Amplitude-Integrated Electroencephalography Predicts Outcome in Patients with Coma After Acute Brain Injury

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Abstract Prognostication of coma patients after brain injury is important, yet challenging. In this study, we evaluated the predictive value of amplitude-integrated electroencephalography (aEEG) for neurological outcomes in coma patients. From January 2013 to January 2016, 128 coma patients after acute brain injury were prospectively enrolled and monitored with aEEG. The 6-month neurological outcome was evaluated using the Cerebral Performance Category Scale. aEEG monitoring commenced at a median of 7.5 days after coma onset. Continuous normal voltage predicted a good 6-month neurological outcome with a sensitivity of 93.6% and specificity of 85.2%. In contrast, continuous extremely low voltage, burst-suppression, or a flat tracing was correlated with poor 6-month neurological outcome with a sensitivity of 76.5% and specificity of 100%. In conclusion, aEEG is a promising predictor of 6-month neurological outcome for coma patients after acute brain injury.

Keywords Amplitude-integrated electroencephalography · Coma · Acute brain injury · Outcome

Introduction

Recent progress in intensive care medicine has allowed a large number of patients to survive acute brain injury [1, 2]. However, patients surviving brain injury usually become comatose [3]. Coma is a transient state and the natural recovery process varies substantially across patients. Some patients recover within the first days after injury, some progress into wakeful unawareness (vegetative state), whereas others permanently lose all brainstem function (brain death) [4]. Thus, the prognosis of these patients is important for both clinicians and families, especially with regard to the planning of treatment and rehabilitation [5].

Many researchers have sought reliable outcome predictors for coma. Clinical examinations such as the Glasgow Coma Scale (GCS) are often used, but they lack definite validation [6]. Functional neuroimaging and biochemical tests have shown some predictive value [7], but their use is restricted in the neurological intensive care unit (NICU) due to methodological limitations [7–11]. Electroencephalography (EEG) is a widely used tool for the detection of seizure activity [12], and has also been reported to predict outcomes in coma patients [13, 14]. However, its use has been hindered by practical difficulties, including the requirement for equipment and specialized physicians to record and interpret the EEG [6, 15, 16]. Therefore, a simpler and more convenient method of prognostication is needed. The amplitude-integrated EEG (aEEG) is a method for the continuous monitoring of brain function [17]. It is simple to perform, allows continuous bedside monitoring, and is easily interpreted. aEEG has been widely used in neonatal ICUs for evaluating brain injury in newborns with hypoxic ischemic encephalopathy, identifying infants suitable for inclusion in cooling trials, and predicting outcomes in this group [18–23]. In recent

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years, it has also been reported that the aEEG patterns correlate with neurological outcome in hypothermia-treated adult patients with coma after cardiac arrest [15, 24–27]. Nevertheless, whether aEEG predicts the outcome of patients in coma due to other causes such as traumatic brain injury (TBI) and stroke remains unknown. Therefore, in the present study we aimed to determine the prognostic value of aEEG for neurological outcome in coma patients after acute brain injury.

Materials and Methods

Study Design and Protocol Approval

We conducted this prospective observational study in the NICU of Renji Hospital affiliated with Shanghai Jiao Tong University School of Medicine. The study protocol was approved by the Ethics Committee of Renji Hospital. Written informed consent was given by the patients' next of kin.

Patients

From January 2013 to January 2016, consecutive patients with coma after acute brain injury admitted to the NICU were screened for eligibility. The inclusion criteria were: (1) age of 18 years or older; (2) a clear history of acute brain injury, including TBI, stroke, subarachnoid hemorrhage, or cardiac arrest; (3) a GCS score of ≤ 8 on admission; and (4) a prolonged state of acute coma (> 7 days). The exclusion criteria were: (1) pre-existing neurological disorders or impairment of consciousness up to the time of the injury; (2) overwhelming concurrent hepatic or metabolic encephalopathy; (3) co-existing systemic diseases and a reduced life expectancy; and (4) a diagnosis of brain death on admission.

