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Stability of Early EEG Background Patterns After Pediatric Cardiac Arrest

Nicholas S. Abend, MD MSCE^a, Rui Xiao, PhD^b, Sudha Kilaru Kessler, MD MSCE^a, and Alexis A. Topjian, MD MSCE^b

^aDepartments of Neurology and Pediatrics, Children's Hospital of Philadelphia and the University of Pennsylvania

^bCenter for Clinical Epidemiology and Biostatistics, the University of Pennsylvania

^cDepartment of Anesthesia and Critical Care Medicine, Children's Hospital of Philadelphia and the University of Pennsylvania

Abstract

Purpose—We aimed to determine whether EEG background characteristics remain stable across discrete time periods during the acute period after resuscitation from pediatric cardiac arrest.

Methods—Children resuscitated from cardiac arrest underwent continuous conventional EEG monitoring. The EEG was scored in 12-hour epochs for up to 72-hours after return of circulation by an electroencephalographer using a Background Category with four-levels (normal, slow-disorganized, discontinuous/burst-suppression, or attenuated-featureless) or two-levels (normal/slow-disorganized or discontinuous/burst-suppression/attenuated-featureless). Survival analyses and mixed-effects ordinal logistic regression models evaluated whether the EEG remained stable across epochs.

Results—EEG monitoring was performed in 89 consecutive children. When EEG was assessed as the four-level Background Category, 30% of subjects changed category over time. Based on initial Background Category, one quarter of subjects changed EEG category by 24 hours if the initial EEG was attenuated-featureless, by 36 hours if the initial EEG was discontinuous or burst-suppression, by 48 hours if the initial EEG was slow-disorganized, and never if the initial EEG was normal. However, regression modeling for the four-level Background Category indicated that the EEG did not change over time (OR=1.06, 95%CI=0.96– 1.17, p=0.26). Similarly, when EEG was assessed as the two-level Background Category, 8% of subjects changed EEG category over time. However, regression modeling for the two-level category indicated that the EEG did not change over time (OR=1.02, 95%CI=0.91–1.13, p=0.75).

Conclusions—The EEG Background Category changes over time whether analyzed as four-levels (30% of subjects) or two-levels (8% of subjects) although regression analyses indicated no significant changes occurred over time for the full cohort. These data indicate that the Background Category is often stable during the acute 72 hours after pediatric cardiac arrest and thus may be a

useful EEG assessment metric in future studies, but that some subjects do have EEG changes over time and therefore serial EEG assessments may be informative.

Keywords

EEG; cardiac arrest; pediatric

Introduction

Cardiac arrest occurs in over 16,000 children per year in the United States, and survivors often experience substantial neurobehavioral morbidity.^{1–9} Clinical and resuscitation characteristics are only moderately predictive of long-term neurobehavioral outcomes,^{10–14} likely because they do not directly assess brain function. Electroencephalographic (EEG) monitoring provides a robust method of assessing brain activity, and it is often acquired early after cardiac arrest to identify non-convulsive seizures.^{15,16} Further, single-center data indicate that specific early post cardiac arrest EEG features are associated with discharge neurologic outcomes,^{15,17–22} and the addition of EEG data to clinical information has been shown to significantly improve prognostication accuracy by clinicians.²³ Thus, EEG features could serve as early, direct, reliable, standardized, and clinically available brain injury severity biomarkers. Recognizing these potential uses for EEG, the International Liaison Committee on Resuscitation (ILCOR) recommended that investigators should “examine a standardized approach to EEG analysis.”²⁴

To establish a standardized EEG analysis approach, we previously assessed the inter-rater agreement of standardized EEG variables.^{25,26} However, a standardized EEG analysis approach also needs to determine when to assess the EEG and whether the EEG changes over time during the acute period. If the EEG is relatively stable during the acute period, then assessing the EEG during a single wide time span could be appropriate for subsequent prospective studies involving EEG assessment. In contrast, if the EEG changes substantially during the acute period in many patients, then EEG biomarker studies would need to assess the EEG in narrower and likely multiple time periods. Thus, we aimed to assess how the EEG background changes during the acute period in children resuscitated after cardiac arrest.

