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Short-Term Outcome Prediction by Electroencephalographic Features in Children Treated with Therapeutic Hypothermia After Cardiac Arrest

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Abstract

Background—Electroencephalographic (EEG) features may provide objective data regarding prognosis in children resuscitated from cardiac arrest (CA), but therapeutic hypothermia (TH) may impact its predictive value. We aimed to determine whether specific EEG features were predictive of short-term outcome in children treated with TH after CA, both during hypothermia and after return to normothermia.

Methods—Thirty-five children managed with a standard clinical TH algorithm after CA were prospectively enrolled. EEG recordings were scored in a standardized manner and categorized. EEG category 1 consisted of continuous and reactive tracings. EEG category 2 consisted of continuous but unreactive tracings. EEG category 3 included those with any degree of discontinuity, burst suppression, or lack of cerebral activity. The primary outcome was unfavorable short-term outcome defined as Pediatric Cerebral Performance Category score of 4–6 (severe disability, vegetative, death) at hospital discharge. Univariate analyses of the association between EEG category and outcome was performed using logistic regression.

Results—For tracings obtained during hypothermia, patients with EEGs in categories 2 or 3 were far more likely to have poor outcome than those in category 1 (OR 10.7, $P = 0.023$ and OR 35, $P = 0.004$, respectively). Similarly, for tracings obtained during normothermia, patients with EEGs in categories 2 or 3 were far more likely to have poor outcomes than those in category 1 (OR 27, $P = 0.006$ and OR 18, $P = 0.02$, respectively).

Conclusions—A simple EEG classification scheme has predictive value for short-term outcome in children undergoing TH after CA.

Keywords

Therapeutic hypothermia; Outcome; Pediatric; Hypoxic ischemic encephalopathy; Heart arrest; Prognosis

Introduction

Early prognostication in children after cardiac arrest (CA) is important for counseling families and making management decisions. Multiple clinical, laboratory, imaging, and neurophysiologic features may be useful in outcome prediction, but few have perfect predictive value [1]. Utilization of electroencephalographic (EEG) features is appealing since EEG can be performed non-invasively at the bedside and provides objective data about the functional status of the brain following an acute insult when clinical data are unclear or unknown. A recent practice parameter addressing outcome prediction in adults after CA described that several EEG features were useful for prognosis. Myoclonic status epilepticus on the first day best predicted unfavorable outcome, while diffuse voltage suppression under 20 μV, burst-suppression, and generalized periodic complexes were strongly but not invariably associated with poor outcome [2]. Several EEG classification systems that group EEG features into predictive categories have been developed in adults [3–5] and children

[6], but recent studies suggest these categories may not be as sensitive for outcome prediction as utilizing component features [7]. Further, a fundamental limitation of EEG-based prognosis is the uncertain reproducibility of EEG interpretation in critically ill and comatose patients [8–11]. However, we recently demonstrated that some EEG features in children with hypoxic-ischemic brain injury have substantial inter-rater agreement [12].

Therapeutic hypothermia (TH) has been shown to improve outcome after CA in adults [13, 14] and hypoxic ischemic encephalopathy in neonates [15–18]. As a result, TH is now being employed as a neuro-protective strategy in children after CA [19, 20], although efficacy has not been established in this population. Deep hypothermia is known to profoundly affect EEG patterns [21]. EEG patterns have also been shown to evolve during the course of moderate TH [22, 23], possibly as a result of evolving brain injury, temperature modulation, and sedative medications, or all three synergistically. Further, if TH is neuroprotective, then EEG prognostic features identified in the era preceding TH utilization may no longer have the same predictive significance. Prior studies in children who underwent continuous EEG monitoring (cEEG) during and after TH have demonstrated that electrographic seizures and electrographic status epilepticus are common [22], but have not addressed prognosis.

We aimed to prospectively determine whether specific EEG features known to have high inter-rater agreement were predictive of short-term outcome in a consecutive cohort of children treated with TH after CA, both during hypothermia and after rewarming to normothermia. We hypothesized that patients whose EEGs lacked reactivity and featured discontinuous backgrounds would have an unfavorable short-term prognosis compared to those whose EEGs were reactive and continuous.