aEEG Monitoring and Analysis

All patients were monitored with aEEG 7 days after coma onset using the NicoletOne Monitor (Natus Neurology Inc., Galway, Ireland). The scalp was cleaned with Nuprep® gel (Weaver and Co., Aurora, CO), then 6-mm disk electrodes were placed at F3, F4, C3, C4, P3, P4, T3, T4, O1, and O2 according to the international 10–20 EEG system. Elefix paste (Nihon Khoden, Tokyo, Japan) was used to maintain a low impedance (< 5 k Ω). aEEG was monitored for 6 h–12 h in each patient. If sedative drugs were used, they were withdrawn > 6 h before the aEEG recording. The raw EEG data were processed and time-compressed, then displayed on the screen at a speed of 6 cm/h. Data were considered acceptable for analysis based on the following criteria: an

absence of movement or electrocardiographic artifact on the raw trace and an absence of interference from other electrical devices. Meanwhile, the GCS scores of patients were also assessed at the time of aEEG recording, at least 6 h after interruption of sedation. Therefore, the GCS score measured was reliable.

Two investigators blinded to the patients' identity and clinical status visually examined the aEEG traces. The raw EEG data were also inspected to verify aEEG assessment. The aEEG background patterns were classified into five types (Fig. 1) according to the modified criteria of Hellström-Westas *et al.* and Toet *et al.* [20, 28].

Flat tracing (FT): continuous low-voltage pattern, upper margin < 5 μ V;

Continuous extremely low voltage (CLV): continuous low-voltage pattern, upper margin < 10 μ V and lower margin < 5 μ V;

Burst suppression (BS): discontinuous pattern, with periods of very low voltage intermixed with high amplitude, lower margin at 0 μ V–1 μ V constantly and a burst amplitude > 25 μ V;

Discontinuous normal voltage (DNV): discontinuous pattern, upper margin > 10 μ V and lower margin < 5 μ V;

Continuous normal voltage (CNV): continuous pattern, lower margin 5 μ V–10 μ V and upper margin 10 μ V–50 μ V.

The classified aEEG data were then subdivided into unfavorable (CLV, BS, or FT), intermediate (DNV), and favorable patterns (CNV) [29, 30].

Treatment Protocol

All patients received standard intensive care in accordance with the existing guidelines, including mechanical ventilation, intracranial hypertension management, nutritional support, and thrombo-embolic prophylaxis. After discharge from the NICU, all patients were transferred to the Rehabilitation Department.

Outcome Assessment

The outcomes were assessed *via* out-patient follow-up or telephone interview by investigators who were blinded to the aEEG patterns. The neurological outcome was assessed at 6 months using the 5-point Glasgow-Pittsburgh Cerebral Performance Category (CPC) scale [10]. The scale points were as follows: CPC1, normal or minor disability, returning to normal living; CPC2, moderate disability, able to lead an independent daily life; CPC3, severe disability, unable to lead an independent daily life; CPC4, coma or vegetative state; CPC5, brain death. Outcomes were classified as good with a CPC of 1–2, or poor with a CPC of 3–5 [7].

Fig. 1 Classification of aEEG patterns. **A** Continuous normal voltage (CNV). **B** Continuous extremely low voltage (CLV). **C** Discontinuous normal voltage (DNV). **D** Burst-suppression (BS). **E** Flat tracing (FT).

Statistical Analysis

SPSS version 17.0 (SPSS Inc., Chicago, IL) and MedCalc version 11.5.1 (MedCalc Software, Ostend, Belgium) were used for statistical analysis. Continuous variables are presented as the mean and standard deviation or the median with interquartile range. Continuous variables were analyzed by Student's *t*-test, or by the Mann-Whitney U-test if non-normally distributed. Categorical variables are reported as numbers and percentages. The χ^2 test was used to analyze categorical data. To compare the GCS scores between different aEEG patterns, one-way analysis of variance was applied followed by a *post hoc* test with Least Significant Difference test correction. The sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of aEEG patterns and GCS scores were calculated. To compare the prognostic value of GCS and aEEG, the area under the receiver operator characteristic (ROC) curve was assessed. Statistical significance was determined at a $P < 0.05$.

