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High incidence of epileptiform activity in adults undergoing extracorporeal membrane oxygenation☆

Edilberto Amorim[a,b,c,1,*], **Marcos S. Firme**[c,1], **Wei-Long Zheng**[c], **Kenneth T. Shelton**[d], **Oluwaseun Akeju**[e], **Gaston Cudemus**[e], **Raz Yuval**[f], **M Brandon Westover**[c,*]

[a]Department of Neurology, University of California, San Francisco, San Francisco, California, USA

[b]Neurology Service, Zuckerberg San Francisco General Hospital, San Francisco, California, USA

[c]Department of Neurology, Massachusetts General Hospital, Boston, Massachusetts, USA

[d]Department of Medicine, Division of Cardiology, Massachusetts General Hospital, Boston, Massachusetts, USA

[e]Department of Anesthesia, Massachusetts General Hospital, Boston, Massachusetts, USA

[f]Department of Medicine, Division of Pulmonary and Critical Care Medicine, Massachusetts General Hospital, Boston, Massachusetts, USA

Abstract

Objective: The prevalence of seizures and other types of epileptiform brain activity in patients undergoing extracorporeal membrane oxygenation (ECMO) is unknown. We aimed to estimate the prevalence of seizures and ictal-interictal continuum patterns in patients undergoing electroencephalography (EEG) during ECMO.

Methods: Retrospective review of a prospective ECMO registry from 2011–2018 in a university-affiliated academic hospital. Adult subjects who had decreased level of consciousness and underwent EEG monitoring for seizure screening were included. EEG classification followed the

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*Corresponding authorsat: Department of Neurology, Weill Institute for Neurosciences, University of California San Francisco, Zuckerberg San Francisco General Hospital, 1001 Potrero Ave, Building 1, Suite 312, San Francisco, California 94110, USA (E Amorim), Department of Neurology, Massachusetts General Hospital, 15 Parkman Street, Wang ACC 739 L, Boston, Massachusetts, 02114, USA(M.B Westover). edilbertoamorim@gmail.com (E. Amorim), mwestover@mgh.harvard.edu (M Brandon Westover).

[1]These authors contributed equally to this work.

Author Contributions.

E.A., M.S.F., M.B.W. conceptualized and designed the study. E.A., M.S.F., W.L.Z. completed the statistical analysis. E.A., M.S.F., drafted the original manuscript. E.A., M.S.F., and M.B.W. contributed to data production and collection. E.A., M.S.F., W.L.Z., K.T.S., A.O., C.G., Y.R., and M.B.W. reviewed and revised the manuscript as well as provided final approval of the version being submitted. The authors confirm that this manuscript does not overlap with previous publications and the manuscript, data, figures, and tables have not been published previously. This manuscript is not under consideration in another journal.

Statistical Analysis.

The statistical analysis was completed by E.A., M.S.F., W.L.Z., and M.B.W.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.clinph.2022.04.018.

American Clinical Neurophysiology Society criteria. Poor neurological outcome was defined as a Cerebral Performance Category of 3–5 at hospital discharge.

Results: Three hundred and ninety-five subjects had ECMO, and one hundred and thirteen (28.6%) had EEG monitoring. Ninety-two (23.3%) subjects had EEG performed during ECMO and were included in the study (average EEG duration 54 h). Veno-arterial ECMO was the most common cannulation strategy (83%) and 26 (28%) subjects had extracorporeal cardiopulmonary resuscitation. Fifty-eight subjects (63%) had epileptiform activity or ictal-interictal continuum patterns on EEG, including three (3%) subjects with nonconvulsive status epilepticus, 33 (36%) generalized periodic discharges, and 4 (5%) lateralized periodic discharges. Comparison between subjects with or without epileptiform activity showed comparable in-hospital mortality (57% vs. 47%, p = 0.38) and poor neurological outcome (and 56% and 36%, p = 0.23). Twenty-seven subjects (33%) had acute neuroimaging abnormalities (stroke N = 21).

Conclusions: Seizures and ictal-interictal continuum patterns are commonly observed in patients managed with ECMO. Further studies are needed to evaluate whether epileptiform activity is an actionable target for interventions.

Significance: Epileptiform and ictal-interictal continuum abnormalities are frequently observed in patients supported with ECMO undergoing EEG monitoring.

Keywords

EEG; ECMO; Extracorporeal membrane oxygenation; Stroke; Critical care

1. Introduction

Extracorporeal membrane oxygenation (ECMO) is a life support technology that has revolutionized the medical management of patients with cardiovascular and respiratory failure. (Abrams et al., 2014) Technical advances in ECMO practice have expanded the indications and utilization of ECMO in critically ill patients, and neurological complications are increasingly recognized. (Lorusso et al., 2017, 2016; Mateen et al., 2011; Migdady et al., 2020; Shoskes et al., 2020) Many patients requiring ECMO are comatose or require deep sedation for mechanical ventilatory support. Therefore early clinical recognition of neurological complications such as seizures, ischemic stroke, or intracranial hemorrhage is challenging as serial comprehensive neurological examinations cannot be reliably obtained. (Cho et al., 2020; deBacker et al., 2018).

