

Original article:

AUDITORY EVENT-RELATED POTENTIALS AS INDICATORS OF GOOD PROGNOSIS IN COMA OF NON-ANOXIC ETIOLOGY

Raja A. Sawaya, M.D*, Rosette Jabbour, M.D.

Department of Internal Medicine, Division of Neurology, American University Medical Center, Beirut, Lebanon

* Corresponding author: Raja A. Sawaya, M.D., Associate Professor of Clinical Medicine, Neurologist, Director Clinical Neurophysiology Laboratory, American University Medical Center, POB: 113 – 6044 / C-27, Beirut, Lebanon, Tel: 961 – 1 – 350000, Fax: 961–1–354305, E-mail: rs01@aub.edu.lb

ABSTRACT

The aim of this study is to evaluate whether auditory event-related potentials can predict the prognosis of recovery from coma resulting from different etiologies. The results of this study could then be used as an adjuvant test in helping the clinician evaluate patients in coma.

We performed P300 auditory event-related potentials on 21 patients who developed a state of coma at our institution. We compared the results to the Glasgow coma scale at the onset of coma, on day 3, and day 21.

We found that patients who developed coma secondary to cardiopulmonary arrest had no P300, and did not develop one, irrespective of their GCS, or their survival. Patients who developed coma from causes other than cardiopulmonary arrest who had a P300 at the onset of their coma, or developed one in the days that followed, ended up surviving their coma. On the other hand, patients in coma from non-cardiac causes who did not have, or developed a P300, did not survive their coma.

We concluded that P300 had no prognostic value in coma secondary to anoxic brain injury, while it was an indicator of good prognosis if it was present in patients in coma from non-anoxic causes.

Keywords: P300, prognosis, coma, electrophysiology, cardiac arrest, awakening, survival, vegetative state

INTRODUCTION

Predicting the likelihood of waking up from a comatose state is an important issue for the physician and the family of the patient. Clinical assessment cannot establish the prognosis of coma with confidence, especially in the early stages of coma. Tests in current use for this purpose are either a function of global cerebral function (EEG), morphology (MRI), blood flow and metabolism (SPECT, PET) or specific sensory modalities (sensory evoked potentials) (De Giorgio et al., 1993).

The P300 event related potential, on the other hand, is a reflection of cognitive processing. It is a scalp-recorded positive wave occurring approximately 300 msec after the onset of either an auditory or visual stimulus. This response indicates that the brain actually perceives a certain incoming stimulus as different or special (Lew et al., 1999). The P300 is invoked by rare or unpredictable task-relevant stimuli. Its amplitude is influenced by task relevance and stimulus probability and is maximal over centroparietal recording sites (Yamagushi and Knight, 1991; Baguley et al., 1997).

In the past the P300 event related potential was thought to exist only using an active paradigm while the patient is awake and responding to the stimuli administered (Squires et al., 1976; Johnson and Donchin, 1978; Polich, 1989). Many studies after that have shown that P300 can be elicited in patients with altered levels of consciousness using a passive paradigm (Polich, 1989; Reuter and Linke, 1989; Gott et al., 1991; Signorino et al., 1995; Mazzini et al., 2001). The passive paradigms can provide similar information as active discrimination tasks, but that amplitude differences between the procedures may make component measurement difficult even though peak latency may be the variable of major interest (Polich, 1989; Kane et al., 1993).

We attempted to study the existence or development of P300 in coma from cardiopulmonary arrest versus non-cardiac coma, in relation to the end stages of awakening or death.

MATERIAL AND METHODS

The patients that were included in the study were patients who presented to the emergency room with sudden onset of coma or who developed a comatose state in hospital secondary to a medical or neurologic illness.

Twenty one patients were studied prospectively. Thirteen patients went into coma after sustaining cardiac arrest and cerebral hypoxia. Eight patients became comatose secondary to other reasons, such as intracerebral bleeding, head trauma, electric shock, sepsis, and brain tumors (Table 1).

The patients were assessed by one or both authors. Glasgow coma scales (GCS), brain stem auditory evoked responses (BAER), and P300 tests were performed on all the patients, on admission, as detailed below. The patients underwent another neurologic examination, GCS, and P300 testing at day 3 and 21 if he/she survived the coma.

Patients who sustained cardiac arrest ranged from 26–71 years of age with a mean of 59.8 years. All were males except

one female patient. One patient was 26 years old and sustained cardiac arrest secondary to drug intoxication. The duration of the asystole ranged from 5 to 45 minutes.

Patients who sustained coma from causes other than cardiac arrest ranged between 23 and 73 years of age, with a mean of 43 years. Six were males and two were females. Two patients sustained head trauma secondary to motor vehicle accidents, one had an intraventricular tumor causing acute hydrocephalus, one sustained cerebral hemorrhage secondary to uncontrolled hypertension, two had an encephalitis, possibly undiagnosed herpes simplex infection, one sustained an electric shock, and one suffered from septicemia.

