Neurocritical Care

ISSN 1541-6933/05/2:159–164
DOI: 10.1385/Neurocrit. Care 2005;2:159–164

Original Article

Anoxic–Ischemic Encephalopathy:
Clinical and Electrophysiological Associations With Outcome

G. Bryan Young,[1,] Gordon Doig,[2] and Aldo Ragazzoni[3]*

[1]Department of Clinical Neurological Sciences, London Health Sciences Centre, London, Ontario, Canada, [2]Royal North Shore Hospital, New South Wales, Australia, [3]Ospedale S. Maria Nuova, Florence, Italy

Abstract

Introduction: Prognostic determination of patients in coma after resuscitation from cardiac arrest is both common and difficult. We explored clinical and electrophysiological testing to determine their associations with favorable and poor outcomes.

Methods: We studied 75 comatose patients resuscitated from cardiac arrest, excluding those who were brain dead or continuously sedated; none received hypothermia therapy. Clinical examinations were performed on day 1.

Results: The following proportions recovered awareness: 2 of 18 patients with absent pupillary reflexes; 18 of 57 with preserved pupillary reflexes ($p = 0.08$); 2 of 32 with absent corneal reflexes; 16 of 43 with preserved corneal reflexes ($p = 0.001$); 0 of 15 with absent oculovestibular reflexes; and 8 of 29 with preserved oculovestibular reflexes ($p < 0.037$). Purposeful movements were associated with a high probability of recovery, whereas other categories were unfavorable. Other categories of motor response were associated with an increased proportion of those who died without recovering awareness, but each category had some survivors. Somatosensory evoked potentials (SSEPs) were recorded from 47 patients. One of 21 patients with loss of the N20 component survived, compared with survival of 11 of 26 patients in whom it was present ($p = 0.003$). All 5 patients with preserved N70 responses recovered awareness in a subgroup of 33 patients. Sixteen of 22 subjects with mild electroencephalogram (EEG) abnormalities recovered consciousness, compared with the survival of 3 of 50 patients with malignant EEG patterns ($p = 0.0000001$). Combining SSEP with EEG findings produced even greater predictive value.

Conclusion: It seems unlikely that any single test will prove to have 100% predictive value for outcome; further studies combining clinical, EEG, and SSEP testing are warranted.

Key Words: EEG; SSEP; cardiac arrest; prognosis; anoxic–ischemic encephalopathy; evoked responses.

(Neurocrit. Care 2005;2:159–164)

***Correspondence and reprint requests to:**

G. Bryan Young
Department of Clinical Neurological Sciences, London Health Sciences Centre, 339 Windermere Road, London, Ontario, Canada N6A 5A5.
E-mail: bryan.young@lhsc.on.ca

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Introduction

Anoxic–ischemic encephalopathy resulting from cardiac arrest is the third leading cause of coma requiring intensive care (following trauma and drug overdose *[1]*). Of comatose survivors who received cardiopulmonary resuscitation (CPR), only about 1 in 4 survives to discharge, only 1 in 5 is able to return home, and fewer than 1 in 10 returns to former status, employability, and independence *(1)*. It is desirable to have reliable predictors of both favorable and unfavorable outcomes for resource allocation, management, and counseling of family members. Clinical, electroencephalogram (EEG), somatosensory evoked potential (SSEP), and biochemical studies have correlated outcomes in patients after cardiac arrest, but few have examined these variables prospectively in the same patients while ensuring that

Table 1
EEG Classification System

Category	*Subcategory*
I. Delta/theta > 50% of recording (not theta coma)	A. With reactivity B. Without reactivity
II. Triphasic waves	
III. Burst-suppression pattern	A. With epileptiform activity B. Without epileptiform activity
IV. Alpha/theta/spindle pattern coma (no reactivity)	
V. Suppression (generalized)	A. <20, but >10 μV B. < 10 μV

patients survived for at least several days to prevent premature "self-fulfilling prophesies" *(2–8)*.

SSEP results serve as a reliable predictor of poor outcome: bilateral abolition of N20 indicates with almost 100% specificity that the patient will not recover *(9)*. However, preservation of the N20 response does not guarantee awakening; greater than 40% of these patients do not recover conscious awareness *(2,10,11)*. However, there is some indication that long-latency SSEPs reliably provide early identification of patients with favorable outcome, presumably because they provide a better evaluation of cortical integrity than short-latency responses *(12)*. Surprisingly, no study has been conducted to confirm these results, and most researchers have focused on early SSEP components.