Non-invasive brain monitoring with EEG has emerged as a useful tool for detecting seizures, delirium, and cerebral ischemia in various neurological and non-neurological patients admitted to intensive care units. (Claassen et al., 2004; Kimchi et al., 2019; Rosenthal et al., 2018) In the general critical care population, non-convulsive seizures can affect approximately 20% of patients. In the post-cardiac arrest population, approximately 33% of patients may have seizures or other ictal-interictal continuum (IIC) events, i.e., periodic or rhythmic epileptiform activity that can affect cerebral metabolism and may cause brain injury. (Amorim et al., 2016; Claassen et al., 2004; Foreman et al., 2012; Vespa et al., 2016; Witsch et al., 2017) Neurological symptoms have also been identified with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic, increasing awareness

about these complications. (Lin et al., 2021) Despite its utility in evaluating brain function in the critically ill, few studies on brain monitoring involving adults undergoing ECMO are available. (Cho et al., 2020; Kim et al., 2020; Kobata et al., 2020; Lin et al., 2021; Magalhaes et al., 2020; Peluso et al., 2020; Pozzebon et al., 2018).

This study aimed to define the EEG characteristics of patients undergoing ECMO, focusing on seizures and IIC patterns. We hypothesized that epileptiform activity is common in patients undergoing ECMO support.

2. Materials and Methods

2.1. Study design and subjects

Adult subjects (≥18 years old) undergoing ECMO in a single university-affiliated hospital from 2011 to 2018 were retrospectively identified using a prospective local ECMO database. Of note, this study preceded the SARS-CoV-2. Only subjects who had EEG monitoring performed during ECMO were included. Thus, patients without EEG monitoring or those with only pre-ECMO or post-ECMO EEG monitoring were excluded (Supplementary Tables S1 and S2).

2.2. Data collection and outcome evaluation

Demographic, clinical, imaging, medication, and neurological outcome information were obtained through retrospective review of electronic health records (EHR). Information about neurological comorbidities preceding ECMO initiation was not systematically documented on EHR. In our institution, all patients undergoing ECMO therapy are evaluated daily by a dedicated ECMO team composed of intensivists with experience and advanced training in ECMO. Information about ECMO procedures, complications, and outcomes are systematically recorded as part of the Extracorporeal Life Support Organization (ELSO) registry. Additional review of all subjects included in this study was performed for abstraction of additional clinical information and information from EEG and neuroimaging reports. Neuroimaging reports (head CT and brain MRI) obtained during or following ECMO initiation were reviewed for acute and chronic structural abnormalities. Only neuroimaging tests obtained in the same admission as ECMO initiation were reviewed. Neurological complications were defined as a diagnosis of seizures, stroke, cerebral edema, or intracranial hemorrhage diagnosed before discharge and during or after ECMO support. Neurological outcome was determined at the time of discharge using the Glasgow-Pittsburgh Cerebral Performance Categories (CPC). (Amorim et al., 2015) Good outcome was defined as independence for activities of daily living (CPC 1–2) and poor outcome as moderate to severe neurological disability or death (CPC 3–5). Sedation and analgesia guidelines in our institution include the use of propofol (usual dose range: 25–80 mcg/kg/h), midazolam (0.1–0.7 mg/kg/h), and fentanyl (25–200 mcg/h) as needed by the treating clinician. The Partners Healthcare Institutional Review Board approved this study (Protocol number 2013P001024). This retrospective study was consider exempt from requiring informed consent.

2.3. EEG recordings and review

EEG monitoring is typically performed in patients undergoing ECMO when there is impaired level of consciousness with clinical suspicion for seizures, and the duration of EEG recordings is determined by the treating team. The EEG recordings use 19-channels, and placement follows the 10–20 international system. Per our institutional protocol, documentation of EEG results in the EHR is routinely done twice a day by an epilepsy fellow and attending epileptologist following American Clinical Neurophysiology Society standardized critical care EEG terminology. (Hirsch et al., 2013) For the purposes of this study, IIC patterns include generalized periodic discharges (GPD), lateralized periodic discharges (LPD), generalized rhythmic delta activity (GRDA), lateralized rhythmic delta activity (LRDA), stimulus-induced periodic discharges (SI-PD), and brief ictal rhythmic discharges (BIRD). The EEG background was considered: continuous: when there was 10% or less suppression; discontinuous: 10–49% suppression; and burst suppression: 50% or more suppression. We used the mean continuity and maximal frequency reported in sequential EEG reports to estimate the average background continuity and maximal frequency for each subject. Mean continuity and mean maximal frequencies were obtained by averaging the continuity and maximal EEG frequency included in the serial EEG reports generated in the electronic medical records. The continuity and frequency were weighted based on the length of EEG included in each EEG report. For example, if four EEG reports were available for one subject and the first report covered one hour of the EEG recording and the following three had 12 h each, the frequency and continuity on the first report would have a weight of one hour while the other EEG reports would have a weight of 12 h each. In this example, the final background frequency and value would be averaged across the 37 h of EEG data available using the respective weights.