Patients and Methods

Children treated in the pediatric intensive care unit (PICU) of the Children's Hospital of Philadelphia (CHOP) with TH after CA were eligible for enrollment. A standard clinical TH protocol in which children were surface cooled by a cooling blanket to 34°C for 24 h, and then slowly re-warmed over 12–24 h [19], was employed. Based on measurements taken every half hour, subjects were within target temperature range 78% of the time, and were below target range 15% of the time and were above target range 8% of the time [19]. In accordance with our clinical pathway, all patients treated with TH underwent continuous video EEG monitoring during hypothermia (24 h), during re-warming (about 24 h), and during the 24 h period that followed return to normothermia. The primary aim of EEG monitoring was to detect electrographic seizures which are common in these children [22]. Continuous EEG monitoring was initiated as soon as the patient was stabilized in the PICU and was performed by on-call registered EEG technologists. EEG was recorded using a Grass-Telefactor (West Warwick, RI) video-EEG system. Twenty-one gold-over-silver scalp surface electrodes were positioned according to the international 10–20 system and affixed with Collodion adhesive. EEG data were acquired on a networked portable bedside monitor. The EEG findings were reported to the clinical teams, who were continually reminded that these EEG findings should not be used for prognosis since little is known about the potentially additive effects of hypoxic ischemic brain injury, hypothermia, and sedatives on the EEG.

The parents/guardians of all eligible subjects were approached for consent to allow subsequent review of EEG and clinical data, and patients were enrolled consecutively to minimize selection bias. This study was approved by the hospital's Institutional Review Board.

After clinical interpretation during the acute hospitalization, EEG recordings were re-interpreted in a standardized manner by three neurophysiologists blind to outcome and clinical information, except for patient age. Inter-rater reliability between these 3 interpretations was high and any disagreements were resolved by consensus reading [12]. For each patient, interpretation was performed on two 30 min epochs. The first epoch was obtained at the onset of EEG monitoring, as soon as possible after the initiation of hypothermia. This time-point was chosen because of its potential clinical utility—EEG features which are predictive at this early time-point may influence early management decisions or may be used in future studies to stratify patients based on initial brain injury severity upon enrollment. The second epoch was obtained upon return to normothermia. This time-point was chosen since it was the earliest time EEG features could be assessed without any potential influence of moderate therapeutic hypothermia. EEG interpretation included documentation of the dominant frequency, fastest frequency, representative voltage, anterior to posterior organization, sleep architecture, reactivity, and continuity. Separate from the characterization of the background, the tracings were judged for non-specific focal features, epileptiform discharges, benzodiazepine-induced beta activity, seizure occurrence, and electrographic seizure morphology and distribution.

The EEG features of continuity and reactivity were chosen a priori to create three EEG categories. EEG category 1 consisted of continuous and reactive tracings. EEG category 2 consisted of continuous but unreactive tracings. Category 3 consisted of tracings with discontinuity, burst suppression, or suppressed, low voltage records.

Short-term outcome was determined by a pediatric intensivist (AT) blinded to the EEG data and not involved in patients' clinical care at the time that outcome was assessed. Outcome was determined on discharge from the intensive care unit based on mortality and Pediatric Cerebral Performance Category score (PCPC) [24]. The PCPC is a validated six-point scale categorizing degrees of functional impairment. PCPC scores and categories are 1 = normal, 2 = mild disability, 3 = moderate disability, 4 = severe disability, 5 = coma and vegetative state, and 6 = death. The primary outcome was unfavorable short-term outcome defined as PCPC score of 4–6.

Descriptive statistics, including means and standard deviations, and medians and ranges, as appropriate, were used to describe baseline characteristics of the cohort. Univariate analyses of the association between EEG categories and outcome was performed using logistic regression. This study was not adequately powered for multivariable regression analyses; however, the presence of confounding by concomitant medication use was investigated using multivariable logistic regression. Positive predictive values (PPV) and area under the receiver operating characteristic (ROC) curve for each EEG category at both time-points are presented. To evaluate whether there were differences in the predictive ability of EEG during hypothermic and normothermic conditions, the areas under the ROC curves were compared using the DeLong method for comparison of two correlated ROC curves [25]. Statistical analyses were performed using STATA Release 10.1 (StataCorp, LP, College Station, TX).

