16.68 ± 7.39	0.165
P_Z (amplitude)	11.41 ± 9.14 μv	13.48 ± 6.05	0.263
Mean P_{300} latency	338.44 ± 53.99 ms	309.96 ± 29.15	0.007*
Mean P_{300} amplitude	13.42 ± 12.9 μv	15.08 ± 6.43	0.471

Abbreviations: EREP, event-related evoked potentials; P_{300}, cognitive event-related potential; SD, standard deviation.

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