2.4. Statistical analysis

In univariate analysis for good and poor outcomes, we used the Mann-Whitney U-test for continuous variables and Pearson Chi-square tests for categorical variables. We determined the confidence intervals (CI) using the Wald method. Statistical significance was determined at the alpha level of 0.05. Missing data imputation was performed through iterative fitting using a nonlinear iterative partial least squares model. (Andrecut, 2008; Folch-Fortuny et al., 2016) We performed two multivariable regression analyses to assess for associations with mortality and poor neurological outcome. Both models utilized baseline subject characteristics, imaging, and EEG findings as predictors. Given the fac that GRDA does not have a strong association with seizures, we only included the remaining IIC patterns and seizures or status epilepticus in the prediction model. Statistical analyses were performed in MATLAB, version 17a (Natick, MA, USA). (Layden et al., 2019).

3. Results

3.1. Cohort characteristics and outcomes

Three hundred and ninety-five subjects had ECMO, and one-hundred and thirteen (28.6%) underwent EEG monitoring. Ninety-two subjects had EEG performed concurrently with ECMO support and were included in this analysis (Table 1). Thirty (33%) subjects survived to hospital discharge, and eleven 11 (12%) achieved a good outcome by discharge. The

most common indication for ECMO in subjects surviving to hospital discharge were ischemic heart failure (22.9%), pulmonary embolism (22.9%), and acute respiratory distress syndrome (20%). Non-ischemic heart failure (41.5%) and ischemic heart failure (29.2%) were the most common indications for ECMO in subjects not survinvg to hospital dicharge. Veno-arterial was the most common mode of cannulation (83%), with heart failure being the most common indication for ECMO (58%). Forty-six (50%) subjects had a cardiac arrest on presentation or during their hospital stay. Extracorporeal cardiopulmonary resuscitation (ECPR) was pursued in 26 (28%) subjects, being the initial indication for ECMO in 12 (13%). The mean duration of ECMO was 9.5 days (range: 1 to 79). Information on the 21 subjects who had EEG after ECMO therapy is available in Supplementary Material (Tables S1–S2)

Neurological complications were observed in 29 (32%) subjects. Twenty-nine (97%) survivors were able to follow commands before hospital discharge, and 15 (50%) could ambulate without assistance. Survivors with a good outcome were younger (mean age 56 vs. 41 years old, $p < 0.001$) and had a lower Charlson comorbidity index (1.8 vs. 2.9, $p < 0.05$). Fifty-six (90%) subjects who died during their hospital stay had withdrawal of life-sustaining therapies (WLST), and two were brain dead. The most common cause of WLST was multiorgan or hemodynamic failure (70%), followed by neurological (27%) or social or ethical reasons (1%). The reason for WLST could not be determined retrospectively for one subject.

Age, gender, and mode of cannulation were similar between the ECMO cohorts with (N = 113) and without (N = 282) EEG monitoring. However in-hospital mortality rate was lower in the cohort without EEG monitoring during ECMO (33.9% vs. 67%, $p < 0.05$).

3.2. EEG findings

The mean duration of EEG recordings was 54 h, with 17 subjects having EEG duration less than four hours. Fifty-eight (63%) subjects had epileptiform activity or IIC diagnosed on EEG. Forty-nine (53%) had epileptiform activity, with three meeting the criteria for non-convulsive status epilepticus (Table 2). Forty-seven subjects (51%) had IIC patterns, with GPDs being the most common IIC pattern (36%) followed by GRDA (27%). Four subjects had LPDs, three had SI-PDs, and one had BIRDs. Sporadic epileptiform discharges were observed in 47% of subjects, with 28% of the sporadic discharges having a triphasic morphology. Non-ischemic heart failure was more common in subjects with epileptiform activity than those without (41% vs. 16%, $p = 0.01$). Pulmonary support was more common in subjects without epileptiform activity (28% vs. 8%, $p = 0.01$). There was no difference in the presence of epileptiform activity or IIC patterns between subjects with or without cardiac arrest or those who had WLST. Absolute thirty-day mortality was higher in subjects with epileptiform activity compared to those without, but this difference did not reach statistical significance (76% vs. 63%, $p = 0.18$).

The mean maximal EEG background was in the theta range (6.4 Hz), but 26% of subjects never exceeded the delta (<4Hz) range. Four subjects had marked asymmetry due to focal slowing. Forty-six (50%) subjects had a predominantly continuous EEG, and the overall mean continuity for the entire recording was 75%. Thirty-six (39%) subjects had burst

suppression at some point during their EEG recording, with 64% being sedated during the time of the EEG recording (86% of these subjects were sedated with propofol, 36% with midazolam, and 23% with dexmedetomidine). Well-defined sleep architecture was present in only four (4.4%) subjects. EEG background reactivity was only formally tested in 46 subjects, of which 23 (50%) had a reactive background.

