Electrographic Seizures in Children and Neonates Undergoing Extracorporeal Membrane Oxygenation

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Objective: We aimed to determine the prevalence and risk factors for electrographic seizures in neonates and children requiring extracorporeal membrane oxygenation support.

Design: Prospective quality improvement project.

Setting: Quaternary care pediatric institution.

Patients: Consistent with American Clinical Neurophysiology Society electroencephalographic monitoring recommendations, neonates and children requiring extracorporeal membrane oxygenation support underwent clinically indicated electroencephalographic monitoring.

Interventions: We performed a 2-year quality improvement study from July 2013 to June 2015 evaluating electrographic seizure prevalence and risk factors.

Main Results: Ninety-nine of 112 patients (88%) requiring extracorporeal membrane oxygenation support underwent electroencephalographic monitoring. Electrographic seizures occurred in 18 patients (18%), of whom 11 patients (61%) had electrographic status epilepticus and 15 patients (83%) had exclusively electrographic-only seizures. Electrographic seizures were more common in patients with low cardiac output syndrome ($p = 0.03$). Patients with electrographic seizures were more likely to die prior to discharge (72% vs 30%; $p = 0.01$) and have unfavorable outcomes (54% vs 17%; $p = 0.004$) than those without electrographic seizures.

Conclusions: Electrographic seizures occurred in 18% of neonates and children requiring extracorporeal membrane oxygenation support, often constituted electrographic status epilepticus, and were often electrographic-only thereby requiring electroencephalographic monitoring for identification. Low cardiac output syndrome was associated with an increased risk for electrographic seizures. Electrographic seizures were associated with higher mortality and unfavorable outcomes. Further investigation is needed to determine whether electrographic seizures identification and management improves outcomes. (*Pediatr Crit Care Med* 2017; 18:249–257)

Key Words: electroencephalography; extracorporeal membrane oxygenation; pediatric; seizures; status epilepticus

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Extracorporeal membrane oxygenation (ECMO) is a temporary support for patients with cardiopulmonary disease. Patients requiring ECMO support are at risk for neurological injury due to pre-ECMO medical conditions, management during ECMO support, or combined effects (1–7), which may result in acute symptomatic seizures (8). As recently reviewed (9), clinical and electrographic seizures (ES) have been reported in 5–30% of neonates and children undergoing ECMO (2, 5, 10–14). Furthermore, seizures during ECMO have been

associated with cerebral injury and worse outcomes in some, but not in all, studies (5, 11, 12, 15, 16). However, most of the studies addressing seizure prevalence and outcome have included nonconsecutive cohorts without standardized use of continuous electroencephalographic monitoring (cEEG) to identify ES (2, 5, 10–14). A recent systematic literature review regarding the use and effectiveness of neuromonitoring methods during ECMO identified only seven studies related to electroencephalogram, including two with one- to two-channel amplitude integrated electroencephalogram and five with intermittent conventional multichannel electroencephalogram. There were no studies that had consistently assessed seizures using cEEG (17). The resulting epidemiologic knowledge gaps (9, 17) lead to uncertainty regarding the appropriate role for cEEG, which is resource intense and not available at all institutions (18, 19). Despite these limited data, a neonatal guideline (20) and a pediatric consensus statement (21) from the American Clinical Neurophysiology Society both recommend cEEG in neonates and children at risk for ES, including those undergoing ECMO support.

To help guide management at our institution, we implemented the American Clinical Neurophysiology Society's recommendations and performed a 2-year quality improvement project that aimed to establish the prevalence and risk factors for ES in a large contemporary cohort of neonates and children requiring ECMO support. Our rationale was that if ES were very uncommon, then cEEG might not be indicated for most patients undergoing ECMO. Alternatively, if ES were common, then use of cEEG to identify and manage ES might be a neuroprotective strategy warranting further evaluation.