We assessed patients in coma following CPR with clinical, EEG, and SSEP testing between 1 and 3 days from restoration of spontaneous circulation and correlated these with neurological outcome. Because our study was aimed at identifying robust predictors of good and poor outcomes, we studied SSEPs up to 200 milliseconds poststimulus in a smaller cohort of our subjects (the 33 patients collected in Florence).

Methods

The project involved the London Health Sciences Centre and Ospedale S. Maria Nuova in Florence, Italy. Patients were collected prospectively by daily surveillance of the intensive care units (ICUs) for comatose, ventilated patients who had been resuscitated from cardiac arrest. Patients with any of the following characteristics were excluded: brain death, age less than 16 years, confounders such as coincident head injury, or the continuous infusion of anesthetic drugs (e.g., midazolam, propofol, or pentobarbital) that could not be discontinued to allow for assessment. Data booklets were maintained for each patient, with the following data later entered into an Excel spreadsheet: age; sex; demographics; Acute Physiology and Chronic Health Evaluation (APACHE) II subset scores; site of cardiac arrest (in or out of hospital); estimated duration from arrest to restoration of circulation; type of arrhythmia; cause of arrest; clinical features on examination at day 1 (including pupillary light reflex, oculocephalic or oculovestibular reflex, corneal reflex, pharyngeal reflex, and motor response [as in Glasgow Coma Scale Score determination]); presence or absence of myoclonus; classification of myoclonus (bilateral, facial, multifocal); concomitant drugs; EEG classification (using classification from ref. *13*; Table 1) between 24 and 48 hours from the time of cardiac arrest; SSEP testing on days 1 and 3, tabulating N20 and N70 responses; and outcomes (death in hospital or status at 3 months using Glasgow Outcome Scale [GOS], with homes of survivors phoned by a trained nurse using a standardized questionnaire).

SSEPs were performed with median nerve stimulation at the wrist. Square-wave electrical pulses were delivered for 0.2 millisecond at 0.5 Hz with intensity sufficient to produce a moderate twitch of the thenar muscles. SSEPs were recorded with a four-channel montage. Stainless steel needle electrodes were placed at CP3, FC3, CP4 or CP4, FC4, CP3 positions of the 10-10 System and referred to the mastoid ipsilateral to the stimulated side *(14)*. For the fourth channel, an electrode was placed at the ipsilateral Erb's point and referred to the contralateral Erb's point. Amplifier bandpass were 1 to 1500 Hz (–6 dB), and signals were digitized with a sampling rate of 512 points every epoch and averaged for 200 milliseconds after the stimulus. At least two averages of 600 responses were acquired from each arm to check for reproducibility. SSEPs in patients were compared with values collected in 15 normal subjects (age range: 22–74 years; seven females) *(15)*.

In normal adult subjects, stimulation of the median nerve evoked a series of negative and positive cortical peaks, each with a specific modal latency and scalp distribution *(16–18)*. In our normal sample, parietal electrodes recorded an earlier negativity (N20: mean latency, 19.4 millisecond; mean amplitude, 2.5 μV) and a later positivity (P27: 27.4 millisecond, 4.3 μV). A positive (P20: 19.7 millisecond) and a negative peak (N30: 28.7 millisecond) are observed at the frontal areas. Parietofrontal N20-P20 and P27-N30 represent opposite peaks of a tangential dipole across the central fissure *(17)*. Central electrodes detect a positive (P22: 22.3 millisecond, 2.0 μV) peak followed by a negative (N33: 33.8 millisecond) peak, which represent perirolandic components generated by a radial dipole located in the crown of the precentral/postcentral gyrus *(19,20)*. A positive (P45: 45.3 millisecond, 4.5 μV) peak follows with a central scalp distribution, and a later negative component is recorded over the central-parietal area (N60: 59.8 millisecond, 5.2 μV). By convention, the short-latency potentials include all SSEPs occurring within the first 40 millisecond after median nerve stimulation, whereas the long-latency potentials are those recorded with latencies greater than 40 millisecond and include components P45 and N60 *(17)*. We measured latencies and amplitudes from the preceding peak of opposite polarity and central conduction time (CCT)—that is, the interval between P14 and N20 *(21)*.