Methods

We enrolled consecutive children resuscitated after cardiac arrest who received care at the Children’s Hospital of Philadelphia (CHOP) in an Institutional Review Board approved prospective observational study of pediatric cardiac arrest. We collected demographic and clinical data related to prior medical history, cardiac arrest characteristics, resuscitation characteristics, and discharge outcome assessed from medical record notes using the Pediatric Cerebral Performance Category Score.²⁷ As part of clinical care guided by an institutional pathway²⁸ derived from recent guidelines and consensus statements regarding EEG monitoring in critically ill patients,^{16,29,30} all patients resuscitated after cardiac arrest underwent continuous conventional full-array EEG monitoring. We initiated EEG monitoring as soon as possible after resuscitation. We performed EEG monitoring with

Grass video EEG equipment and the international 10–20 montage with modification for neonates as needed.

This study evaluated 10-minute long EEG segments scored by a pediatric electroencephalographer blind to all clinical information. We removed all clinical annotations in the EEG tracing prior to blinded review. The video was not available, but the reviewer could adjust the montage, filters, and voltage settings. The reviewer scored the EEG using an electronic case report form in Research Electronic Data Capture (REDCap) which is a web-based electronic data application hosted at CHOP Research Institute.³¹ Use of the electronic case report form ensured there were no missing data. The reviewer assessed the EEG at the earliest time available after resuscitation and at up to six subsequent times relative to the time of return of circulation (12, 24, 36, 48, 60, and 72 hours). Thus, a maximum of 70 minutes of EEG were scored per subject. The reviewer scored the Background Category which consisted of: (1) normal (including sedated sleep), (2) slow-disorganized, (3) discontinuous (which had to be excessive for gestational age in neonates) or burst-suppression, and (4) attenuated-featureless. Prior studies of EEG monitoring in critically ill children have used this categorical system,^{20–22,32} and a prior study involving four pediatric electroencephalographers demonstrated almost perfect interrater agreement (kappa 0.89).²⁶ The EEG background was also combined into two background categories including: (1) favorable (normal or slow-disorganized categories), and (2) unfavorable (discontinuous/burst-suppression or attenuated-featureless categories).

We performed statistical analyses using Stata 12 (College Station, Texas). We used standard descriptive statistics to summarize the data as medians (with interquartile ranges (IQR) or counts (with percentages) as appropriate. We aimed to assess whether the background remained stable for individual subjects. Because of the variability in EEG monitoring duration across subjects, we used survival analysis methods to evaluate the time from EEG initiation until a change in EEG to a better or worse category occurred for each individual subject. An event was defined as a change in EEG at the first of each subsequent evaluation times (12, 24, 36, 48, 60, and 72 hours), compared to the Background Category at the earliest EEG time. Subjects without a change in Background Category to a better or worse category were censored at the time closest to the time the EEG recording was discontinued. Since the entire study occurred in the acute period following resuscitation from cardiac arrest, no subjects were censored due to loss to follow-up. We generated Kaplan-Meier curves to show the estimated number of subjects without a change in EEG at various time points after EEG onset (12, 24, 36, 48, 60, and 72 hours after return of circulation). We performed separate survival analyses for the EEG data categorized into four-level and two-level categories. We created Heat Maps to visualize the EEG category over time for each individual subject. To assess whether the EEG background changed over time for the full cohort, we performed a mixed-effects ordinal logistic regression for the four-level EEG category data and a mixed-effects logistic regression for the two-level EEG category data. This method takes into account within-subject correlation due to repeated measures by including subject-specific random effects.

Results

The study included 89 subjects who experienced cardiac arrests between August 2012 and April 2016. Table 1 provides the demographic and clinical data from this cohort. The median patient age was 2.1 years (IQR 0.27, 9.1 years). The median duration of cardiopulmonary resuscitation was 10 minutes (IQR 4, 20 minutes), and 58 (65%) subjects had in-hospital cardiac arrests. The initial EEG was recorded 7.0 hours (IQR 4.4, 11.4 hours) after return of circulation.

