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Clinical paper

Electroencephalographic patterns preceding cardiac arrest in neonates following cardiac surgery

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Abstract

Aim: To identify EEG changes that could predict impending cardiac arrest (CA) in neonates with congenital heart disease undergoing postoperative continuous EEG monitoring.

Methods: Single-center observational study of neonates who underwent cardiac surgery and had CA postoperatively while undergoing EEG monitoring from 2012-2018. Clinical data were extracted from the medical record. EEG backgrounds were evaluated at defined time-points using standardized terminology.

Results: We assessed 22 neonates. The median gestational age was 38.7 weeks (IQR 37.6, 39), the median age at surgery was 5 days (IQR 2, 8), 12 patients (55%) underwent repair for hypoplastic left heart syndrome, and the median time from cardiac intensive care unit arrival postoperatively to CA was 9.5 h (IQR 7, 23). The initial EEG background was abnormal in 15 (68%). All 22 neonates (100%) had worsening of the EEG background prior to initiation of chest compressions for CA at a median of 3 min (IQR 1.5, 3). Eighteen neonates (82%) had an EEG change more than 1 min prior to chest compressions. The EEG backgrounds immediately prior to CA were continuous low voltage in 1 (5%), excessive discontinuity in 8 (36%), burst-suppression in 2 (9%), and low voltage suppression in 11 (50%).

Conclusion: EEG background was abnormal in 68% of neonates at EEG monitoring onset and worsened in all minutes before CA. EEG background changes may be an early sign of impending CA and indicative of developing cerebral dysfunction. Further study is needed to determine whether rapid identification of EEG changes could drive implementation of interventions to prevent CA.

Keywords: Neonate, Cardiac arrest, Prediction, Electroencephalogram

Abbreviations: ACNS, American Clinical Neurophysiology Society; CA, cardiac arrest; CBF, cerebral blood flow; CHD, congenital heart disease; CICU, cardiac intensive care unit; CPB, cardiopulmonary bypass; CPR, cardiopulmonary resuscitation; CR, cardiorespiratory; DHCA, deep hypothermic circulatory arrest; ECG, electrocardiogram; ECMO, extracorporeal membrane oxygenation; EEG, electroencephalogram; PICU, pediatric intensive care unit; QEEG, quantitative electroencephalogram.

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Introduction

Congenital heart disease (CHD) is the most common birth defect in the United States, affecting approximately 40,000 births annually, and almost one-quarter of affected newborns require surgery in the neonatal period.[1,2] The use of cardiopulmonary bypass (CPB) and deep hypothermic circulatory arrest (DHCA) have revolutionized neonatal heart surgery, yielding improved outcomes with decreased mortality.[3–5] However, potential sequelae including formation of emboli, hemorrhage, hypoperfusion, and infarction can cause acute brain injury which may impact neurodevelopmental outcomes.[6–10] Seizures are the most common acute manifestation of neonatal brain injury[11] and are often subclinical (non-convulsive, electroencephalogram-only), therefore requiring electroencephalographic (EEG) monitoring for identification.[4,12–15] As a result, a guideline from the American Clinical Neurophysiology Society (ACNS) recommends that neonates with CHD requiring early repair with CPB undergo at least 24 h of continuous, conventional EEG monitoring.[16]

While EEG monitoring is primarily performed for seizure identification, some neonates undergoing EEG monitoring will coincidently experience a cardiac arrest (CA). Approximately 9% of neonates with CHD have a CA in the post-operative period, typically within the initial 24 h of returning from the operating room (during the time EEG monitoring is ongoing), and the occurrence of post-operative CA is associated with increased mortality and unfavorable long-term outcomes.[15,17,18] Typically, bedside providers are alerted to cardiorespiratory (CR) decompensation and impending CA by vital sign changes such as hypotension, bradycardia, oxygen desaturation, and respiratory distress. Though CR decompensation may occur gradually over hours, obviously recognizable changes in traditional bedside measures of CR decompensation are often only apparent immediately prior to CA, limiting the opportunity for bedside providers to intervene and potentially prevent the CA. In contrast, EEG provides a direct measure of brain function, including serving as a measure for changes in cerebral perfusion. If clear and recognizable EEG changes occur and are identified prior to CA, clinicians may have a period to intervene and prevent CA, yielding more favorable outcomes. However, it is currently unknown whether neonates' EEG patterns change prior to CA. To fill this knowledge gap, we evaluated neonates undergoing postoperative EEG monitoring during CA. We hypothesized that EEG background patterns would worsen prior to CA and the initiation of cardiopulmonary resuscitation (CPR).