To allow a global analysis of the cortical-evoked responses, SSEPs were classified in four categories according to the pattern of abnormalities: category (1), in which all the short- and long-latency components from N20 to N60 were detectable; category (2), persistence of only the short-latency components (N20, P22, P27, N30, and N33); category (3), persistence of only N20; category (4) bilateral absence of all cortical responses. (An asymmetry of SSEP over the two hemispheres was not observed in our patients.)

EEGs were performed with commercial digital EEG machines with 18 channels using both bipolar and referential montages, the 10 to 20 system of electrode placement, and at least 20 minutes of recording *(7)*. Stimulation (nailbed

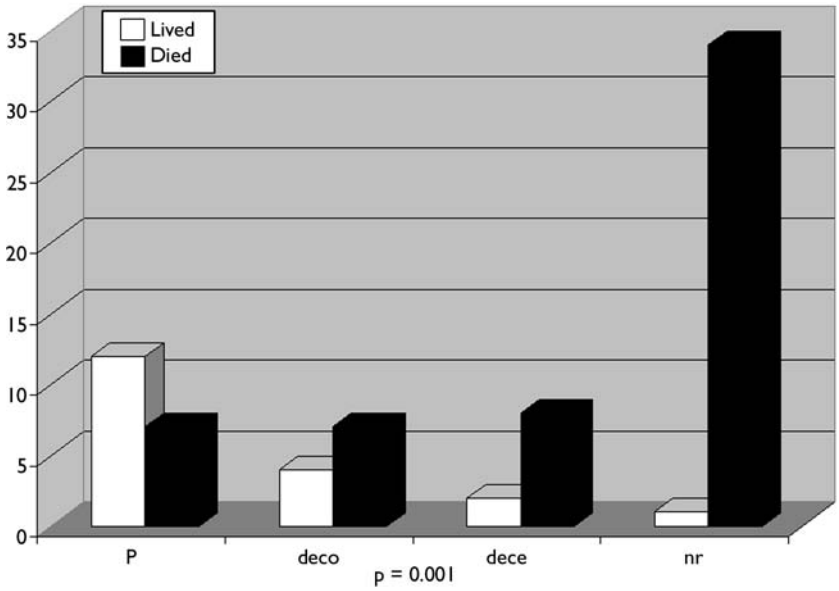

Fig. 1. P, purposeful movement; deco, decorticate posturing; dece, decerebrate posturing; nr, no response.

pressure, passive eye opening, nasal tickle, and shouting in the ear) was routinely performed.

Statistics were preformed using the SAS software package; Chi-Square or Fisher's Exact Test was used for categorical variables in comparing those who recovered awareness versus those who died without recovering awareness. Logistical regression analysis was performed on selected tests when there were multiple categories within the test.

Table 2
SSEP and Outcome

	Lived	*Died*
N20 present	15	11
N20 absent	1	20
Sensitivity = 0.57, specificity = 0.92. $p = 0.003$		

Results

Our study group comprised 75 patients (46 men and 29 women) who ranged in age from 21 to 85 years (mean: 66 years; standard deviation [SD]: 13 years). Our study anteceded hypothermia protocols, and none received this therapy *(22,23)*.The average duration of cardiac arrest was 18 minutes (SD: 13 minutes). Fifty-seven (76%) of the cardiac arrests occurred outside of hospital. Forty-four (59%) of the patients who experienced cardiac arrest had ventricular fibrillation, 19 (25%) were asystolic, 6 (8%) had pulseless electrical activity, 4 (5%) showed ventricular tachycardia, and 1.3%) showed varied patterns. Cardiac arrest was related to heart disease in 70 (93%) of the incidences and to pulmonary and other conditions in the remainder.