When the EEG Background Category was assessed with four-levels, 30% of subjects changed categories over time (Table 2). Figure 1a is the Kaplan-Meier curve. For all initial EEG background categories, fewer than 50% of subjects experienced changes in Background Category over time. Thus, the median number of subjects without a change in Background Category cannot be reported, and we instead summarized when 25% of subjects changed Background Category. One quarter of subjects changed Background Category by 24 hours if the initial EEG was attenuated-featureless, 36 hours if the initial EEG was discontinuous or burst-suppression, 48 hours if the initial EEG was slow-disorganized, and never if the initial EEG was normal. Differences in rates of subjects who did not have a change in their Background Category over time by initial Background Category were not statistically significant (log rank test, $p=0.28$). Although the survival analysis indicated 30% of subjects changed Background Category over time, the regression modeling indicated that there were no changes in Background Category over time for the full cohort (OR = 1.06, 95%CI = 0.96 – 1.17, $p=0.26$). Twenty-six subjects transitioned between the four-level categories including ten who worsened, twelve who improved, and four who briefly improved and then returned to initial worse category. Figure 2a is a Heat Map showing Background Category over time for each subject.

Similar results occurred when the EEG was categorized as two-levels. When the EEG Background Category was assessed as two-levels, 8% of subjects changed categories over time (Table 2). Figure 1b is the Kaplan-Meier curve. Although the survival analysis indicated 8% of subjects changed Background Category over time, the regression modeling indicated there were no changes in Background Category over time for the full cohort (OR = 1.02, 95%CI = 0.91 – 1.13, $p=0.75$). Seven subjects transitioned between the two-level categories including two who worsened, four who improved, and one who briefly improved and then worsened again. Figure 2b is a Heat Map showing Background Category over time for each subject.

Discussion

The Background Category EEG variable has been used in pediatric prognostication systems,^{15,17–22} and we have previously shown that that assessments of Background Category by four pediatric electroencephalographers had almost-perfect interrater agreement.²⁶ Thus, it may be a useful EEG exposure variable for future large multi-center studies assessing EEG as a biomarker of early brain injury severity after pediatric cardiac arrest. The current study adds two key findings which impact use of the Background Category EEG variable as a standardized EEG system in future studies. First, a meaningful proportion of individual

subjects have changes in their Background Category assessments during the initial 72 hours after cardiac arrest. The Background Category changes for 30% of subjects when analyzed as four-levels and 8% of subjects when analyzed as two-levels. Thus, future studies assessing EEG as a brain injury severity biomarker or using EEG for neuroprognostication purposes may benefit from EEG assessment at multiple timepoints and analysis of changes in EEG over time. Several studies in adults after cardiac arrest have demonstrated that changes in EEG over time may be informative in terms of outcome prediction with improvements in EEG assessments associated with more favorable outcomes^{44–47} Second, and somewhat contradictory, is the finding that when analyzed as a cohort, no statistically significant changes in EEG were identified using Background Category as either four-levels or two-levels. Establishing that EEG background categories do not significantly change over time when analyzed among the full cohort may indicate that this is a reasonably stable assessment system. This approach could serve as a standardized and reliable system to EEG scoring for future multicenter prospective pediatric cardiac arrest trials aiming to stratify subjects using EEG as an early and clinically available biomarker of initial brain injury severity.

In considering survival analysis requirements,⁴⁸ clinical management leading to study data did not change during the study, the risk of consequences did not change during the study, and events occurred uniformly over the follow-up intervals. However, subjects represented by censored data may not have experienced the same consequences as those remaining under study. Patients with very normal or very abnormal EEGs may have been censored since EEG monitoring might have been discontinued earlier in patients who had a return to normal mental status or progressed to death, respectively. Thus, the uncensored subjects with mid-level EEG abnormalities tended to undergo longer durations of EEG monitoring. As a result, the survival analyses might underestimate the stability of EEG findings since more stable patients were more likely to be censored.