Results

Patient and Cardiac Arrest Characteristics

Between June 2007 and July 2009, 35 consecutive children underwent TH after CA, including 20 males and 15 females, with a median age 1.02 years (range 0.18–16.6 years). Prior to CA, 21 were normal, 9 had a chronic static encephalopathy or other developmental problem, and 5 had pre-existing medical conditions but were considered neurodevelopmentally normal. Six (17%) suffered an in-hospital cardiac arrest and 29 (83%)

suffered an out-of-hospital cardiac arrest. Four (11%) had initial ventricular fibrillation or pulseless ventricular tachycardia. Duration of cardio-pulmonary resuscitation was unknown for 12 subjects. For the other 23, the median duration of CPR was 15 min [interquartile range 6, 21]. Arrest etiologies were asphyxia/ respiratory in 16, drowning in 8, cardiac in 5, and other in 4 (2 near-SIDS, 1 anaphylaxis, 1 unknown). For 24 subjects with detailed timing data available, the mean duration between return of spontaneous circulation and hypothermia (temperature < 34°C) was 7.3 ± 0.2 h and the mean duration between return of spontaneous circulation and the onset of EEG monitoring (the initial EEG epoch) was 9.3 ± 0.3 h. Twenty-one (60%) survived to hospital discharge.

Eleven subjects with clinically apparent or electrographic seizures were treated with antiepileptic medications during hypothermia, and an additional four patients received anti-epileptic medication during normothermia. Medication levels at the time of EEG were not available in all subjects. No independent association of unfavorable outcome and presence or absence of antiepileptic medications was found. The majority of patients received sedating medications for pain: during hypothermia, 26 received fentanyl and 20 received midazolam; during normothermia, 29 received fentanyl and 23 received midazolam. During hypothermia, the proportion of patients receiving either of these medications did not differ between EEG score groups 1, 2, and 3 (Fisher's exact test, $P = 0.6$ for midazolam and $P = 0.07$ for fentanyl). During normothermia, significant differences were found, with midazolam use in 85% of the EEG score 1 group, 54% of the EEG score 2 group, and 22% of the EEG score 3 group ($P = 0.01$). However, no independent association of unfavorable outcome and use of midazolam or fentanyl was found, and in an adjusted model, the presence of these medications did not appear to be a confounding factor.

EEG Findings

During hypothermia, EEG tracings were reactive in 11, continuous in 21, discontinuous in 10, and attenuated/featureless in 4. Of the 10 discontinuous tracings, 6 had a pattern of burst suppression. During normothermia, EEG tracings were reactive in 14, continuous in 26, discontinuous in 5, and attenuated/featureless in 4. Of the 5 discontinuous tracings, 3 were burst suppression. EEG categories and the proportion of subjects in each category with unfavorable outcome are shown in Table 1.

EEG Categories and Short-Term Outcome

Tables 2 and 3 summarize the predictive value of the EEG scores for a poor outcome (PCPC score of 4, 5, or 6) at the time of hospital discharge. For EEG tracings during hypothermia, patients with a score of 2 were 10.7 times more likely to have a poor outcome than those with a score of 1 ($P = 0.023$), and patients with a score of 3 were 35 times more likely to have a poor outcome than those with a score of 1 ($P = 0.004$). Similarly, for tracings obtained during normothermia, patients with a score of 2 were 27 times more likely to have a poor outcome than those with a score of 1 ($P = 0.006$), and patients with a score of 3 were 18 times more likely to have a poor outcome than those with a score of 1 ($P = 0.018$). Only one patient with a score of 3 during hypothermia and normothermia had a good outcome according to our outcome definition, but this individual had a PCPC score of 1 at baseline and 3 after cardiac arrest. The PPV for a poor outcome of a score of 2 or 3 during hypothermia was 88% (95% CI 77–98%) and the PPV for a poor outcome of a score of 2 or 3 during normothermia was 91% (95% CI 81–100%). The areas under the ROC curve for scores of 2 or 3 versus a score of 1 on hypothermia and normothermia tracings were comparable and there was no statistically significant difference between them (0.84 vs 0.82, $P = 0.6$), indicating that the predictive value of EEG scores during these two conditions are similar.

Differences in outcome between patients in the three EEG groups were also seen when the outcome was death at hospital discharge. None of the eleven patients who had reactive and continuous EEGs during hypothermia died prior to discharge; four (40%) of those with reactive and discontinuous EEG tracings died; and 10(71%) of those with EEGs in the worst category died ($P = 0.001$). Similarly, during normothermia, none of the 13 patients with an EEG score of 1 died; 7(54%) with an EEG score of 2 died; and 7 (78%) with an EEG score of 3 died ($P < 0.001$). Because an EEG score of 1 perfectly predicted survival, odds ratios describing the relationship between EEG score and death were inestimable.