Outcomes were grouped into two categories: those who died without recovery of consciousness (none remained in a vegetative state beyond 2 months) and those who recovered awareness. There were 2 survivors of the 18 patients who had absent pupillary reflexes on day 1, compared with 18 survivors of the 57 patients in whom pupillary reflexes were preserved ($p = 0.08$). Two of the 32 patients with absent corneal reflexes survived, compared with 17 of 43 patients in whom corneal reflexes were present ($p = 0.001$). There were no survivors of the 15 patients with absent oculovestibular reflexes, compared with 8 of the 29 patients in whom oculovestibular reflexes were present ($p < 0.037$). Figure 1 demonstrates the association of motor response and outcome. Note that purposeful movements are associated with a high probability of recovery, compared to other categories of motor response. The other categories of motor response were associated with an increased proportion of those who died without recovering awareness. Nearly all those with absent motor response died. Bilaterally synchronous myoclonus occurred in 19 patients, all of whom died without recovering awareness ($p = 0.08$).

For logistical reasons (technologist availability on weekends), it was not possible to perform SSEP studies on all patients. The N20 response of the SSEP (Table 2) was absent in 20 patients, 1 of whom recovered awareness; of the 26 patients in whom N20 response of the SSEP was present, 42% died ($p = 0.003$).

In the subgroup of 33 patients collected in Florence, we examined short-latency components following N20 (P22, P27, N30, N33) and the long-latency components P45 and N70. None of the 16 patients in SSEP category 4 (absent cortical responses) recovered consciousness. Three of the six patients in category 3 (persistence of component N20 only) awakened, whereas three never regained awareness. Of the six patients in SSEP category 2 (persistence of all the short-latency components: N20, P22, P27, N30, N33), one patient died, one became vegetative, and four had a favorable evolution and awakened.

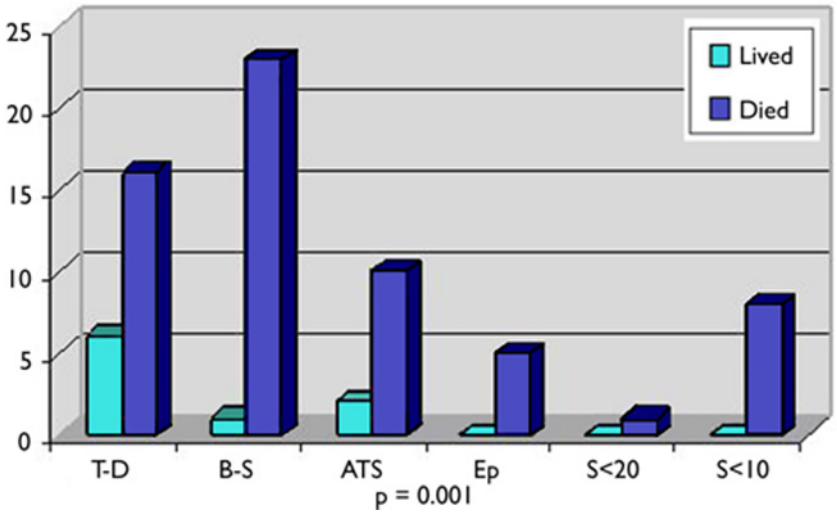

Fig. 2. EEG categories and associated survival.

Note: See Table 1. T-D, theta/delta(Category I); B-S, burst suppression (Category III); ATS, Alpha-theta-spindle (Category IV); S < 20, suppression (Category V.B.).

Table 3
EEG Classification and Outcome

EEG Classification	*Alive*	*Dead*
I A or B	16	6
Others	3	47

Sensitivity = 0.89, specificity = 0.84, Likelihood ratio = 5.61 $p = 0.0000001$.

Table 4
SSEPs and EEGs
N20 Present

EEG Category	*Lived*	*Died*
1A and B	10	4
Others	10	14

Sensitivity 0.78, Specificity 0.90, Likelihood Ratio = 8.56

N20 Absent

EEG Category	*Lived*	*Died*
1A and B	1	0
Others	0	20

Sensitivity 1.0, Specificity 0, Likelihood Ratio 2.95.

All five patients in SSEP category 1 (persistence of long-latency components P45 and N70) made a good recovery.

EEG categorization created groups with such small numbers that analysis was problematic (Fig. 2). However, it is noteworthy that there were no survivors of those few who had generalized epileptiform discharges or who had suppression with voltage less than 20 μV. There were some survivors in those with predominantly Δ-activity, α/− pattern coma, or a generalized burst-suppression pattern. In Table 3, categories 1A and 1B were considered together with a mortality of 27%, compared with 94% mortality when the other groups were combined ($p = 0.0000001$; likelihood ratio: 34.6).