This study has several notable strengths. The EEG studies were obtained from a cohort of consecutive children resuscitated after cardiac arrest, so the EEG patterns likely represented the full spectrum of findings and the true prevalence of the various EEG patterns. The EEG reviewer could modify any settings, which mimics real-world EEG reading. However, there are also limitations. First, the EEG epochs were only assessed by one pediatric electroencephalographer, and interpretation may have varied by reviewer. However, our prior interrater agreement data in this cohort indicated almost-perfect agreement for the EEG categorization system.²⁶ Second, we assessed one overarching categorization system and did not assess each EEG component such as voltage, frequency, continuity, reactivity, or variability. Future work assessing individual EEG components is important since they might provide additional and more nuanced information than the categorical approach. Third, we assessed ten-minute segments of EEG data within each 12-hour epoch. This approach has been used in similar studies of adult cardiac arrest cohorts.⁴⁵ However, more frequent EEG assessments might have shown changes or fluctuations not identified by this analysis. Several similar adult cardiac arrest cohorts performed analysis on 5-minute epochs per hour^{46,47} and several studies showed EEG changes over time periods shorter than 12-hour epochs were informative in terms of prognosis.^{45–47}

Overall, these data indicate that the EEG Background Category changes over time in some subjects. Thus, repeated assessments may be needed for the highest accuracy in future studies assessing whether EEG predicts neurobehavioral outcomes in individual patients. However, for the full cohort, statistically significant changes in the Background Category were not identified indicating that the initial EEG assessment may provide a relatively stable assessment of early brain function which could be used to stratify patients by early brain injury severity in future neuroprotection trials.

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Figure 1.

Kaplan-Meier survival curves by initial Background Category indicating the percentages of subjects with unchanged EEGs at various time-points after return of circulation with the (a) Background Category scored as four-levels or (b) two-levels. Subjects are censored the first time they change categories or when EEG monitoring ends.

Figure 2. Heat maps illustrating the EEG Background Category by initial Background Category at various time-points after return of spontaneous circulation for subjects who changed category with the EEG categorized into (a) four-levels or (b) two-levels.

Table 1

Subject characteristics (N=89)

Clinical Variable	N (%) or Median [IQR]
Age at Arrest (years)	2.1 [0.27, 9.1]
Sex: Male	56 (62%)
Race	
White	46 (52%)
Black	19 (21%)
Other	24 (27%)
Hispanic	14 (16%)
Pre-arrest PCPC Score	
1 = Normal	58 (65%)
2 = Mild Disability	12 (13%)
3 = Moderate Disability	8 (9%)
4 = Severe Disability	9 (10%)
5 = Coma or Vegetative State	2 (2%)
Pre-Existing Medical Condition: no	21 (24%)
Cardiac Arrest location	
In-Hospital	58 (65%)
Out-of-Hospital	31 (35%)
Bystander Cardiopulmonary Resuscitation for Out-of-Hospital Cardiac Arrest (n=31)	25 (81%)
Cardiopulmonary Resuscitation Duration (minutes) (n=70)	10 [4, 20]
Initial Rhythm	
Asystole/pea	26 (29%)
Bradycardia	33 (37%)
Ventricular fibrillation or tachycardia	11 (13%)
Other/unknown	19 (21%)
Epinephrine Doses	
0	14 (16%)
1	15 (17%)
2	10 (11%)
3	18 (20%)
4	7 (8%)
5	20 (22%)
Unknown	5 (6%)
Induced Hypothermia	10 (11%)

Clinical Variable	N (%) or Median [IQR]
Benzodiazepine Infusion (during EEG monitoring)	69 (78%)
Time from Cardiac Arrest to Electroencephalogram Initiation (hours)	7 [4.4, 11.4]
Mortality	30 (34%)
Post-arrest PCPC Score (Discharge)	
1 = Normal	16 (18%)
2 = Mild Disability	16 (18%)
3 = Moderate Disability	11 (12%)
4 = Severe Disability	16 (18%)
5 = Coma or Vegetative State	30 (34%)
Unfavorable Outcome (Death or PCPC Score Change >1 Level)	45 (51%)

PCPC, pediatric cerebral performance category.

Table 2

Summary of Kaplan-Meier Estimates for Stability (no change) of EEG Background Category at Each Timepoint Categorized as Four-Levels and Two-Levels.

Duration Since Return of Circulation (hours)	EEG Background Categorized as Four Levels		EEG Background Categorized as Two Levels	
	EEG Stable ^a (%)	95% CI (%)	EEG Stable ^a (%)	95% CI (%)
12	93	86–97	98	91–99
24	83	74–89	98	91–99
36	75	65–83	94	87–98
48	70	60–79	93	86–97
60	70	60–79	92	84–96
72	70	60–79	92	84–96

^aEEG stability is the equivalent of “survival” without a change in Background Category.