Methods

Patient population

Beginning on June 15, 2012, we implemented the ACNS neonatal EEG monitoring recommendations through an institutional clinical pathway which calls for continuous video EEG monitoring of all neonates (<30 days of age or corrected gestational age < 44 weeks) following cardiac surgery with CPB.[19] We analyzed all neonates who underwent CHD surgery with CPB and had an in-hospital CA during concurrent postoperative EEG monitoring. If a patient underwent multiple surgeries in the neonatal period, then only the EEG data concurrent with their subsequent CA was analyzed. We excluded neonates whose CA was not captured while undergoing EEG, or who had inadequate baseline EEG monitoring (<1 h) before CA. The Institutional Review Board at the Children's Hospital of Philadelphia approved review of this data as part of an on-going quality improvement project in the Cardiac Intensive Care Unit (CICU).

Electroencephalographic monitoring

Continuous, conventional EEG was performed as part of a standardized clinical care pathway at the Children's Hospital of Philadelphia. EEG monitoring was initiated within six hours of returning to the CICU and continued for a minimum of 48 h, with longer EEG monitoring utilized as deemed clinically necessary. EEG monitoring was performed by in-house registered EEG Technologists to provide expedient EEG initiation and review 24 h per day 7 days per week, along with frequent review of EEG tracings by pediatric electroencephalographers. EEG monitoring was performed using a Grass-Telefactor video-EEG system (Grass Technologies, West Warwick, RI) from June 2012 to December 2015 or Natus Neuroworks Software (Natus Neuro, Middleton, WI or Warwick, RI) from January 2016 to August 2018. EEG was performed with gold-over-silver electrodes applied in accordance with the 10–20 International System modified for neonates and affixed with collodion adhesive (or paste for neonates on extracorporeal membrane oxygenation [ECMO]). If electrographic seizures occurred, the EEG Service notified the CICU clinicians who determined management of seizures in conjunction with the NeuroICU Consultation Service. If seizures occurred, then EEG monitoring was continued for at least 24 h after the last recorded electrographic seizure. If no seizures were recorded, then EEG monitoring was continued for 48 h. Full EEG records were stored on research or clinical servers.

Data collection

We obtained clinical data, including intra-operative data, from review of the electronic medical record. Patients were classified by a system incorporating the cardiac abnormality and perioperative physiology, with Class I representing two ventricles with no aortic arch obstruction (e.g. transposition of the great arteries), Class II representing two ventricles with aortic arch obstruction, Class III representing a single ventricle with no aortic arch obstruction, and Class IV representing a single ventricle with aortic arch obstruction (e.g. hypoplastic left heart syndrome).[20] Though EEG tracings were collected as standard clinical care, for this study, EEG tracings were reviewed by a pediatric electroencephalographer (SLM) retrospectively using a standardized 5-level neonatal-specific EEG background grading scale which incorporated standardized neonatal terminology defined by ACNS for voltage and continuity.[21,22] The background categories, numbered from normal to most severely abnormal, were: (1) normal continuous/discontinuous, (2) continuous low voltage, (3) excessively discontinuous, (4) burst-suppression, and (5) low voltage suppressed (Fig. 1). This classification system has good inter-rater agreement between electroencephalographers23. The background categories were assigned numerical values to one decimal point to further define worsening or improvement of a background within a scoring category (i.e., 3 = excessively discontinuous background, 3.5 = worsening excessively discontinuous background) (Fig. 2). We assessed up to 10 min epochs of EEG using the scoring criteria at specific time points: (1) the initial background, (2) one hour prior to CA, (3) five minutes prior to CA, and (4) immediately pre-CA. If multiple background patterns existed within an epoch, the initial pattern was included in analysis. The moments of CA (defined as initiation of chest