Results

Patient Characteristics

From January 2013 to January 2016, 179 patients with coma after acute brain injury were screened for eligibility. Thirty-six patients were excluded based on the exclusion

criteria. Of the 143 eligible patients, 11 were lost to follow-up and 4 died of non-neurological diseases. Thus, 128 patients were included in the final data set. The participant recruitment and follow-up are summarized in Figure 2. The characteristics of the participants are shown in Table 1. The mean age of the study population was 48.3 ± 11.3 years, and 85 patients (66.4%) were male.

Fig. 2 Flowchart of the recruitment and follow-up of patients.

Table 1 Patient characteristics.

Characteristic	Value
Number of patients	128
Sex, <i>n</i> (%)	
Male	85 (66.4)
Female	35 (33.6)
Age, years, mean $\pm$ SD	48.3 $\pm$ 11.3
Causes of coma, <i>n</i> (%)	
Traumatic brain injury	65 (50.8)
Stroke/subarachnoid hemorrhage	41 (32.0)
Cardiac arrest	22 (17.2)
GCS at the time of aEEG recording, mean $\pm$ SD	6.1 $\pm$ 1.4
Time from coma onset to aEEG recording, days, median (IQR)	7.5 (7–14)
Duration of aEEG monitoring, h, median (IQR)	8.5 (6–12)
aEEG, <i>n</i> (%)	
CNV	56 (43.8)
DNV	10 (7.8)
CLV	41 (32.0)
BS	3 (2.3)
FT	18 (14.1)
Seizure activity, <i>n</i> (%)	9 (7.0%)

aEEG, amplitude-integrated electroencephalogram; BS, burst-suppression; CLV, continuous extremely low voltage; CNV, continuous normal voltage; DNV, discontinuous normal voltage; FT, flat tracing; GCS, Glasgow coma scale; IQR, interquartile range.

The mean GCS score on admission was 6.1 ± 1.4 . The main cause of coma was TBI ($n = 65$, 50.8%), followed by stroke or subarachnoid hemorrhage ($n = 41$, 32.0%) and cardiac arrest ($n = 22$, 17.2%). aEEG monitoring commenced at a median time of 7.5 days [interquartile range (IQR) 7–14] after the onset of coma. The median duration of aEEG monitoring was 8.5 h (IQR 6–12). aEEG monitoring was technically successful in all patients, and no significant change was observed in the aEEG patterns during the monitoring period.

aEEG Patterns and Seizure Identification

Fifty-six patients (43.8%) displayed a favorable pattern (CNV), 10 (7.8%) exhibited an intermediate pattern (DNV), and 62 (48.4%) displayed unfavorable patterns (CLV, FT, or BS). Single events of electrical seizure activity were identified in 9 (7.0%) patients, 6 of whom presented a CLV pattern and 3 presented an FT pattern. No status epilepticus was observed in the study population.

Relationships Between aEEG Patterns and GCS Scores at the Time of aEEG Recording

The GCS score of the favorable pattern (CNV) group was higher than that of those with the unfavorable patterns CLV, BS and FT ($P < 0.001$). The GCS score of the

intermediate pattern (DNV) group was higher than those of the BS and FT groups ($P < 0.001$). No significant difference was found between the groups with the favorable (CNV) and intermediate patterns (DNV) ($P = 0.064$) (Table 2).

aEEG Patterns and 6-Month Neurological Outcome

At the 6-month follow-up, 47 patients exhibited a good neurological outcome and 81 a poor neurological outcome (Table 2). Of the 56 patients with a favorable aEEG pattern (CNV), 44 (78.6%) had a good 6-month neurological outcome. The favorable pattern had a PPV of 78.6% and an NPV of 95.8% for predicting good neurological outcome (sensitivity and specificity of 93.6% and 85.2%, respectively). Sixty-two patients had an unfavorable aEEG pattern (CLV, BS, or FT), and all had a poor neurological outcome at the 6-month follow-up. The presence of unfavorable patterns was strongly indicative of a poor 6-month neurological outcome, with a PPV of 100.0% and an NPV of 71.2% (sensitivity of 76.5% and specificity of 100%) (Table 3). Of the 10 patients with an intermediate aEEG pattern (DNV), 3 had a good outcome and 7 a poor outcome at 6-month follow up. The intermediate pattern predicted a good outcome with a sensitivity of 6.4% and specificity of 91.4%, and predicted a poor outcome with a sensitivity of 8.6% and specificity of 91.4%.