METHODS

Design and Clinical Context

This was a single-center observational project. Consistent with the American Clinical Neurophysiology Society's neonatal guideline (20) and pediatric consensus statement (21) regarding cEEG, patients requiring ECMO support underwent clinically indicated cEEG to screen for ES. Implementation was guided by an interdisciplinary ICU cEEG pathway developed as part of the institution's quality improvement framework (22). To evaluate whether to continue or modify this practice, we performed a quality improvement project over 2 years (July 2013 to June 2015). We aimed to determine the prevalence and risk factors for ES to guide subsequent use of limited and resource-intense cEEG at our institution (18, 19).

Patients were managed in closed ICUs by neonatologists and/or critical care medicine physicians. The electroencephalographic service interpreted the electroencephalograms, and the neurology service consulted on all patients with seizures.

Data were collected and managed using Research Electronic Data Capture, a web-based electronic data application hosted at the Children's Hospital of Philadelphia Research Institute (23). The project was reviewed by the institutional review board and was considered as exempt from requiring approval. The study is presented in accordance with the Guidelines for the Standardized Quality Improvement Reporting Excellence (24, 25).

Clinical Data

Data obtained from the electronic medical record included age at ICU admission, age at ECMO initiation, sex, weight, medical and neurologic diagnoses prior to ECMO initiation, ICU type (neonatal, cardiac, or pediatric), ECMO indication, ECMO type (veno-arterial [VA] or veno-venous [VV]), ECMO cannulation site (neck or chest), ECMO duration, ventilator type (conventional, oscillation, or volumetric diffusion respirator), paralytic use, clinical seizures prior to ECMO initiation, complications during ECMO, neuroimaging findings, mortality, and survival outcome.

Medical conditions leading to ECMO and pre-existing neurologic conditions are provided in **Table 1**. Patients could have more than one condition. Because some of these categories involved only a small number of patients, we created a "Main ECMO Indication" variable that categorized ECMO indications into five discrete categories: 1) ECMO cardiopulmonary resuscitation (E-CPR), 2) cardiac arrest, 3) postbypass, 4) cardiac etiology, and 5) respiratory etiology. For categories 1–3, patients were categorized as the lowest numerical category for which they qualified (i.e., a patient with E-CPR who was postbypass would be categorized as E-CPR). A low cardiac output syndrome was defined as administration of an inotropic or vasopressor agent (dopamine, dobutamine, milrinone, or epinephrine) prior to ECMO initiation to maintain a normal systolic blood pressure for age. Patients not categorized as 1–3 were assigned to either category 4 or 5. If patients had multiple neuroimaging modalities, we included the best imaging modality in the analysis (i.e., MRI over CT over ultrasound). Outcome was assessed at hospital discharge using the pediatric cerebral performance category (PCPC) score, which is a validated six-point scale categorizing degrees of functional impairment (1 = normal, 2 = mild disability, 3 = moderate disability, 4 = severe disability, 5 = coma and vegetative state, and 6 = death) (26). Favorable outcome was defined as a PCPC scores of 1–2 and unfavorable outcome was defined as PCPC scores of 3–6.

Electroencephalographic Monitoring, Electroencephalographic Data, and Seizure Management

Monitoring used a conventional video-electroencephalographic system (Grass Technologies, West Warwick, RI) and electrodes placed according to the international 10–20 system with standard neonatal modification when appropriate. Based on our institutional ICU cEEG pathway (22) and published consensus statements (21, 27), cEEG lasted 1–2 days when screening for ES, with the exact duration at the discretion of the primary clinical service. If clinical changes occurred leading the clinical team to suspect seizures might occur later, then cEEG could be continued for longer. If ES were identified, then cEEG occurred until at least 24 hours after the end of the last ES. Electroencephalographic tracings were reviewed by a combination of electroencephalographic technologists and pediatric electroencephalographers about every 6 hours or more often if clinical changes occurred or the primary team noted events of unclear etiology. Electroencephalographic data were