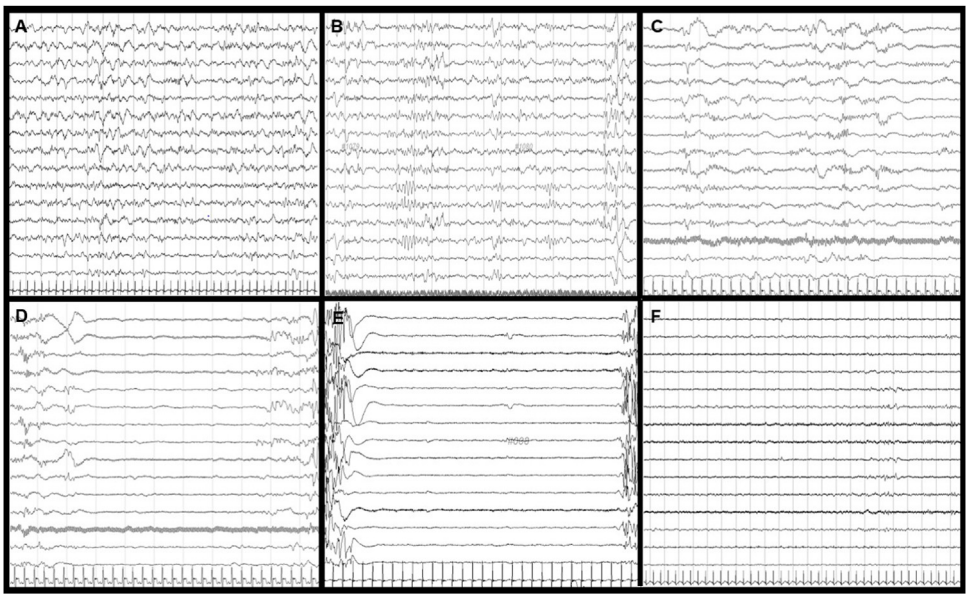

Fig. 1 – Examples of EEG Background Assessment Scale Categories.
(A) Normal Continuous Background with uninterrupted electrical activity of $>25\ \mu V$.
(B) Normal Discontinuous Background with alternating bursts of 50-150 μV activity lasting 2-10 seconds and brief inter-bursts intervals of 25-50 μV lasting less than 6 s.
(C) Continuous Low Voltage Background with uninterrupted electrical activity of 10-25 μV.
(D) Excessively Discontinuous Background with alternating bursts of 50-150 μV activity lasting 2-10 seconds and inter-bursts intervals of $<25\ \mu V$ lasting longer than 6 s.
(E) Burst Suppression Background with invariant bursts of activity without normal neonatal features alternating with inter-burst intervals of $<5\ \mu V$.
(F) Low Voltage Suppressed Background with invariant and persistently low voltage activity of $<10\ \mu V$ without normal neonatal features.