Table 4 shows the value of combining SSEP and EEG data. When the N20 is absent and the EEG shows a "malignant" pattern (other than Classification 1 A or B), no patient recovered awareness.

Discussion

Our study has several limitations: small numbers in some categories, lack of testing of some patients for logistical reasons, differences in SSEP capacity between centers, and lack of availability of biochemical testing for prognosis. Nonetheless, we produced interesting findings and suggestions for further research. Although the absence of various cranial nerve reflexes beyond day 1 (as found in our study and those of others) is strongly supportive of lack of neurological recovery, such reflexes are most often regained, even in those who fare badly. The use of such reflexes to assess outcome is based on the inference that the cerebral cortex is usually more vulnerable to anoxic–ischemic insult than brain stem nuclei. However, they do not provide a direct assessment of thalamo-cortical function. It is interesting that even the loss of the pupillary light reflex by day 1 is not always predictive of a hopeless outcome.

Compared with the clinical examination, electrophysiological tests provide a more direct assessment of cerebral cortical and/or integrated cerebral cortical-thalamic function. Loss of the N20 response to median nerve stimulation had the highest positive predictive value of any available test *(9)*. The N20 SSEP result is specific, but not very sensitive, for poor outcome. However, we found that the analysis of SSEP components following N20 markedly improved the identification of those patients who recovered awareness (GOS >2). Although this observation is based on results obtained in a limited number of patients ($n = 33$), it is in agreement with the results of Madl et al. *(12)*, who reported that later SSEP components (especially the N70) possess a 100% ability to predict both favorable and poor outcome. Our study included a detailed analysis of

all the tangential (N20-P20, P27-N30) and perirolandic radial (P22, N33) components, which are best identified by the use of a parietal and a frontal electrode. It is apparent that in addition to N20, other short-latency responses and long-latency SSEPs significantly improved the SSEP prognostic power. If we had examined only the short-latency component N20, then the positive predictive value of SSEPs for prediction of recovery would have been 70%. Adding the assessment of middle- and long-latency SSEP components, the positive predictive value for prognosis of recovery increased to 82%. When all the early SSEP components are detectable, a good outcome can be predicted with 66% accuracy, and the presence of P45 and N70 was consistently associated with recovery of conscious awareness.

The N20-P20 and P27-N30 complexes arise from the posterior bank of the central fissure, area 3b, whereas the perirolandic components P22 and N33 are generated at the crown of the precentral (area 4) and/or postcentral (area 1) gyrus *(10,24,25)*. Components P45 and N60 take origin from activation of cerebral areas, other than the primary somatosensory (SI) cortex. P45 arises from the perirolandic region and N60 is generated in/near the contralateral second sensory area (SII) area *(26)*. The preservation of these components in patients with anoxic coma confirms the functional integrity of larger cortical areas better than that explored by N20 alone. As we have shown, these findings are valid for the first 24 to 48 hours from the arrest.

In our series, those with EEGs showing generalized epileptiform activity or suppression of less than 20μV have a stronger association with poor outcome than do some other patterns (e.g., α/τ-coma or burst-suppression pattern). However, numbers in these categories are too small and confidence intervals are too large to permit any definitive statements. Our observation holds promise and may prove that the EEG is more prognostically useful than the previous lumping of "malignant" categories. Larger numbers are clearly needed. Serial or continuous raw or trended EEGs may allow for more definitive prognosis, so long as confounders such as sepsis or sedation are not present *(27)*. The pattern of evolution over several days can be reliably predictive for at least some patterns (e.g., α/τ-coma pattern). Quantitative techniques may provide additional prognostic information, but more study in humans is needed *(28,29)*. Although our patient numbers did not allow us to combine variables or to perform multivariate analyses, this direction may yield more robust predictors of outcome *(30,31)*.

Our findings demonstrate the value of electrophysiological tests in addition to clinical evaluation in establishing the prognosis of comatose survivors of cardiac arrest. However, we caution that both EEG and long-latency potentials are sensitive to recording conditions and can be substantially reduced by sedative drugs. Therefore, great care has to be taken to avoid or to make allowances for such drugs, which are often used in patients in the ICU. The use of ultra-short acting agents that are without active metabolites and can be discontinued for recording purposes is suggested. Combining EEG with SSEPs (and possibly including clinical and biochemical data) will likely produce greater predictive power.

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