TABLE 1. Clinical and Electroencephalographic Data in Subjects With and Without Electrographic Seizures

Variable	Total (*n* = 99)	No Seizures (*n* = 81; 82%)	Electrographic Seizures (*n* = 18; 18%)	*p*
Sex female	47 (47%)	40 (85%)	7 (15%)	0.42
Age at ICU admission (d)	4 (0–229)	3 (0–316)	16 (0–112)	0.50
Age at ECMO initiation (d)	14 (3–281)	13 (3–364)	20 (3–120)	0.58
Weight (kg)	4.7 (3.9–9.4)	4.7 (3.9–9.8)	4.6 (3.5–6.5)	0.25
ICU				0.05
Neonatal	35 (35%)	32 (91%)	3 (9%)	
Cardiac	51 (52%)	37 (73%)	14 (27%)	
Pediatric	13 (13%)	12 (92%)	1 (8%)	
Diagnoses prior to ECMO initiation[a]				
Cardiac diagnoses				
Cardiac arrest (with or without E-CPR)	33 (33%)	28 (84%)	5 (15%)	0.58
Congenital heart disease: preoperative	8 (8%)	7 (88%)	1 (13%)	0.66
Congenital heart disease: postoperative	45 (45%)	33 (73%)	12 (27%)	0.05
Low cardiac output syndrome	48 (48%)	35 (73%)	13 (27%)	**0.03**
Cardiopulmonary bypass (with or without E-CPR or cardiac arrest)	39 (39%)	29 (74%)	10 (25%)	0.12
Arrhythmia	8 (8%)	7 (88%)	1 (13%)	0.66
Pulmonary diagnoses				
Congenital diaphragmatic hernia	17 (17%)	15 (88%)	2 (12%)	0.45
Persistent pulmonary hypertension	42 (42%)	38 (90%)	4 (10%)	0.06
Meconium aspiration	8 (8%)	8 (100%)	0 (0%)	0.16
Acute respiratory distress syndrome/pneumonia/hypoxic respiratory failure	16 (16%)	15 (94%)	1 (6%)	0.17
Other				
Sepsis	3 (3%)	2 (67%)	1 (33%)	0.49
Prior neurologic disorder	20 (20%)	16 (80%)	4 (20%)	0.81
Main ECMO Indication				0.19
E-CPR	14 (14%)	10 (71%)	4 (29%)	
Cardiac arrest (no E-CPR)	19 (19%)	18 (95%)	1 (5%)	
Post bypass (no E-CPR or cardiac arrest)	27 (27%)	20 (74%)	7 (26%)	
Cardiac etiology	16 (16%)	12 (75%)	4 (25%)	
Respiratory etiology	23 (23%)	21 (91%)	2 (9%)	
Paralytics administered	83 (84%)	69 (83%)	14 (17%)	0.44
Ventilator mode				0.33
Conventional	70 (71%)	55 (79%)	15 (21%)	
Oscillation	23 (23%)	20 (87%)	3 (13%)	
Volumetric diffusive respirator	6 (6%)	6 (100%)	0 (0%)	

(*Continued*)

TABLE 1. (*Continued*). Clinical and Electroencephalographic Data in Subjects With and Without Electrographic Seizures