Table 2 GCS at the time of aEEG recording and 6-month neurological outcomes.

aEEG	Number	GCS (mean $\pm$ SD)	Good outcome (CPC 1–2)	Poor outcome (CPC 3–5)
CNV	56	7.1 $\pm$ 0.96	44	12
DNV	10	6.5 $\pm$ 1.08	3	7
CLV	41	5.6 $\pm$ 0.95	0	41
BS	3	3.7 $\pm$ 0.58	0	3
FT	18	4.3 $\pm$ 1.07	0	18

aEEG, amplitude-integrated electroencephalogram; BS, burst-suppression; CLV, continuous extremely low voltage; CNV, continuous normal voltage; CPC, cerebral performance category; DNV, discontinuous normal voltage; FT, flat tracing; GCS, Glasgow coma scale.

Table 3 Predictive values of aEEG patterns and GCS for neurological outcomes of coma patients.

aEEG	Prediction of outcome	Sensitivity (95% CI)	Specificity (95% CI)	Positive Predictive Value (95% CI)	Negative Predictive Value (95% CI)
CNV	Good	93.6 (82.5–98.7)	85.2 (75.6–92.1)	78.6 (65.6–88.4)	95.8 (88.2–99.1)
CLV, BS, FT	Poor	76.5 (65.8–85.2)	100.0 (92.5–100.0)	100.0 (94.2–100.0)	71.2 (58.7–81.2)
DNV	Good	6.4 (1.3–17.5)	91.4 (83.0–96.5)	30.0 (5.9–67.2)	62.7 (53.3–71.4)
DNV	Poor	8.6 (3.5–17.0)	93.6 (82.5–98.7)	70.0 (32.8–94.1)	37.3 (28.6–46.7)
GCS (7–8)	Good	63.8 (48.5–77.3)	71.6 (60.5–81.1)	56.6 (42.3–70.2)	77.3 (66.2–86.2)
GCS (3–6)	Poor	71.6 (60.5–81.1)	63.8 (48.5–77.3)	77.3 (66.2–86.2)	56.6 (42.3–70.2)

aEEG, amplitude-integrated electroencephalogram; BS, burst-suppression; CI, confidence interval; CLV, continuous extremely low voltage; CNV, continuous normal voltage; DNV, discontinuous normal voltage; FT, flat tracing; GCS, Glasgow coma scale.

The aEEG patterns and 6-month neurological outcomes based on different etiologies are shown in Table 4. The favorable aEEG pattern (CNV) predicted a good neurological outcome with a PPV of 83.3% and an NPV of 94.3% in TBI-induced coma patients, a PPV of 77.8% and an NPV of 100.0% in stroke or subarachnoid hemorrhage patients, and a PPV of 62.5% and an NPV of 92.9% in cardiac arrest patients. The unfavorable aEEG patterns (CLV, BS, and FT) indicated a poor neurological outcome with a PPV of 100.0% and an NPV of 75.0% in TBI patients, a PPV of 100.0% and an NPV of 66.7% in stroke or subarachnoid hemorrhage patients, and a PPV of 100.0% and an NPV of 66.7% in cardiac arrest patients.

Prognostic Values of aEEG and GCS

A GCS of 7–8 predicted a good neurological outcome with a PPV of 56.6% and an NPV of 77.3% (sensitivity and specificity of 63.8% and 71.6%, respectively). A GCS of 3–6 predicted a poor neurological outcome with a PPV of 77.3% and an NPV of 56.6% (sensitivity and specificity of 71.6% and 63.8%). The ROC curves of aEEG and GCS are shown in Figure 3. The area under the curve (AUC) showed that aEEG (0.918; 0.857–0.959) was superior to GCS (0.711; 0.624–0.788) in predicting outcomes ($P < 0.001$).