3.3. Neuroimaging findings

Eighty-three (90%) subjects had acute brain imaging during or after ECMO initiation, and twenty-seven (33%) had acute structural abnormalities (Table 3). Twenty-one (25%) had an acute ischemic or hemorrhagic stroke, six (7%) subarachnoid hemorrhage, and four (5%) subdural hemorrhage. Three (3%) subjects who had a cardiac arrest developed diffuse cortical edema, and one (1%) subject had posterior reversible encephalopathy syndrome preceding ECMO initiation (cases with structural abnormalities add to more than 100% due to more than one finding per subject). There were 11 multifocal embolic infarcts and four ischemic strokes having hemorrhagic transformation. The presence of acute structural abnormalities on neuroimaging was not associated with presence of epileptiform activity, mortality, neurological outcomes, nor WLST ($p = 0.75$; 0.54; 0.86; 0.54 respectively) (Fig. 1).

3.4. Association of EEG and imaging abnormalities with mortality and neurological outcome

The AUC for mortality and poor outcome prediction for the model including baseline clinical characteristics (age, Charlson score, and ECMO mode [VV vs. VA]), EEG characteristics (presence of epileptiform abnormalities or ictal-interictal patterns and seizures), and acute abnormalities on neuroimaging was 0.72 and 0.84 respectively. Individual models including baseline clinical characteristics, EEG characteristics and neuroimaging individually had worse predictive performance (baseline:0.71 and 0.77; EEG 0.57 and 0.62; and neuroimaging 0.55 and 0.58 for mortality and poor outcome, respectively). In the multivariable model, age was the only independent predictor of mortality and poor outcome (OR 1.05, 95% Confidence Interval [CI]: 0.01–0.09, $p = 0.02$ and OR 1.07, 95% CI: 0.01–0.2, $p = 0.02$) (Table 4).

4. Discussion

The main contribution of this study is the identification of epileptiform activity and IIC patterns in nearly two out of three patients managed with ECMO. Identifying these EEG patterns in the absence of frank seizures reflects the significant and often unappreciated derangement in cerebral function seen in patients on ECMO support. (Lorusso et al., 2017, 2016; Magalhaes et al., 2020; Migdady et al., 2020; Peluso et al., 2020) In addition, several other EEG background features consistent with severe encephalopathy were present in the majority of patients, such as delta-theta slowing, burst suppression, and lack of sleep features or background reactivity. The rate of neurological complications (32%) and EEG abnormalities described in this study corroborates prior reports demonstrating a high incidence of neurological dysfunction in patients undergoing ECMO. (Cho et al., 2019; Kim et al., 2020; Kobata et al., 2020; Lorusso et al., 2017, 2016; Magalhaes et al., 2020; Mateen

et al., 2011; Migdady et al., 2020; Peluso et al., 2020; Shoskes et al., 2020) These results highlight the need to better understand the effects of ECMO on cerebral physiology and the potential of neuromonitoring implementation for improving the timeliness of diagnosis of neurologic complications, which might contribute to better functional outcomes.

The incidence of seizures in our cohort was within the range of previous reports for adult patients undergoing ECMO (4% vs. 1–10%, respectively). (Cho et al., 2019; Haas et al., 2017; Kobata et al., 2020; Lorusso et al., 2017; Magalhaes et al., 2020; Mateen et al., 2011; Migdady et al., 2020; Peluso et al., 2020) However, the rate of periodic or rhythmic patterns in the IIC reported here was higher than previous reports (62% vs. 3–57%). (Kim et al., 2020; Magalhaes et al., 2020; Peluso et al., 2020; Sinnah et al., 2018) The rate of epileptiform activity and IIC patterns in this study was similar to the report from Kim et al., which involved 69 subjects who underwent ECPR, indicating that patients with cardiac arrest likely have a more severe brain injury and increased likelihood of developing seizure and IIC patterns. (Kim et al., 2020) In our cohort, non-ischemic heart failure indications were associated with worse outcomes and increased incidence of epileptiform activity. In comparison, ECMO for pulmonary support had better outcomes and less epileptiform activity. However, we were unable to determine whether there is a causal contribution of epileptiform activity and outcomes or whether epileptiform activity is a marker of brain injury. IIC patterns in critically ill patients are common, and their clinical significance and management are under active investigation. (Rodríguez et al., 2016) Periodic or rhythmic activity can lead to metabolic supply–demand mismatch and cause or exacerbate brain injury. Therefore treatment of these patterns may be recommended depending on the clinical context. (Subramaniam et al., 2019; Vespa et al., 2016; Witsch et al., 2017) Of note, IIC patterns are associated with an increased risk of non-convulsive seizures. Therefore, identifying these patterns on EEG may affect clinician decision-making about seizure prophylaxis initiation or pursuing further investigation for other toxic-metabolic factors or medications that may exacerbate these patterns. (Struck et al., 2017) The presence of seizures, seizure burden, and some specific types of IIC patterns has been associated with worse functional outcomes in patients managed with ECMO and ECPR in previous single-center studies. (Kim et al., 2020; Sansevere et al., 2020) In the present study, patients with poor outcomes had a near 20% higher incidence of epileptiform activity, and those who died 10%. However, these differences did not reach statistical significance potentially due to the small sample size. Another notable point is that all seizures in our study were non-convulsive, underscoring the potential role of non-invasive EEG monitoring for seizure screening in critically ill patients undergoing ECMO who lack a reliable neurological exam. (Peluso et al., 2020).