The P300 auditory event related potential was performed bedside using a portable EMG apparatus and headphones. The paradigm used was the passive auditory oddball paradigm using binaural stimulation at 1000 Hz for the frequent tones and 2000 Hz for the rare tones presented at 85 decibels. A total of 100 tones were delivered at 1.1/sec with rare tones occurring randomly with a probability of 20 %. Recordings were made from scalp electrodes placed at Cz and Pz referenced to linked A1 and A2. The filter bandpass was 1–40 Hz. Analysis time was 750 msec. Responses with artifact were automatically rejected, and trials were replicated to determine reproducibility. A P300 was determined to be present if a well-defined positive peak occurred, and that in response to rare tones not to frequent tones, irrespective of its latency (De Giorgio et al., 1993).

The study has been funded by the Medical Practice Plan of the Medical Center where the research was performed. Informed consent was received from the nearest of kin.

Table 1: Patients' demographics, diagnosis, GCS and P300 on admission and follow up, and outcome upon discharge.

	Age	Sex	Diagnosis	Duration (minutes)	GCS admission	GCS day 3	GCS day 21	P300 admission	P300 day 3	P300 day 21	Outcome
1	58	M	asystole	30	3	10	9	absent	absent	absent	discharged
2	62	M	asystole		3	3	3	absent	absent	absent	death
3	63	M	asystole	20	6	-	-	absent	-	-	death
4	71	M	asystole	5	3	-	-	absent	-	-	death
5	51	M	asystole	45	5	-	-	absent	-	-	death
6	71	M	asystole	10	6	3	-	absent	absent	-	death
7	69	M	asystole	30	3	-	-	absent	-	-	death
8	61	M	asystole	30	3	3	-	absent	absent	-	death
9	68	M	asystole	10	4	3	-	absent	absent	-	death
10	51	M	asystole	5	3	7	7	absent	absent	absent	discharged
11	58	M	asystole		4	-	-	absent	-	-	death
12	69	F	asystole		3	-	-	absent	absent	-	death
13	26	M	asystole	10	4	6	6	absent	absent	absent	vegetative
14	73	F	hemorrhage		4	-	-	absent	-	-	death
15	73	M	head trauma		7	7	-	232	300	304	discharged
16	26	M	head trauma		4	-	-	absent	-	-	death
17	26	M	electric shock		3	7	7	absent	317	-	discharged
18	23	M	encephalitis		4	12	15	absent	469	380	discharged
19	37	M	tumor		4	5	7	absent	absent	absent	vegetative
20	42	M	sepsis		6	3	-	absent	absent	-	death
21	45	F	encephalitis		6	7	9	615	450	-	discharged

RESULTS

All the patients were admitted to the hospital for treatment. They were followed up by the authors until death in the hospital or discharge. Fourteen patients (66.7 %) died in hospital, five patients (23.9 %) were discharged home alive, and two patients (9.5 %) remained in hospital in a vegetative state.

Patients who sustained a comatose state after cardiopulmonary arrest (13 patients) had their GCS on admission between 3 and 6. All the patients had normal BAERs from both ears. Three out of the 13 patients had an improvement in their GCS from 3 or 4, to 6, 7 and 9. Except these three patients, all the patients died in hospital between 3 and 20 days. The three patients who had an improvement in their GCS were eventually discharged home or to another hospital alive. On follow up one of them had died several months after discharge. None of these 13 patients had a P300 response neither on presentation nor upon follow up.

Patients who sustained coma from non-cardiac causes (8 patients) had their GCS between 3 and 7. All the patients had normal BAERs from both ears. Two of the eight patients who had their GCS on admission of 4, with no improvement in the following days, died 3 days after admission. One patient had a deterioration of his GCS from 6 to 3 and died 16 days after admission. These patients had no P300 response.

The remaining five patients had an improvement of their GCS, in spite of an admission GCS of 3 or 4 in some of them. One patient had his GCS stable at 7 throughout his stay in hospital. One of these patients never had a P300. Two did not have a P300 on admission, but developed a wave at 317 and 380 msec on follow up. One patient had a stable wave with a latency of 232–304 msec. The last patient had a wave at 615 msec., which dropped down to 450 msec, simultaneously with the improvement of his GCS (Figure 1). These patients remained alive in hospital or were discharged home.

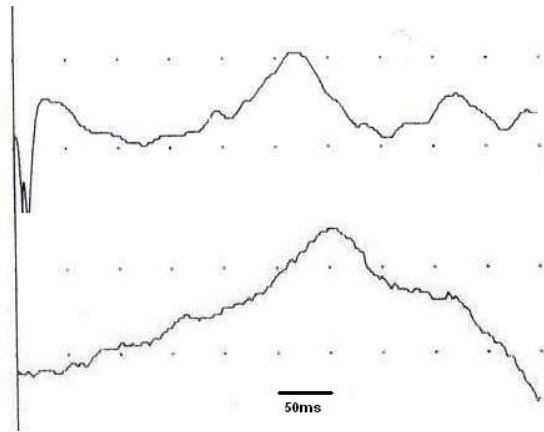


Figure 1: Samples of P300 waves in two patients. Stimulation with frequent and rare tones were applied by headphones to the patient's ears. Recording of the P300 cortical wave from the Cz electrode applied on the scalp. X-axis represents time in milliseconds. Y-axis represents amplitude in microvolts. Positivity upwards.