Five patients in this cohort had PCPC scores of 4 at baseline, and thus were in the unfavorable outcome category prior to cardiac arrest. Of these, three subjects had no change in PCPC score after CA and two did not survive to discharge (PCPC score of 6). To understand the impact on our prediction model of the three subjects whose PCPC scores remained at 4, we repeated our analyses with these individuals excluded. The odds ratios for unfavorable outcome were larger. During hypothermia, for subjects with EEG score 2, OR (95% CI) was 14 (1.5–127, $P = 0.02$) and for subjects with EEG score 3, OR (95% CI) was 48 (3.7–622, $P = 0.003$). During normothermia, for subjects with EEG score 2, OR (95% CI) was 33 (2.9–374, $P = 0.005$), and for subjects with EEG score 3, OR (95% CI) was 21 (1.7–248, $P = 0.016$). The difference in odds ratios indicates that any bias introduced by including subjects with a baseline PCPC score of 4 did not exaggerate, but diminished our estimates.

Twenty-seven patients (77%) did not change EEG categories between the hypothermia and normothermia assessments. One patient's score worsened from hypothermia to normothermia, and seven improved. Five of the seven moved from a score of 3 to a score of 2, one moved from a score of 2 to a score of 1, and one moved from a score of 3 to a score of 1. All but one (the patient with a score of 2 on hypothermia and 1 on normothermia) had unfavorable outcomes. No statistically significant association between improvement on EEG score and outcome was found.

Discussion

This prospective study of consecutive children treated with TH after CA establishes that EEG discontinuity and lack of reactivity predict unfavorable short-term outcome by PCPC score compared to EEGs that are continuous and reactive. The scoring system devised for this study has several key advantages. The system is simple, containing only three categories. Further, the features which define each category, reactivity and continuity, can be easily assessed at the bedside and continuity interpretation has substantial inter-rater reliability [12]. Though all patients in this study underwent 24 h EEG monitoring, we applied this scoring system to 30 min epochs, essentially replicating two routine EEGs, making this method accessible to centers without the capacity for continuous EEG monitoring.

In acutely ill patients not treated with TH, EEG background features are known to have prognostic significance in adults [2, 26] and children [6, 27–33]. Lack of electro-graphic reactivity to stimulation, the feature which distinguished a score of 1 from 2 in our schema, also predicts poor prognosis in adults treated with TH [3, 7, 34, 35]. Of note, in one of the largest series involving 111 adults treated with TH after CA, an unreactive EEG background was a more sensitive predictor of neurologic recovery than clinical signs such as motor responsiveness [34]. Similarly, in adults treated with TH after CA, bi-spectral index monitoring scores of zero (reflecting a low amplitude, featureless, unreactive EEG) predict unfavorable outcome or death [36–38]. In our study, lack of reactivity (a score of 2 in the categorization scheme) was highly associated with a poor prognosis, with essentially no difference between assessments made during hypothermia or normothermia. However, it is

unclear whether this factor is best used alone as a predictor or combined with other EEG features such as voltage suppression, burst suppression patterns, or generalized epileptiform discharges in a composite “malignant EEG” categorization [3, 7].

In adult studies of EEG predictors of outcome after TH, continuity had predictive value [3–5, 7, 23, 39]. However, while most of the studies described burst-suppression as a predictive feature, they did not address discontinuity that was not regular and unreactive, and thus not fully developed burst suppression. Whether the presence of discontinuity during TH is as reliable a predictor of outcome as discontinuity after rewarming is still unclear, with at least one study using amplitude integrated EEG showing that patients with initially flat EEGs may develop continuous tracings during normothermia, and subsequently regain consciousness [23]. In our study, category 3 defined as lack of continuity on EEG (including discontinuity and formal burst suppression) during hypothermia or during normothermia, was highly predictive of poor outcome. While several patients with discontinuity during hypothermia achieved continuous tracings during normothermia, none had a favorable outcome.

There is often uncertainty regarding the meaning of EEG features such as discontinuity during hypothermia, since body temperature is known to impact EEG features. At extremely low temperatures such as used in deep hypothermic circulatory arrest, the EEG develops a discontinuous and then isoelectric pattern, but these severe EEG abnormalities are not reported with the moderate hypothermia temperatures used in TH [21]. We found that using this categorization system, EEG features were equally predictive during hypothermia and normothermia. This finding suggests that EEG features predicting unfavorable outcome have predictive value even during moderate therapeutic hypothermia, and a discontinuous or unreactive EEG cannot be attributed solely to reduced body temperature.