Beyond diagnosis of seizure and other types of epileptiform activity, the present study identified several abnormalities in EEG function consistent with severe encephalopathy in patients on ECMO, such as burst suppression, diffuse delta-theta slowing, and lack of sleep architecture. These EEG characteristics have been validated for prognostication post-cardiac arrest. However, our findings did not show an association of these findings with poor outcomes in ECMO. (Amorim et al., 2016; Hofmeijer et al., 2015; Magalhaes et al., 2020; Peluso et al., 2020; Westhall et al., 2016) Unfortunately, EEG reactivity was not systematically tested in half of the subjects evaluated in this study. We cannot confirm

whether an unreactive EEG was associated with poor outcomes in this cohort demonstrated in previous studies. (Magalhaes et al., 2020; Peluso et al., 2020; Sinnah et al., 2018) Quantitative metrics of EEG background features such as amplitude-integrated EEG and bispectral index (BIS) were predictive of outcomes in ECPR studies, and this might be a reasonable alternative for background evaluation when epileptologists are not available for EEG interpretation. (Jouffroy et al., 2017; Kobata et al., 2020).

Prediction of functional recovery for patients managed with ECMO is challenging, and the presence of neurological complications and sedative use can make prognostication even more complex. (Cho et al., 2019) The rate of neurological complications in this study (32%) was comparable to previous reports (7–50%). (Lorusso et al., 2017, 2016; Mateen et al., 2011; Migdady et al., 2020; Shoskes et al., 2020) Surveillance neuroimaging showed that stroke was the most common acute structural abnormality (ischemic 66% and hemorrhagic 15%). Near one in four ischemic strokes experienced hemorrhagic transformation. The incidence of these complications varies widely in previous studies (ischemic [1–14%] and hemorrhagic [1–8%] strokes), with ischemic strokes being more common with venoarterial than venovenous cannulation. (Haas et al., 2017; Lorusso et al., 2016; Mateen et al., 2011; Migdady et al., 2020; Shoskes et al., 2020) Two subjects were diagnosed with brain death, which is within the range of previous reports (2–17%). (Haas et al., 2017; Lorusso et al., 2016; Mateen et al., 2011; Migdady et al., 2020; Shoskes et al., 2020) The presence of epileptiform activity or IIC patterns was not associated with acute structural abnormalities on neuroimaging or cardiac arrest diagnosis in this study, indicating that these patterns can also emerge independently of severe vascular or hypoxic-ischemic brain injury. Importantly, six subjects were diagnosed with a subarachnoid hemorrhage and four with subdural hematomas, which happened in association or not with ischemic and hemorrhagic strokes. Those hemorrhages were not thought to be traumatic in nature and were likely spontaneous in the setting of coagulopathy or anticoagulation.

This study has important limitations. The incidence of IIC patterns in our cohort may have been inflated due to an enriched dataset with patients with higher clinical suspicion for seizures having EEG monitoring initiated. The time of initiation and duration of EEG was not standardized, limiting interpretation of the timing and incidence of IIC patterns and their association with outcomes in ECMO. Also, the duration of EEG monitoring was inferior to the duration of ECMO support. Therefore it is possible that non-convulsive seizures or other serious EEG abnormalities were missed due to insufficient recording duration. While IIC patterns are associated with increased seizure risk, lack of seizures after 48 h of EEG monitoring is associated with a low risk of seizure emergence. (Westover et al., 2015) Also, the potential impact of anti-seizure medications and anesthetics initiation on seizure prevention, background changes, or neuroprotection could not be determined retrospectively. This study predated the SARS-CoV-2 pandemic, therefore the results cannot add information to the body of literature about SARS-CoV-2 neurological complications in the setting of ECMO. Prospective studies with the systematic deployment of continuous EEG early after ECMO initiation or even before ECMO is started would help define the spectrum of epileptiform and IIC abnormalities associated with ECMO as well as determine if ECMO support can cause or exacerbate this type of physiology. A previous small pilot study of systematic neuromonitoring using a comprehensive neurological evaluation with

multimodal neurophysiology, neurovascular, and neuroimaging testing identified an 85% rate of neurological complications. (Cho et al., 2020) Another important limitations are the study's retrospective design. A substantial part of our study cohort's outcome was censored due to WLST, therefore bias from self-fulfilling prophecies likely contributes to mortality rate ni this cohort/ In previous studies, neurological injury was associated with an increased risk of WLST, which was not observed in this study. (Lorusso et al., 2017) The majority of cases undergoing WLST in this cohort had multiorgan or hemodynamic failure. Therefore our ability to identify the impact of neurological injury on WLST is limited.