Table 4 aEEG patterns and neurological outcomes for different etiologies.

Etiologies	CNV	DNV	CLV, BS, FT	Good outcome	Poor outcome
Traumatic brain injury	30	6	29	27	28
Stroke/Subarachnoid hemorrhage	18	3	20	14	27
Cardiac arrest	8	1	13	6	16

CNV, continuous normal voltage; DNV, discontinuous normal voltage; CLV, continuous extremely low voltage; BS, burst-suppression; FT, flat tracing.

Fig. 3 Receiver operator characteristic (ROC) curves showing the accuracy of outcome prediction by GCS and aEEG. The ordinate shows the test sensitivity, with a range of 0–100%; the abscissa shows the percentage of false-positive results (1-specificity). An area under the ROC curve (AUC) of 1.0 is characteristic of an ideal test, whereas an AUC of ≤ 0.5 indicates a test with no predictive value. aEEG, amplitude-integrated electroencephalogram; GCS, Glasgow coma scale; CI, confidence interval.

Discussion

In the present study, we evaluated the prognostic value of aEEG in patients with coma after acute brain injury. Our data demonstrated that a favorable aEEG pattern (CNV) was associated with a good 6-month neurological outcome with a sensitivity of 93.6% and specificity of 85.2%. An unfavorable aEEG pattern (CLV, BS, or FT) was indicative of a poor 6-month neurological outcome with sensitivity and specificity of 76.5% and 100%. However, the intermediate pattern (DNV) showed limited predictive value for both good and poor outcomes.

Our results are largely in accord with previous reports that aEEG background patterns correlated with the neurological outcomes of adult patients who were in a coma after cardiac arrest and treated with hypothermia [15, 25–27, 31]. aEEG has been widely used for the prognosis of neonates with hypoxic-ischemic encephalopathy [21–23, 32]. The predictive value of aEEG in adult patients was first evaluated by Rundgren *et al.* in coma patients following cardiac arrest. In that study, aEEG was monitored at a median time of 8 h after cardiac arrest, and they found that an initial continuous aEEG pattern and the return to a continuous pattern at normothermia correlated with a higher rate of survival and better recovery of consciousness. However, an FT, BS, or status epilepticus

aEEG was strongly predictive of an unfavorable outcome [15, 26]. Then the prognostic value of aEEG for cardiac arrest patients treated with hypothermia was confirmed by further studies by Oh *et al.* and Sugiyama *et al.* They not only demonstrated that BS and status epilepticus were correlated with a poor outcome, but also found that the recovery time of a continuous normal pattern was a predictor of outcome. Recovery of a continuous normal pattern within 24 h predicted a good neurological outcome, and delayed recovery of a normal aEEG pattern indicated a poor outcome [25, 27, 31].

A major difference between previous studies and this study was the type of patients included. Previous studies only enrolled patients with coma after cardiac arrest, while in our study, 128 coma patients with different etiologies were included. About fifty percent of them were caused by TBI and 32% were affected by stroke or subarachnoid hemorrhage. It is known that the type and severity of brain injury largely depend on their causes, and the pathophysiological processes of etiologically diverse patients are different [13]. Evidence has shown that the most common pathological substrate of traumatic coma is diffuse axonal injury, followed by ischemic and hemorrhagic lesions [33, 34]. In patients with non-traumatic brain injury, lesions in the neocortex and in subcortical structures are the main pathological substrate, and the predictive value of aEEG for cardiac arrest patients may not apply to patients in coma due to other causes. Therefore, we further analyzed the aEEG patterns and neurological outcomes according to the etiology of coma. We found that a favorable aEEG pattern predicted a good neurological outcome well in all coma patients of different etiologies, while unfavorable aEEG patterns were correlated with a poor neurological outcome in the etiologically varied coma patients. Thus our results not only confirmed the value of aEEG for outcome prediction in comatose patients after cardiac arrest, but also demonstrated that aEEG is a promising predictor of outcome for coma patients of varied etiologies including TBI and stroke.