Variable	Total (*n* = 99)	No Seizures (*n* = 81; 82%)	Electrographic Seizures (*n* = 18; 18%)	*p*
Clinical seizures prior to ECMO	5 (5%)	4 (80%)	1 (20%)	0.91
ECMO type				0.06
Veno-arterial	85 (86%)	67 (79%)	19 (21%)	
Veno-venous	14 (14%)	14 (100%)	0 (0%)	
ECMO cannulation site				0.53
Neck	77 (78%)	64 (83%)	13 (17%)	
Chest	22 (22%)	17 (77%)	5 (23%)	
Electroencephalographic initial background category				0.05
Normal	16 (16%)	16 (100%)	0 (0%)	
Slow-disorganized	68 (69%)	52 (76%)	16 (24%)	
Excessive discontinuity or burst- suppression	6 (6%)	4 (67%)	2 (33%)	
Attenuated-featureless	9 (9%)	9 (100%)	0 (0%)	
Electroencephalographic focal abnormalities[a]				
None	87 (88%)	71 (82%)	16 (18%)	0.85
Slowing	3 (3%)	3 (100%)	0 (0%)	0.47
Attenuation	7 (7%)	6 (86%)	1 (14%)	0.78
Interictal epileptiform discharges	5 (5%)	4 (80%)	1 (20%)	0.91
Electroencephalographic duration (hr)	49 (47–80)	48 (46–61)	90 (80–118)	**<0.01**
ECMO duration (d)	7 (3–11)	7 (3–11)	8 (4–11)	0.52

E-CPR = ECMO cardiopulmonary resuscitation, ECMO = extracorporeal membrane oxygenation.

[a]Total is greater than 99 subjects because each subject may have more than one diagnosis prior to ECMO or more than one focal electroencephalographic abnormality.

Data are presented as *n* (%) or median (interquartile range).

provided to the clinical teams at least daily or more often if any change occurred including the occurrence of ES.

Electroencephalographic tracings were interpreted using standardized American Clinical Neurophysiology Society terminology (20, 28). Initial electroencephalographic background categories were scored at the start of the recording and were categorized as 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. Focal abnormalities including slowing, attenuation, and interictal epileptiform discharges were scored as present if they occurred at any point during the recording. ES were scored as present if they occurred at any point during the recording. ES were defined as an abnormal paroxysmal event that was different from the background, lasting longer than 10 seconds (or shorter if associated with a clinical change) with a temporal-spatial evolution in morphology, frequency, and amplitude, and with a plausible electrographic field. Electrographic status epilepticus was defined as either a single 30-minute ES or a series of recurrent ES totaling more than 30 minutes in any 1-hour period (50% seizure burden). Patients were scored as having electrographic status epilepticus if it occurred at any point during the recording. ES were classified as electroencephalographic-only seizures (no clinical signs observed by bedside caregivers or on video review) or electroclinical seizures (clinical abnormal stereotypic and paroxysmal movements associated with the electroencephalographic seizure). These definitions are consistent with prior ICU electroencephalographic studies (29–31).

Prophylactic antiseizure medications were not administered. If ES were identified, then the initial antiseizure medications were selected by the primary ICU service and the neurology consultation service. Clinical practice at our institution is to generally initiate treatment with intravenous loading doses of levetiracetam (20–40 mg/kg) for non-neonates or phenobarbital (20 mg/kg) for neonates, which is sometimes divided into two boluses for patients with hemodynamic instability.

Analysis

Statistical analyses were performed using Stata 12 (College Station, TX). Descriptive data were presented as medians with interquartile ranges or percentages. For key proportions (prevalence of ES and electrographic status epilepticus), exact 95%

CIs were calculated. Risk factors for ESs and outcomes were assessed with the Wilcoxon rank-sum or chi-square tests. p value of less than 0.05 was considered significant.

RESULTS

Clinical Characteristics

A total of 112 neonates and children received ECMO support within the project period, and 99 (88%) underwent cEEG. Patients who underwent cEEG constituted the quality improvement project cohort. Electroencephalographic monitoring was initiated within 24 hours of ECMO initiation in 84 patients (85%), within 24–48 hours in seven patients (7%), and after 48 hours in eight patients (8%). Electroencephalographic monitoring lasted 1 day for 11 patients (11%), 2 days for 40 patients (40%), 3 days for 22 patients (22%), and more than 3 days for 26 patients (26%).