5. Conclusions

Epileptiform activity and severe encephalopathy are commonly observed in patients managed with ECMO. Given the high incidence of neurological complications and signs indicative of severe cerebral dysfunction on EEG during ECMO, additional prospective studies using a systematic approach to multimodal brain monitoring are warranted to help elucidate the mechanisms contributing to neurological dysfunction in ECMO and to guide the development of timely and individualized interventions to prevent neurological complications and improve functional outcomes.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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HIGHLIGHTS

- Near two thirds of subjects undergoing ECMO in this cohort had epileptiform or ictal-interictal continuum abnormalities on EEG.
- Nonconvulsive status epilepticus was infrequent (3%) for subjects undergoing ECMO support.
- Acute neuroimaging findings were not associated with epileptiform abnormalities in subjects undergoing ECMO support.

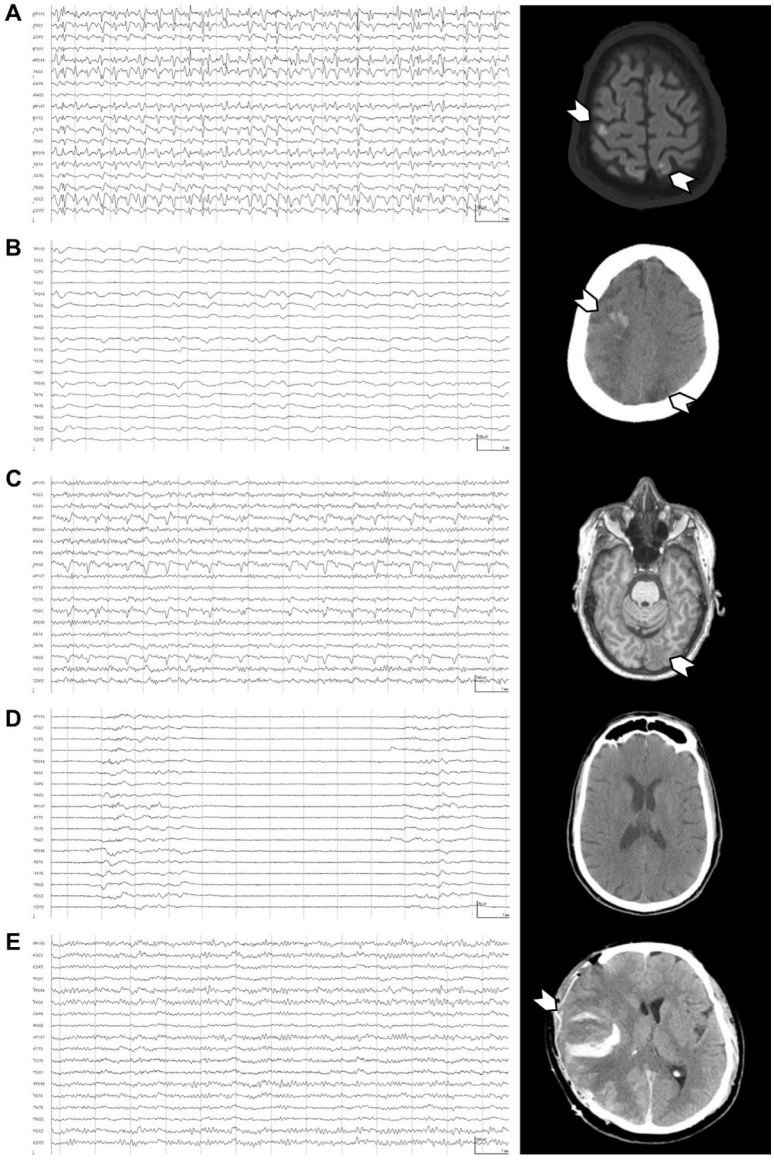

Fig. 1. Examples of abnormal EEGs recorded during extracorporeal membrane oxygenation and corresponding neuroimaging (arrows indicate location of acute lesion).

A: EEG: nonconvulsive status epilepticus characterized by fluctuating generalized periodic discharges; MRI: diffusion-weighted imaging sequence shows multifocal bihemispheric embolic infarcts. **B:** EEG: generalized periodic discharges at 0.5–1 Hz, frontal predominant, superimposed in a diffuse polymorphic delta slowing background; CT: bihemispheric infarcts with hemorrhagic transformation. **C:** bi-occipital periodic discharges at 1–2 Hz superimposed on an alpha background; MRI: T1 sequence shows a small hyperintense lesion in the left occipital lobe. **D:** Burst suppression with 70% suppression; CT head: no acute abnormalities. **E:** Alpha background with superimposed diffuse polymorphic delta slowing; CT: large right middle cerebral artery infarct with hemorrhagic transformation status post right hemicraniectomy. EEG: electroencephalography. MRI: magnetic resonance imaging. CT: computerized tomography.