DISCUSSION

All the patients who sustained a comatose state secondary to cardiac arrest, and thus diffuse cerebral anoxia, never had a P300, neither on admission, nor on follow up. This finding was irrespective of the GCS on admission, which was 3 or 4 in most cases, but even reached 6 in one case. The P300 wave also did not appear in patients with cardiac arrest who had an improvement in their GCS to 9. In fact, the patients who had an improvement in their GCS to 6 or 9 eventually were discharged from hospital alive in spite of their persistently absent P300. Similar findings were reported by De Giorgio et al., who found that the presence of P300 is a good predictor of awakening, but its absence is not a predictor of bad prognosis (De Giorgio et al., 1993). Other authors who studied P300 in non-traumatic coma found that the presence of the P300 wave was associated with awakening, but they did not differentiate the causes of coma between anoxic and non-anoxic. In fact, their patients who did not have a P300 had anoxic causes for their coma (Gott et al., 1991).

P300 is absent in as many as one-sixth of fully conscious, alert cooperative individuals, whether an auditory or visual target

is used (Donchin et al., 1986). Thus, the absence of a P300 response in a comatose patient does not necessarily point to a worse prognosis. Our results concerning patients who develop coma secondary to cardiac arrest seem to agree with the literature, and confirm that there is no role for P300 analysis on admission in patients with cardiac arrest, as this test will not have any prognostic value (O'Mahony et al., 1990; Yingling et al., 1990).

The P300 analysis in patients who become comatosed secondary to causes other than cardiac arrest, such as cerebral hemorrhage, head trauma, or brain tumors has a better prognostic value. Patients who have a P300 wave on admission, irrespective of its value, even above 600 msec, and irrespective of their admission GCS, will eventually survive their coma. Patients who do not have a P300 wave on admission, but develop a wave in the following days, irrespective of its value, will also survive their coma. This condition seems also to be independent of the baseline GCS level, as the 2 patients that fell in this category had a GCS of 3 and 4. Patients who never revealed a P300 wave, neither on admission, nor in the days or weeks that followed did not survive their coma. One patient had a slight improvement in his GCS level from 4 to 7 over 3 weeks, but never had a P300 wave. This patient remained in a vegetative state and was then discharged in this condition from hospital and was lost to follow up.

These results seem to conclude that the existence of a P300 wave on admission or in the days that followed is a good prognostic sign for survival in patients who develop coma from causes other than cardiac arrest. It is worth mentioning that the GCS on presentation did not correlate with prognosis, as patients with a baseline GCS of 3 or 4 ended up dying or surviving the comatosed state. It is the improvement in the value of the GCS or its stability over time at a "good" level, such as 7, that correlated with a good prognosis. In fact, it is the existence or development of a P300 wave which correlated with the improvement of the GCS

and a favorable prognosis in patients who develop coma from non cardiac causes.

Similar findings have been reported in coma patients secondary to severe traumatic brain injury. A positive correlation was found between the presence of a P300 wave and recovery from coma. Nevertheless, the absence of a P300 did not preclude a good prognosis in this form of coma (Greenberg and Ducker, 1982; Doebrich et al., 1986). The P300 could be associated with an automatic orienting of attention towards the stimulus and not just with a nonspecific level of alertness (Mazzini et al., 2001). The abnormality of P300 in patients with brain concussions and its improvement with the clinical amelioration of consciousness further emphasizes the value of P300 as a reflection of cognition (Pratap-Chand et al., 1988). Preservation of the P300 in coma is most likely dependent on the sparing of one or more of the anatomical generators for this potential, mainly the hippocampus, frontal cortex, and parietal cortex (Gott et al., 1991; Kropotov and Ponomarev, 1991).

One can thus say that the P300 has a limited prognostic value for survival when used alone because its presence is a good predictor of awakening, but its absence is not a predictor of bad prognosis, and therefore it must be associated with other neurophysiological tests (SEPs, BAERs, EEG) and clinical evaluation.

In conclusion, attempting to measure a P300 wave in patients who sustain a comatosed state following cardiac arrest is of no use in determining the prognosis for survival. It is better to rely on the direction and degree of change of the GCS and somatosensory evoked potentials. On the other hand, any P300 value on admission, or follow up, in patients who develop coma secondary to a non-cardiac cause, is a good indicator of survival irrespective of the GCS on admission. Even if the absence of P300 in comatosed patients does not have any prognostic value, their presence implies a high probability of conscious recovery.

It is important to point out that this prospective study is limited by the small number of patients in both categories. Neverthe-

less, there seems to be a trend between the causes of coma, clinical evolution, direction of change in the GCS, and the P300. A more extensive study would be necessary to evaluate further the value of P300 in the prognosis of coma.

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