ES occurred in 18 of 99 patients who underwent cEEG (18%) (95% CI, 11–27%). Thirteen patients did not undergo cEEG monitoring; if none of those patients experienced seizures, then the prevalence would have been 16% (18 of 112). Among patients with ES, 11 patients (61%) had electrographic status epilepticus (95% CI, 36–83%). Seizures were exclusively electrographic-only in 15 patients (83%), and three patients (17%) had both electrographic-only and electroclinical seizures. Fourteen patients were receiving paralytics that may have masked observable clinical manifestations. The median duration from cEEG initiation to the initial ES was 15 hours (interquartile range [IQR], 6–24 hr).

Table 1 compares patients with and without ES. The only significant risk factor for ES was low cardiac output syndrome prior to ECMO initiation, which occurred in 72% with ES (13 of 18) and 43% without ES (25 of 81) ($p = 0.03$). Although not statistically significant, several trends may warrant evaluation in larger cohorts. Seizures occurred in 21% of patients (19 of 85) who received VA ECMO support and 0% of patients (0 of 14) who received VV ECMO support ($p = 0.06$). Seizures occurred in 28% of patients (14 of 51) in the cardiac ICU, 9% of patients (3 of 35) in the neonatal ICU, and 8% of patients (1 of 13) in the PICU ($p = 0.05$). However, that relationship may reflect that VV ECMO was used more often in the NICU (20%) and PICU (54%) than in the CICU (0%) ($p < 0.001$). Some of these predictor variables are collinear; all patients postoperative for congenital heart disease received VA ECMO in the CICU, all but one patient with low cardiac output syndrome received VA ECMO, and persistent pulmonary hypertension was more common in NICU patients. ES did not occur in any patients when the initial electroencephalographic background was normal (16 patients) or attenuated-featureless (nine patients), but occurred in 24% of patients (16 of 68) with a slow-disorganized initial electroencephalographic background and 33% of patients (2 of 6) with an excessively discontinuous or burst-suppression initial electroencephalographic background ($p = 0.05$). The median cEEG duration was longer in patients with ES (median, 90 hr; IQR, 80–118) than in those without ES (median, 48 hr; IQR, 46–61)($p < 0.001$), consistent with our clinical practice of continuing cEEG during and for 24 hours after ES management.

Table 2 describes ES characteristics and management by patient. Of the 18 patients with ES, the initial antiseizure medication administered was phenobarbital for 72% of patients (13) and levetiracetam for 22% of patients (4). One patient with myoclonic electrographic status epilepticus in the context of diffuse hypoxic-ischemic encephalopathy had seizure cessation without administration of any antiseizure medication during progression to brain death. Among the 17 patients who received antiseizure medications, ES ceased after the initial antiseizure medication in 29% of patients (5), after two antiseizure medications in 29% of patients (5), after three or more antiseizure medications in 18% of patients (3), and remained refractory in 24% of patients (4).

Neuroimaging Data

Neuroimaging studies were performed in 83% of patients (82 of 99) who underwent cEEG, and the best neuroimaging technique performed was ultrasound in 56% of patients (46), CT in 17% of patients (14), and MRI in 27% of patients (22). The duration from ECMO initiation to neuroimaging was median 9 days (IQR, 2–16 d). The duration from seizure identification to neuroimaging was median 8 days (IQR, 4–12 d) in patients with both seizures and neuroimaging. Acute abnormalities were described in 50% of patients (41 of 82). The most common acute abnormality was intracranial hemorrhage that occurred in 37% of patients (30) and included intraventricular hemorrhage in 22% of patients (18), subdural hemorrhage in 7% of patients (6), and parenchymal hemorrhage in 11% of patients (9). Other acute abnormalities included hypoxic-ischemic brain injury in 13% of patients (11), thrombotic stroke in 12% of patients (10), and cerebral edema in 5% of patients (4). Acute abnormalities occurred in 45% of patients without ES (29 of 65) and in 71% of patients with ES (12 of 17) ($p = 0.057$). Acute abnormalities occurred in two of two patients with focal electroencephalographic slowing, four of four patients with focal electroencephalographic attenuation, and three of five patients with focal epileptiform discharges. Neuroimaging abnormalities were equally likely in patients receiving VA (48%) and VV (64%) ECMO support ($p = 0.33$). Table 2 provides the neuroimaging findings for the patients with ES.