Table 1

Subjects Characteristics Stratified by Outcomes.

Subject Characteristics	Dead (N = 62)	Alive (N = 30)	p	CPC 3–5 (N = 81)	CPC 1–2 (N = 11)	p
Age (mean, std)	58, 12.6	47.9, 16.3	0.002	56, 13.5	41, 16	<0.001
Gender (Female)	21 (33.8%)	10 (33.3%)	0.96	27 (33.3%)	4 (36.4%)	0.84
CCI (mean, std)	3.1, 2	2.1, 1.8	0.03	2.9, 2	1.8, 2	0.05
Cardiac Arrest (%)	32 (51.6%)	14 (46.7%)	0.66	41 (50.6%)	5 (45.5%)	0.75
ECMO Primary Support Type (%)						
Pulmonary	6 (9.7%)	10 (33.3%)	<0.01	11 (14.6%)	5 (45.5%)	0.01
Cardiac	49 (79%)	24 (46.7%)	<0.01	58 (71.6%)	5 (45.5%)	0.08
ECPR	3 (4.8%)	1 (5.7%)	0.74	4 (4.9%)	0 (0%)	0.45
Cardiac and Pulmonary	4 (6.5%)	6 (20.0%)	0.05	9 (11.1%)	1 (9.1%)	0.84
ECMO Mode (%)						
VV	7 (11.3%)	9 (30%)	0.027	12 (14.8%)	4 (36.4%)	0.08
VA	54 (87.1%)	21 (70%)	0.048	68 (84%)	7 (63.6%)	0.1
VVA	1 (1.6%)	0 (0%)	0.48	1 (1.2%)	0 (0%)	0.71
ECMO Primary Indication (%)						
Heart Failure (Ischemic)	18 (29%)	8 (26.7%)	0.8	24 (29.6%)	2 (18.2%)	0.43
Heart Failure (Non-Ischemic)	26 (41.9%)	1 (3.3%)	<0.01	26 (32.1%)	1 (9.1%)	0.12
ARDS	6 (9.7%)	7 (23.3%)	0.078	10 (12.3%)	3 (27.3%)	0.18
ECPR	9 (14.5%)	3 (10%)	0.55	12 (14.8%)	0 (0%)	0.17
Asthma	0 (0%)	2 (6.7%)	0.04	0 (0%)	2 (18.2%)	<0.001
Pulmonary Embolus	3 (4.8%)	8 (26.7%)	0.002	8 (9.9%)	3 (27.3%)	0.1
Pulmonary Hypertension	0 (0%)	0 (0%)	n/a	0 (0%)	0 (0%)	n/a
Bridge Lung Transplant	0 (0%)	1 (3.3%)	0.15	1 (1.2%)	0 (0%)	0.71
Lung Transplant Rejection	0 (0%)	0 (0%)	n/a	0 (0%)	0 (0%)	n/a
ECPR at Any Point (%)	19 (30.6%)	7 (23.3%)	0.47	25 (30.9%)	1 (9.1%)	0.13
Duration ECMO Support (median, days)	5	9	0.03	6	5	0.97
Followed Commands Before Discharge (%)	0 (0%)	29 (96.7%)	n/a	18 (22.2%)	11 (100%)	<0.01
Able to ambulate at discharge (%)	0 (0%)	15 (50%)	n/a	4 (4.9%)	11 (100%)	<0.01
Mortality at discharge (%)	62 (100%)	0 (0%)	n/a	62 (76.5%)	0 (0%)	<0.01

Subject Characteristics	Dead (N = 62)	Alive (N = 30)	p	CPC 3–5 (N = 81)	CPC 1–2 (N = 11)	p
Withdrawal of life-sustaining therapies (%)	56 (90.3%)	0 (0%)	<0.01	56 (69.1%)	0 (0%)	<0.01
Length of Stay (mean, std)	20	55	<0.01	31	39	0.08
30-day Mortality (%)	62 (100%)	2 (6.7%)	<0.01	64 (79%)	0 (0%)	n/a

CCI: Charlson Comorbidity Index; ECMO: extracorporeal membrane oxygenation; ECPR: Extracorporeal pulmonary resuscitation VV: venovenous; VA: venoarterial; VVA: venovenous arterial; CPC: Cerebral Performance Category; n/a: not applicable.

Table 2

EEG Characteristics Stratified by Outcome.