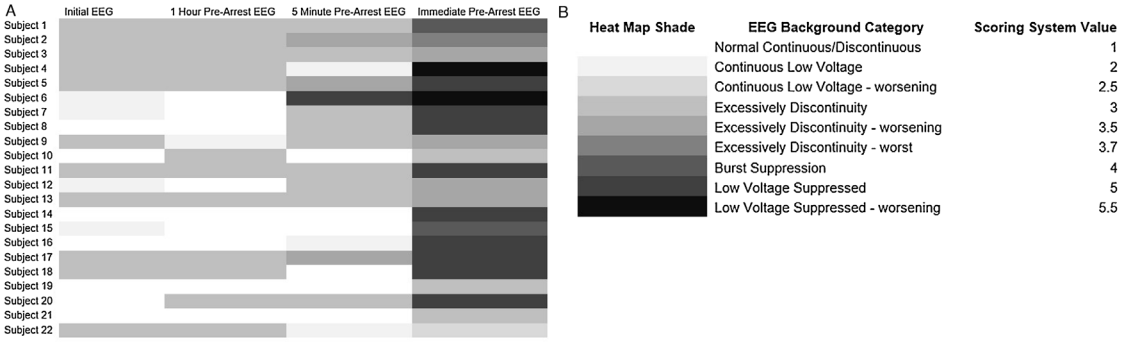

Fig. 2 – Heat Map for EEG Background Categories at Each Time-point.
Epochs of EEG were assessed at EEG onset, 1 h prior to cardiac arrest, 5 min prior to cardiac arrest, and immediately prior to cardiac arrest. Each EEG epoch was assigned a background category with an associated numeric value ranging from 1 (normal; white) to 5 (most severely abnormal; black). The heat map demonstrates that EEG background assessment at each time-point. Immediately prior to cardiac arrest, all EEG backgrounds worsened.

compressions for bradycardia or hypotension) were identified on each EEG tracing, and from that point, the specific aforementioned time points were identified and the EEG was reviewed in reverse to identify the first irreversible change in the EEG background prior to CA. The EEG tracing was also reviewed from 1 h prior to CA advancing forward to confirm the first irreversible EEG change prior to CA. Once the first EEG was identified, the electroencephalographer (SLM) and cardiac intensivist (MYN) also reviewed the code documentation, concurrent EEG video, and single channel electrocardiogram (ECG) tracing on EEG for each neonatal record to detail changes on the ECG preceding CA and notate the clinical narrative as bedside providers recognized and intervened on signs of CA.

Statistical analysis

Descriptive statistics were performed using Stata statistical analysis software. Categorical data are reported as counts and frequencies. Continuous data are reported as medians and interquartile ranges.

Pearson's chi squared and Fisher's exact tests were used for comparison of categorical data, and Wilcoxon rank sum test was used for comparison of continuous data.

Results

Patient characteristics

Between June 15, 2012 and September 1, 2018, 710 neonates with CHD who underwent surgery with CPB were monitored with continuous EEG, including 29 neonates who underwent two or more surgeries during that time (24 of whom had EEG monitoring on multiple post-surgical sessions). CA occurred in 45 patients (6.3%) in the perioperative period (within 48 h following surgery), including 1 neonate with two CAs. Twenty-three patients with CAs were not included for analysis due to insufficient data– 1 CA occurred after EEG monitoring cessation, 3 were not captured on EEG, 1 occurred less than 1 h after EEG monitoring onset, and 18 occurred prior to EEG monitoring onset. Thus, we analyzed the EEG tracings from 22 neonates. There were no significant differences in baseline characteristics between neonates with CA included versus not included for analysis (Table 1).

Table 1 provides patient characteristics for the 22 neonates. Seventeen neonates (77%) were male. The median gestational age at birth was 38.7 weeks (IQR 37.6, 39), and the median birthweight was

Table 1 – Patient and cardiac arrest characteristics.