Outcomes

Forty-five percent of patients (45) died. Mortality occurred due to cardiac arrest without return of spontaneous circulation in 13% of patients (6) and withdrawal of technological support in 87% of patients (39), including withdrawal of ECMO in 28 patients. Mortality did not differ by type of ECMO support: VA (48%) or VV (29%) ($p = 0.17$). Death was more common in patients with ES (13 of 18, 72%) than in those without ES (32 of 81, 30%) ($p = 0.01$). Forty-seven percent of patients (47) had a favorable neurologic outcome and 53% of patients (52) had an unfavorable neurologic outcome. Patients with ES (3 of 18, 17%) were less likely to have a favorable neurologic outcome than those without ES (44 of 81, 54%) ($p = 0.004$).

TABLE 2. Seizure, Seizure Management, and Neuroimaging Data in Subjects With Electrographic Seizures

Subject	ESE	Exclusively Electroencephalogram-Only Seizures	Seizure Description	Antiseizure Medications	Neuroimaging
1	No	Yes	Six right central-temporal ES lasting 2 min	PB	US: normal
2	No	Yes	~6 ES per hour from right central-temporal regions lasting 0.5–3 min	PB, LEV	US: normal
3	No	Yes	~9 ES per hour from right occipital regions lasting 0.5–1 min	PB,	US: multifocal hemorrhage centered in the right parietal region
4	No	Yes	Three right occipital ES lasting <1 min	PB	US: normal
5	No	Yes	One right occipital ES lasting ~3 min	PB	MRI: punctate hemorrhage in the right parietal and left frontal lobe
6	No	Yes	10 right frontal ES lasting 0.5–0.75 min	PB	US: normal
7	No	Yes	Seven right frontal and bi-frontal ES lasting 0.2–3 min	LEV, PB	US: normal
8	Yes	Yes	Bilateral independent ESE (continuous seizure)	PB, PHT	CT: multiple infarctions in the right hemisphere
9	Yes	Yes	Left occipital seizures ESE (continuous seizure).	LEV, PB	US: increased echogenicity in the bilateral thalami
10	Yes	Yes	Right hemisphere ESE (continuous seizure).	PB, LEV	Not performed (withdrawal of technological support).
11	Yes	No	Left occipital ESE (independent seizures each lasting for 0.5–5 min).	PB, LEV	US: hemorrhagic infarction in the left parieto-occipital region
12	Yes	No	Bilateral independent ESE (independent seizures each lasting ~1.5 min)	PB, PHT	MRI: multiple infarction through the left hemisphere and basal ganglia.
13	Yes	Yes	Bilateral temporal and left occipital independent ESE (independent seizures each lasting 0.5–1.5 min)	LEV, PB	US: periventricular leukomalacia
14	Yes	No	Bicentral ESE (independent seizures each lasting 1–2 min)	PB, PHT, LEV, MDZ	MRI: acute-subacute hypoxic-ischemic injury
15	Yes	Yes	Left hemisphere ESE (independent seizures each lasting 0.5–2 min)	PB, LEV	US: hemorrhage in the left temporal region with significant mass effect
16	Yes	Yes	Left occipital ESE (independent seizures each lasting 1–2 min)	PB, PHT, LEV	CT: small left posterior temporal-occipital hemorrhage
17	Yes	Yes	Right central-temporal ESE.	LEV, PB, MDZ, pentobarbital	MRI: hypoxic-ischemic injury
18	Yes	Yes	Diffuse ESE	No	CT: hypoxic-ischemic injury

ES = electrographic seizure(s), ESE = electrographic status epilepticus, LEV = levetiracetam, MDZ = midazolam, PB = phenobarbital, PHT = phenytoin, US = ultrasound.