The GCS is an easy-to-use tool for evaluating neurological function in comatose patients, particularly in the acute stages of TBI or illness [35]. It is the most commonly used method of neurological examination, and has also shown some predictive value for the outcome in coma patients. However, GCS evaluation can be affected by various factors in the intensive care setting [36]. In addition, a higher GCS score does not always indicate a better outcome [6]. In this study, a GCS score of 7–8 predicted a good neurological outcome with a sensitivity and specificity of 63.8% and 71.6%, while a GCS score of 3–6 predicted a poor neurological outcome with a sensitivity of 71.6% and specificity of 63.8%; these were lower than the values for aEEG. Moreover, the AUC

demonstrated that aEEG (0.918; 0.857–0.959) was superior to the GCS (0.711; 0.624–0.788) in predicting outcome. The AUC of GCS in this study is similar to that of Kang *et al.* in a study comparing the predictive values of EEG reactivity, sleep spindles, and GCS, and they reported that GCS predicted awakening with an AUC of 0.767; 0.677–0.857 [37].

The optimal timing of aEEG monitoring to achieve the greatest predictive value is a major concern in studies of this kind. In previous studies, aEEG was recorded upon arrival at the ICU and usually lasted for > 72 h. However, it has also been reported that aEEG patterns change during the period of monitoring and that some of the initial patterns have no prognostic value, which adds to the difficulty of aEEG interpretation [15]. In our study, ~80% of the enrolled patients suffered TBI or stroke, most of whom underwent cranial surgery. Both the more complex intracranial conditions, including intracranial hemorrhage, cerebral edema, and elevated intracranial pressure, and non-neurological factors such as temperature management, sedation, and the surgical site on the scalp make early aEEG monitoring difficult and unreliable. Furthermore, prediction may not be necessary in the super-acute stage, because at this stage, physicians and family members usually do not consider suspending treatment despite a poor prognosis. For the purpose of excluding potential factors that may affect aEEG recording during the early phase of coma, we included patients 7 days after coma onset at a median of 7.5 days (7–14). At this time, the patient's clinical situation was more stable, and the aEEG recorded was more stable and thus had higher predictive values for the outcome. As a result, the aEEG patterns showed good consistency and did not change during the monitoring period in our study. In addition, the aEEG patterns displayed a good predictive value for both favorable and unfavorable outcomes.

The number of electrodes is another point of dispute [38]; single-channel or two channels are the most commonly reported in the literature. However, it is unclear whether the reliability of reduced-channel aEEG is comparable to that of conventional multichannel EEG. Previous researchers have pointed out that it is possible that localized EEG abnormalities are missed by simplified two-channel aEEG recordings [15]. In addition, the patients in our study had different etiologies. For these reasons, we used a 10-electrode aEEG protocol. Electrical seizure activity was identified in 9 (7.0%) patients but status epilepticus was not observed in the present cohort. However, in previous reports, status epilepticus was identified in up to 21.5% of patients [15, 25]; the difference may be due to the longer time from coma onset to aEEG recording and the early seizure prophylaxis in our study.

This study suffers from some potential weaknesses. First, was the small sample size, especially when analyzed according to the different causes of coma. Second, a 10-electrode protocol may add to the practical difficulty compared with reduced-channel methods. Third, this study was conducted in a single center with a unique health-care environment, which raises important questions regarding the generalizability of these results. Further multi-center studies with larger sample sizes are necessary to evaluate the prognostic value of aEEG for etiologically different coma patients.

In conclusion, aEEG patterns in the sub-acute stage of coma (> 7 days) are informative for predicting both good and poor outcomes of coma patients after acute brain injury. A favorable aEEG pattern (CNV) is a good indicator of a favorable 6-month neurological outcome. Conversely, unfavorable aEEG patterns (CLV, BS, and FT) are associated with a poor 6-month neurological outcome. Though with limitations, we believe that aEEG can be an effective prognostic tool for coma survival after acute brain injury.

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Compliance with Ethical Standards

Conflict of interest All authors claim that there are no conflicts of interest.

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