Demographics

	Analyzed patients, N = 22	Unanalyzed patients, N = 23	P-value
Male, N (%)	17 (77)	13 (56)	0.22
Race, N (%)			0.62
White	11 (50)	12 (52)	
Black	3 (14)	1 (4)	
Other	8 (36)	10 (44)	
Ethnicity– Hispanic, N (%)	2 (9)	3 (13)	1.00
Gestational age (at birth), median (IQR)	38.7 (37.6, 39)	38 (36.6, 39.1)	0.30
Age at surgery (days), median (IQR)	5 (2,8)	5 (3, 8)	0.53
Congenital heart disease, N (%)			0.18
Single ventricle, arch obstruction	12 (55)	11 (48)	
Single ventricle, no arch obstruction	5 (23)	2 (9)	
Two ventricle, arch obstruction	3 (14)	2 (9)	
Two ventricle, no arch obstruction	2 (9)	8 (35)	
Surgical procedure, N (%)			0.37
Norwood operation	11 (50)	10 (42)	
Systemic to pulmonary artery shunt	3 (14)	2 (8)	
ASO, ventricular septal defect closure, aortic arch augmentation	2 (9)	0 (0)	
Total anomalous venous connection	2 (9)	0 (0)	
Arterial switch operation (ASO)	1 (5)	3 (12)	
Atrial septectomy	1 (5)	0 (0)	
PAPVR repair	1 (5)	0 (0)	
Tetralogy of Fallot repair	1 (5)	0 (0)	
Atrioventricular valvuloplasty, main pulmonary artery band	1 (5)	0 (0)	
Yasui operation	1 (5)	0 (0)	
Other	1 (5)	2 (8)	
ALCAPA	0 (0)	1 (4)	
Cardiac tumor resection, aortic arch augmentation	0 (0)	1 (4)	
Pulmonary artery reimplantation	0 (0)	1 (4)	
Transplant	0 (0)	1 (4)	
Truncus arteriosus	0 (0)	3 (12)	
Birth weight (kg), median (IQR)	3.19 (2.82,3.36)	2.88 (2.55, 3.46)	0.25
Time from ICU arrival after surgery to arrest (hours), median (IQR)	9.5 (7, 23)	n/a	–
Duration of cardiac arrest (minutes), median (IQR)	34.5 (1049)	n/a	–
Post-arrest extracorporeal membrane oxygenation, N (%)	14 (64)	n/a	–
Post-arrest seizures, N (%)	4 (18)	6 (26)	0.72
In-hospital mortality, N (%)	6 (27)	10 (44)	0.31

3.19 kg (IQR 2.82, 3.36). Two patients (9%) had class I defects, 3 patients (14%) had class II defects, 5 patients (23%) had class III defects, and 12 patients (55%) had class IV defects. The median postnatal age at time of cardiac surgery was 5 days (IQR 2, 8). Patients underwent a variety of surgical procedures, and the most common was the Norwood procedure for 11 neonates (50%). CA occurred at a median of 9.5 h (IQR 7, 23) after arrival to the CICU following surgery. The median CA duration was 34.5 min (IQR 10, 49). On review of code sheets and single channel ECG tracing obtained as part of the EEG tracing, all neonates had bradycardia prior to pulseless electrical activity. Bradycardia and hypotension were the identifiable clinical parameters that resulted in CPR initiation. Epicardial pacing was initiated for bradycardia prior to the onset of compressions for two neonates. Return of spontaneous circulation occurred in 8 patients (36%). Fourteen patients (64%) were placed onto ECMO. Four patients (18%) had seizures following the CA. No patients experienced seizures prior to CA. Six patients (27%) died prior to hospital discharge.

EEG background and pre-arrest data

EEG monitoring was initiated within 6 h of admission to the CICU following surgical repair for all patients. Table 2 details the EEG background information for all patients at each distinct time-point, and Fig. 2 demonstrates the EEG background patterns of each patient at the various recorded time-points using a heat map. The initial EEG background was normal for 7 patients (32%) and abnormal in 15 patients (68%) including 4 patients (18%) with a continuous low voltage background and 11 patients (50%) with an excessively discontinuous background.

Immediately prior to CA, all 22 patients (100%) had a worsening of their EEG background. The first irreversible sign of worsening EEG background occurred at a median of three minutes (IQR 1.5, 3) prior to CA and CPR initiation. Eighteen patients (82%) had an irreversible EEG worsening more than one minute prior to the onset of CPR. No patients had a normal background immediately prior to CA. One patient (5%) had a continuous low voltage background, 8 patients (36%) had an excessively discontinuous background, 2 patients (9%) had a burst suppression background, and 11 patients (50%) had a low voltage suppressed background. Though our sample was not powered to assess EEG changes by CHD class, pre-arrest background was 50% low voltage suppressed in class I, 67% low voltage suppressed in class II, 60% excessive discontinuity in class III, and 50% low voltage suppressed in class IV. Fig. 3 shows the EEG progression prior to CA for one representative patient.