Among the 54 patients who survived to discharge, patients without ES were not significantly more likely to have favorable outcomes than those with ES (44 of 49, 90% vs 3 of 5, 60%; $p = 0.06$). Worse electroencephalographic background categories were associated with mortality and unfavorable outcomes among survivors (**Table 3**).

DISCUSSION

Given recent recommendations to perform cEEG in neonates and children at risk for ES (20, 21) despite many knowledge gaps regarding the utility of cEEG in this population (17), we performed a single-center quality improvement project to determine the prevalence and risk factors for ES among

TABLE 3. Outcome by Electroencephalographic Background Categories

Outcome	Initial Background Electroencephalogram Category				
	Normal	Slow-Disorganized	Excessively Discontinuous or Burst-Suppression	Attenuated-Featureless	*p*
Survive to discharge	75% (12 of 16)	54% (37 of 68)	67% (4 of 6)	11% (1 of 9)	**0.02**
Favorable outcome (pediatric cerebral performance category 1–2) among survivors	83% (10 of 12)	92% (34 of 37)	75% (3 of 4)	0% (0 of 1)	**0.04**

neonates and children requiring ECMO support. Continuous electroencephalographic monitoring was performed in 88% of 112 eligible patients. ES occurred in 18% (95% CI, 11–27%). If none of the 13 patients who did not undergo cEEG experienced ES, then the lower prevalence would have been 16%. Among patients with ES, the seizure exposure was often high (61% experienced electrographic status epilepticus) and cEEG was often required for ES identification (83% had exclusively electrographic-only seizures).

A recent systematic literature review of neuromonitoring during ECMO support indicated data are very limited regarding electroencephalogram use in patients requiring ECMO support, including only seven total studies that used either one- to two-channel amplitude integrated electroencephalogram or intermittent conventional multichannel electroencephalogram (17). By providing a large contemporary cohort of nearly consecutive patients requiring ECMO support with concurrent cEEG, our data add substantially to the epidemiologic literature regarding seizures among patients requiring ECMO (9). A study of the Extracorporeal Life Support Organization Registry that included 26,529 patients reported clinical seizures in 8% and ES in 2% of patients. The study excluded patients with cardiopulmonary arrest and most patients did not undergo cEEG (2). A registry study that included only cardiac cases of varying ages reported clinical seizures in 6–10% (10). A single-center study reported clinical seizures in 30% of 50 infants undergoing ECMO (11). ES have been described as more common than clinically evident seizures with ES reported in 8–21% and electrographic status epilepticus in 11–50% of those with ES (5, 12–14). However, these studies were smaller and did not perform cEEG in all consecutive patients, and this may explain why the prevalence in our project (18%) is higher than previously reported, particularly because 83% of patients with ES experienced exclusively electrographic-only seizures, which would not be identified without cEEG.

We aimed to identify risk factors for ES because these might help direct limited and resource-intense cEEG to the patients most likely to experience seizures. Only patients with low cardiac output syndrome prior to ECMO had a significantly higher seizure risk. These patients may have been at increased risk for acute brain injury leading to acute symptomatic seizures although our project did not allow investigation of causative mechanisms such as assessment of cerebral blood flow or oxygenation. Several potential risk factors were not significantly associated with seizures in our study, but may warrant further study in larger cohorts; these included patients requiring VA ECMO, postoperative patients with congenital heart disease surgery receiving care in the cardiac ICU, and patients with persistent pulmonary hypertension. Further, because ES only occurred in patients with initial electroencephalographic backgrounds that are slow-disorganized or excessively discontinuous or burst-suppression, patients with more normal (slow-disorganized) or more abnormal (flat-attenuated) background patterns on an initial electroencephalogram might not require cEEG. These variables warrant study in future larger prospective cohort studies to develop ES prediction models that could improve utilization of limited cEEG resources.