EEG Characteristics	Dead (N = 62)	Alive (N = 30)	p	CPC 3–5 (N = 81)	CPC 1–2 (N = 11)	p
Maximal Background Frequency (Hz)	6.3	6.7	0.25	6.4	6.2	0.68
Mean Continuity (%)	74.4%	76.5%	0.92	74.2%	81.4%	0.34
Continuous Background	30 (48.4%)	16 (53.3%)	0.66	38 (46.9%)	8 (72.7%)	0.11
Burst Suppression	23 (37.1%)	13 (43.3%)	0.57	32 (39.5%)	4 (36.4%)	0.84
Any Epileptiform Activity	35 (56.5%)	14 (46.7%)	0.38	45 (55.6%)	4 (36.4%)	0.23
Sporadic Epileptiform Activity	31 (50%)	12 (40%)	0.37	40 (49.4%)	3 (27.3%)	0.17
Triphasics	11 (17.7%)	1 (3.3%)	0.05	14.8%	0.0%	0.17
Ictal Interictal Continuum	30 (48.4%)	17 (56.7%)	0.46	41 (50.6%)	6 (54.5%)	0.81
Generalized Rhythmic Delta Activity	14 (22.6%)	11 (36.7%)	0.15	21 (25.9%)	4 (36.4%)	0.47
Lateralized Periodic Discharges	3 (4.8%)	1 (3.3%)	0.74	4 (4.9%)	0 (0%)	0.45
Generalized Periodic Discharges	23 (37.1%)	10 (33.3%)	0.72	31 (38.3%)	2 (18.2%)	0.19
Brief Ictal Rhythmic Discharges	0 (0%)	1 (3.3%)	0.15	1 (1.2%)	0 (0%)	0.71
Stimulus-Induced Periodic Discharges	1 (1.6%)	2 (6.7%)	0.20	2 (2.5%)	1 (9.1%)	0.25
Nonconvulsive Status Epilepticus	1 (1.6%)	2 (6.7%)	0.20	3 (3.7%)	0 (0%)	0.52

CPC: Cerebral Performance Category. EEG: electroencephalography.

Table 3

Acute Neuroimaging Stratified by Outcome.

Neuroimaging Characteristics	Dead (N = 56)	Alive (N = 27)	p	CPC 3–5 (N = 73)	CPC 1–2 (N = 10)	p
Any Ischemic or Hemorrhagic Stroke (%)	15 (26.8%)	6 (22.2%)	0.65	19 (26.0%)	2 (20.0%)	0.68
Acute Multifocal Stroke (%)	7 (12.5%)	4 (14.8%)	0.77	10 (13.7%)	1 (10.0%)	0.75
Hemorrhagic Stroke (%)	5 (3.6%)	3 (7.4%)	0.44	6 (2.7%)	2 (20.0%)	0.02
Ischemic Stroke (%)	13 (23.2%)	4 (14.8%)	0.37	13 (23.3%)	0 (0.0%)	0.09
Ischemic Stroke with Hemorrhagic Transformation (%)	3 (5.4%)	1 (3.7%)	0.74	4 (5.5%)	0 (0.0%)	0.45
Subdural Hemorrhage (%)	1 (1.8%)	3 (11.1%)	0.06	3 (4.1%)	1 (10.0%)	0.41
Subarachnoid Hemorrhage (%)	3 (5.4%)	3 (11.1%)	0.34	4 (5.5%)	2 (20.0%)	0.10

CPC: Cerebral Performance Category.

Table 4

Multivariable Logistic Regression.

Mortality			
Variables	**OR**	**95% CI**	**p**
Intercept	0.22	−3.94–0.93	0.23
Age	1.05	0.01–0.09	0.01
CCI	1.15	−0.16–0.43	0.36
ECMO Mode	2.02	−0.60–2	0.29
IIC	0.59	−2.17–1.13	0.54
Presence Epileptiform Activity	1.56	−1.10–2	0.57
Max. Frequency (Hz)	1.00	0–0	0.55
Mean Continuity (%)	0.99	−0.03–0.01	0.26
Burst Suppression	0.49	−1.930.5	0.25
Abnormal Imaging	0.52	−1.78–0.48	0.26
Outcome CPC 3–5			
Variables	**OR**	**95% CI**	**p**
Intercept	1.07	−3.38–3.52	0.97
Age	1.07	0.01–0.12	0.02
CCI	1.14	−0.32–0.59	0.56
ECMO Mode	1.41	−1.38–2.06	0.70
IIC	4.49	−1.03–4.03	0.24
Presence Epileptiform Activity	0.61	−2.44–1.46	0.62
Max. Frequency (Hz)	1.00	0–0	0.66
Continuity (%)	0.98	−0.05–0.01	0.20
Burst Suppression	0.37	−2.83–0.87	0.30
Abnormal Imaging	0.90	−1.83–1.61	0.90

OR: Odds Ratio; CI: Confidence Interval; CCI: Charlson Comorbidity Index; ECMO: extracorporeal membrane oxygenation; IIC: Ictal Interictal Continuum.