The single channel ECG was also reviewed to assess the relationship between onset of bradycardia (defined as <100bpm) and EEG change. Of the neonates with interpretable ECG, the first irreversible EEG change preceded bradycardia detection on single channel ECG by a mean 2 min 33 s. This includes 18 neonates in which EEG changes preceded ECG changes (mean 3 min 1 s) and 2 neonates in which ECG bradycardia preceded EEG changes (mean 2 min 33 s).

Table 2 – Electroencephalographic data.

Electroencephalogram background data

N = 22	EEG background category	EEG background change
Initial	7 (32%) Normal continuous/discontinuous 4 (18%) Continuous low voltage 11 (50%) Excessively discontinuous 0 (0%) Burst suppression 0 (0%) Low voltage suppressed 0 (0%) Not recorded	n/a Improved background n/a Unchanged background n/a Worsening background
1 h pre-arrest	9 (41%) Normal continuous/discontinuous 1 (5%) Continuous low voltage 12 (54%) Excessively discontinuous 0 (0%) Burst suppression 0 (0%) Low voltage suppressed 0 (0%) Not recorded	5 (23%) Improved background 15 (68%) Unchanged background 2 (9%) Worsening background
5 min pre-arrest	6 (27%) Normal continuous/discontinuous 3 (14%) Continuous low voltage 12 (54%) Excessively discontinuous 0 (0%) Burst suppression 1 (5%) Low voltage suppressed 0 (0%) Not recorded	4 (18%) Improved background 9 (41%) Unchanged background 9 (41%) Worsening background
Immediate pre-arrest	0 (0%) Normal continuous/discontinuous 1 (5%) Continuous low voltage 8 (36%) Excessively discontinuous 2 (9%) Burst Suppression 11 (50%) Low voltage suppressed 0 (0%) Not recorded	0 (0%) Improved background 0 (0%) Unchanged background 22 (100%) Worsening background
Duration of EEG change prior to cardiac arrest (minutes), median (IQR)		3 (1.5,3)