The impact of seizures on outcome remains uncertain. Several studies have found that ES are risk factors for subsequent mortality and neurodevelopmental disorders among survivors (11–13, 15, 16). In contrast, a recent study of ECMO in 19 children did not find an association between seizures and outcome (5). Our data add to this literature by addressing the full spectrum of seizures through the use of cEEG. ES were associated with mortality and unfavorable outcomes among survivors. Further, the fact that most patients had exclusively electrographic-only seizures suggests that studies relying on clinical identification of seizures may experience misclassification bias in which patients experiencing exclusively electrographic-only seizures are classified as "no-seizure" patients. Further study is needed to determine whether seizure management is associated with improved outcomes. In our cohort, seizures terminated after one to two antiseizure medications were administered in 58% of patients, indicating management may often be achieved with administration of standard antiseizure medications. However, our study cannot establish any causal relationship between ES and unfavorable outcomes; ES might simply be a biomarker of underlying brain injury.

Our data indicate that patients with attenuated-featureless electroencephalographic backgrounds were more likely to experience unfavorable outcomes, whereas other initial electroencephalographic background patterns including discontinuous or burst-suppression patterns were not associated with unfavorable outcomes. In a prior study of 36 neonates undergoing ECMO, a burst-suppression pattern was associated with a significantly increased risk of death or severe outcome (12). Similarly, in a study of 199 neonates followed up at 12–45 months of age, neonates with two electroencephalographic

tracings with ES or burst-suppression had an increased odds ratio for poor prognosis (32). However, a follow-up study by the same group reported that in 66 school age survivors of neonatal ECMO without severe brain injury who could undergo neuropsychological testing, electroencephalographic background severity during ECMO did not predict academic and achievement testing at school age (33). With further development, electroencephalogram might allow not only prognostication but modification of acute management to reduce the likelihood of acute brain injury.

There were several limitations to this project. First, we monitored the majority of patients very soon after ECMO initiation and some patients may have had ES after cEEG was discontinued. Additionally, some patients could have experienced ES before cEEG initiation. Studies using more immediate and longer duration cEEG could better characterize ES epidemiology. Second, a small proportion of patients did not undergo cEEG. Most likely given the common use of cEEG at our institution, primary teams chose not to use cEEG, but the reasons underlying those clinical decisions are unknown. Third, clinicians managed ES using antiseizure medications, yet patients with ES still had unfavorable outcomes. We cannot determine whether outcomes might have been worse had ES gone unmanaged, or whether more optimized management might improve outcomes. Finally, because neuroimaging was performed at varying times and patient's underlying medical diagnoses may have evolved along varying time-courses relative to ECMO initiation, cEEG monitoring, and neuroimaging, we cannot establish causal relationships between these variables; there may be confounding between the effects of seizures and structural brain abnormalities on outcomes. Overall, given the limitations including etiologic heterogeneity in this cohort, variable electroencephalographic initiation timing, variable neuroimaging timing, and other confounders not accounted for in our data, the data do not establish that seizures cause worse outcomes. The data merely indicate that ESs occur in a substantial minority of patients undergoing ECMO, and further study is indicated to determine whether seizure identification and management might reduce secondary brain injury and improve neurobehavioral outcomes.

CONCLUSIONS

We implemented American Clinical Neurophysiology Society recommendations for cEEG during ECMO (21, 27) for 99 of 112 patients (88%) requiring ECMO support. ES occurred in 18% of patients. Among patients with ES, 61% experienced electrographic status epilepticus and 83% experienced electrographic-only seizures only identifiable by cEEG. Further study is needed to determine whether ES prediction models can be developed from larger datasets to improve utilization of limited cEEG resources and also to determine whether optimized seizure identification and management strategies improve patient outcomes. Although recognizing these limitations, given the 18% prevalence of ES and the often high seizure burden, our institution has decided to continue our practice of performing cEEG for 1–2 days at ECMO initiation and to perform additional cEEG monitoring later if there are clinical changes suggesting a neurologic insult may have occurred (22).

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