The current study has several limitations. First, we aimed to create a simple interpretation system using only features expected to have good inter-reader agreement which could be assessed during a 30 min recording. However, this strategy may have led us to discount important EEG features that might have improved prediction. For example, seizures, which may influence outcome, were not included in the categorization system because their absence during a 30 min recording may not adequately reflect their absence over a longer time periods. In a study of 51 comatose adults after CA, 10% of patients had electrographic status epilepticus, all of whom died [40]. In contrast, another series of six adults with postanoxic status epilepticus reported that a favorable outcome was possible if they had preserved brainstem reactions, somatosensory evoked potentials, and EEG reactivity [35]. Thus, seizure occurrence may only have predictive value when used in a multi-modal model that includes physical examination signs and evoked potentials. The second major constraint on the current study was the small sample size, which restricted our ability to develop a more comprehensive prediction model with multiple EEG variables. In addition, our small sample limited our ability to adjust for factors such as the presence of anticonvulsants or sedating medications in estimating the association between EEG characteristics and outcome. However, identifying key EEG features which have significant associations with outcome is an important first step for planning larger prospective studies, where a greater number of factors can be incorporated into a predictive model. Changes in critical care management are likely to occur every several years, and given that CA is rare in children, multi-center studies are needed to enroll patients quickly enough to avoid the confounding impact of substantive management changes on outcome. A third limitation was the provision of clinical care without masking of the EEG results. Despite our admonitions, EEG results may have influenced caregiver decisions to withdraw care based on their perceptions about the association between EEG background abnormalities and the high likelihood of a poor outcome. To minimize the influence of decisions to withdraw technological support, the

primary outcome encompassed not only death but also severe disability (a PCPC score of 4, 5, or 6). Whether a family chose to withdraw support or continue support of a child with severe neurologic injury, the child's outcome would have been scored as unfavorable. Finally, we examined only short-term outcomes. Future studies evaluating long-term outcomes of death, neurologic disability, and significant co-morbidities such as epilepsy will be important in providing a more comprehensive picture of the clinical course of children with CA treated with TH.

In summary, our findings represent an important first step in identifying predictors of outcome which can be reliably measured during hypothermia after cardiac arrest. Our data indicate that a simple scheme for categorizing EEGs based on reactivity and continuity is highly associated with short-term outcome in children with CA treated with TH, both during hypothermia and normothermia. Further validation of these results is needed, along with larger prospective studies to build more comprehensive predictive models.

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Table 1

EEG categories and unfavorable outcome

	EEG category	*N*	Outcome *N* (%)	
			Unfavorable (PCPC 4, 5, 6)	Death
Same EEG category during hypothermia and normothermia (*N* = 27)	Continuous and reactive	11	3 (27)	0 (0)
	Continuous and unreactive	8	7 (88)	3 (37.5)
	Discontinuous and/or suppressed	8	7 (88)	6 (75)
Change in EEG category from hypothermia to normothermia (*N* = 8)	Continuous and unreactive ↓ Continuous and reactive	1	0 (0)	0 (0)
	Discontinuous and/or suppressed ↓ Continuous and reactive	1	1 (100)	0 (0)
	Discontinuous and/or suppressed ↓ Continuous and unreactive	5	5 (100)	4 (80)
	Continuous and unreactive ↓ Discontinuous and/or suppressed	1	1 (100)	0 (0)

Category 1 = continuous and reactive tracings

Category 2 = continuous but unreactive tracings

Category 3 = tracings with discontinuity, burst suppression, or suppressed low voltage records

Table 2

Odds ratios for unfavorable outcome based on EEG category and EEG epoch

EEG categories compared	Epoch	Odds ratio	*P*
Continuous and unreactive vs continuous and reactive	Hypothermia	10.7	0.02
Continuous and unreactive vs continuous and reactive	Normothermia	27	0.006
Discontinuous and/or suppressed vs continuous and reactive	Hypothermia	34.6	0.004
Discontinuous and/or suppressed vs continuous and reactive	Normothermia	18	0.018
Continuous and unreactive or discontinuous and/or suppressed vs continuous and reactive	Hypothermia	18.6	0.008
Continuous and unreactive or discontinuous and/or Suppressed vs continuous and reactive	Normothermia	22.5	0.0004

Table 3

Positive predictive values for EEG categories for unfavorable outcome when scored during hypothermia and normothermia

EEG category	PPV for unfavorable outcome (95% CI)	
	Hypothermic	Normothermic
Continuous and reactive	27% (12–42%)	31% (15–46%)
Continuous and unreactive	80% (67–93%)	92% (83–100%)
Discontinuous and/or suppressed	93% (84–100%)	89% (78–99%)
Continuous and unreactive or discontinuous and/or suppressed	88% (77–98%)	91% (81–100%)

PPV positive predictive value, *CI* confidence interval