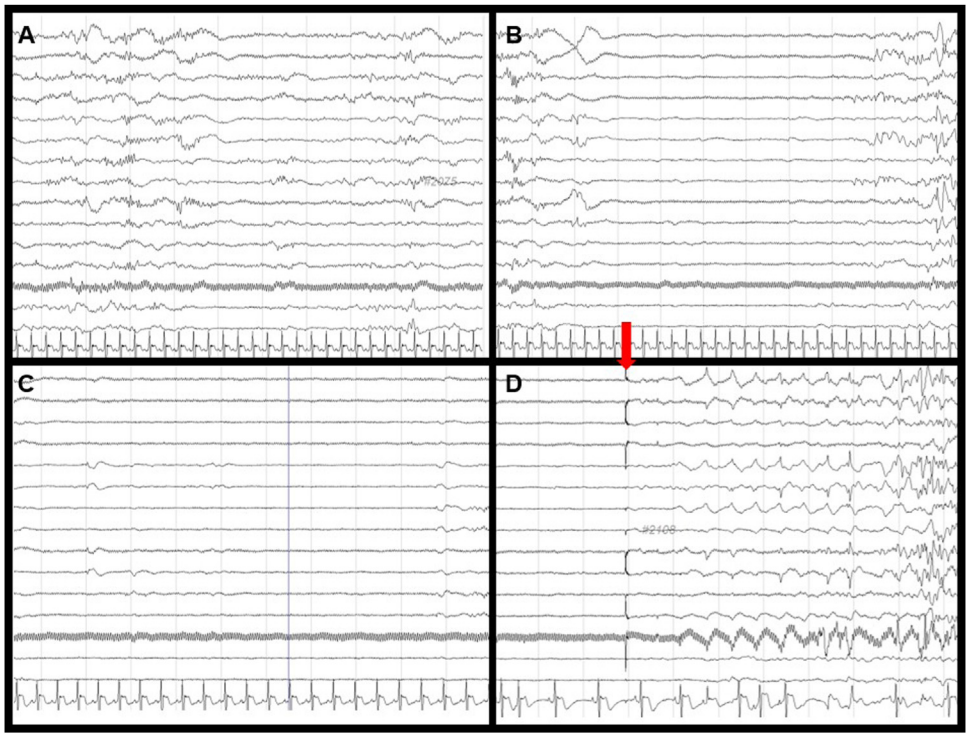

Fig. 3 – Example of EEG Changes Preceding Cardiac Arrest.
Time-lapsed presentation of a subject's EEG changes prior to cardiac arrest. Initial EEG background upon monitoring onset was continuous low voltage (A). The first irreversible EEG change prior to cardiac arrest was when the background became excessively discontinuous due to prolonged, attenuated interburst intervals (B). This change occurred at a median of 3 min prior to cardiac arrest across the cohort. The EEG background continued to decline and the background immediately prior to cardiac arrest was low voltage suppressed with invariant, attenuated activity (C). Cardiac arrest is recognized with irregular heart rate shown in bottom single electrocardiogram channel with subsequent cardiopulmonary resuscitation artifact [onset of CPR denoted by arrow] (D).

Discussion

We aimed to characterize the changes that occur on continuous EEG prior to post-operative CA in a large, contemporary, prospectively acquired cohort of neonates with CHD undergoing surgical repair with CPB. The EEGs of all included neonates had an acute worsening of the EEG background prior to CA at a median of three minutes prior to recognition of CA by traditional CR markers and initiation of CPR. Eighty-two percent of patients had an irreversible EEG change identified at least one minute prior to CA. Thus, we have demonstrated the ability to detect irreversible changes preceding CA in neonates with CHD using conventional visual analysis of EEG minutes before changes were identified in more traditional markers of impending CA. Though the changes detected on EEG are secondary to the underlying CR collapse that the neonates were experiencing, EEG offers a second-by-second monitor of function of an organ affected by changes in perfusion, thereby providing a unique opportunity to continually assess the cerebral effects of CR decompensation. Our goal is to operationalize this information to provide an actionable window of opportunity for intervention prior to CA to protect the brain from secondary hypoperfusion injury and ultimately prevent CA to reduce subsequent mortality and neurodevelopmental morbidity.[17]

There is a strong correlation between systemic and cerebral perfusion. While the blood supply to the brain is typically preserved in early phases of systemic hypoperfusion,[24,25] continued low systemic blood flow eventually impacts cerebral perfusion.[26] In adult populations, EEG data not only correlate with changes in cerebral blood flow (CBF), but also to predict worsening brain ischemia. In adults, EEG changes such as diffuse background slowing and focal abnormalities are persistently present at a decreasing CBF of 17 milliliters per minute or less.[27] More recently, with increased use of EEG monitoring in medical and surgical intensive care units, a focus has been placed on the correlation between EEG changes and CBF, and the ability to use EEG data to predict outcomes in brain-injured adults and detect pre-symptomatic changes in brain ischemia.[28–30] To date, this work has not been replicated in children or neonates.

While prediction models of CA do not exist for neonates, they have been developed for other pediatric populations, demonstrating feasibility. Several groups have developed and described processes for successfully creating prediction models for CA for patients in the pediatric intensive care unit (PICU) using various methods. Kennedy et al. used a combination of multivariate clinical data, trend analysis data, and support vector machine learning algorithms to identify CA cases with 94% accuracy.[31,32] In 2016, Niles et al developed a checklist for in-hospital CA that included five domains of variables

(respiratory, circulatory, neurologic, metabolic, other) and had a sensitivity of 100% and specificity of 98% for code bell activation within the ensuing 24 h.[33] While the neurologic criterion did not include EEG data, the presence of elevated intracranial pressures with concurrent need for blood pressure support to maintain cerebral perfusion pressure was included, allowing the model to account for the intricate relationship between systemic and cerebral perfusion. Other investigators have focused on identifying clinical features with early predictive ability for CA among patients in the PICU.[34] While prediction models for CA in critically ill pediatric populations show promise, they rely solely on clinical, often subjective, data. To date, none of the models have utilized objective neurophysiologic markers of cerebral activity, such as EEG. EEG data may increase the predictive ability of these models as EEG is an objective measure of brain function and prior studies have demonstrated that EEG background patterns and features are highly predictive of various acute and chronic outcomes in neonatal populations.[35]

While our findings provide a promising first step, additional work is needed to validate and extend these findings. We have only evaluated EEG of neonates with CA. It will be imperative to next examine postoperative EEG changes among neonates with CHD who do not experience CA. Next steps will also include quantitative assessment of EEG changes that precede CA. Quantitative EEG (QEEG) transforms raw EEG data mathematically to derive objective data which is not visually identifiable from the time varying EEG signal, limiting subjectivity from visual analysis of EEG and permitting EEG assessment automation so EEG data can be more readily incorporated into clinical care and decision-making. QEEG features are currently clinically used in adult populations to detect changes in CBF.[28] QEEG may better define the changes that we have detected through visual analysis in the pre-arrest period and reveal novel changes that are not visible to the human eye but may be more predictive and readily available at the bedside than visually assessed EEG changes. Lastly, given that EEG changes represent a secondary effect of hypoperfusion of the brain from the primary issue of CR decompensation, we ultimately plan to incorporate the continuous EEG data into multi-modal models of neonatal CA prediction that include relevant clinical data (gestational age, CHD type, surgical repair type and details) and time varying CR measures (blood pressure, pulse, and peripheral and central oxygenation). The combination of EEG data with clinical features and traditional means of assessing CR status may maximize prediction of CA leading to earlier identification of at-risk neonates and expanding the window for intervention and prevention.

There are limitations to this work. First, the reported EEG changes were discovered through visual EEG analysis. While EEG is an objective measure of brain cortical and subcortical network activity, the interpretation of EEG signals is subjective.[36–39] Specifically for neonatal EEG interpretation, variability exists in interpretation of background features and patterns for term neonates, even among experts trained in neonatal EEG interpretation.[22,23] Therefore, studies utilizing visual analysis of EEG are subject to interrater agreement limitations, potentially limiting reproducibility. It is notable, however, that despite the degree of variability that exists for specific neonatal feature interpretation, agreement improves dramatically when electroencephalographers are asked to provide an overall assessment of the background. Studies have demonstrated moderate interrater agreement in overall background assessment using four-level [normal, mildly abnormal, moderately abnormal, severely abnormal][22] and 5-level [normal, excessively discontinuous, burst suppression, status epilepticus, electrocerebral inactivity][23] scales like used in this study. Thus, the use of an overall EEG background assessment scale would suggest acceptable reliability. Second, this initial work only analyzed the EEG patterns of neonates with CA. Without evaluation for similar peri-CA patterns among a control group of neonates without CA who underwent EEG monitoring, we cannot state definitively that these EEG patterns are only seen with impending CA. The next phase of the current study will assess the positive and negative predictive values of these EEG patterns for impending CA.

Conclusion

EEG changes precede neonatal post-operative CA at a median of three minutes prior to bedside recognition of impending CR failure using traditional markers. Further exploration is required to develop clinically relevant and useful EEG biomarkers for CA. Multimodal CA prediction models that incorporate EEG, clinical, and CR biomarkers may ultimately provide a longer period for intervention prior to CA to prevent unfavorable acute and chronic outcomes in this fragile population.

Conflicts of interest

None.

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