Neurophysiologic Features Predicting Brain Injury During Pediatric ECMO Support

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Research Article

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Abstract

Background/Objective:

Extracorporeal membrane oxygenation (ECMO) provides life-saving support to critically ill patients who experience refractory cardiopulmonary failure but carries high risk of acute brain injury. We aimed to identify characteristics predicting acute brain injury in children requiring ECMO support.

Methods

This is a prospective observational study from 2019–2022 of pediatric ECMO patients undergoing neuromonitoring including continuous electroencephalography, cerebral oximetry, and transcranial Doppler ultrasound (TCD). Primary outcome was acute brain injury. Clinical and neuromonitoring characteristics were collected. Multivariate logistic regression was implemented to model odds ratios (OR) and identify the combined characteristics that best discriminate risk of acute brain injury using the area under the receiver operating characteristic curve (AUROC).

Results

Seventy-five pediatric patients requiring ECMO support were enrolled in this study. Of the seventy-five patients enrolled, nineteen experienced acute brain injury (25.3%), including seven (36.8%) with arterial ischemic stroke, four (21.1%) with hemorrhagic stroke, seven with hypoxic ischemic brain injury (36.8%) and one (5.3%) with both arterial ischemic stroke and hypoxic ischemic brain injury. Univariate analysis demonstrated acute brain injury to be associated with maximum hourly seizure burden (p = 0.026), epileptiform discharges (p = 0.020), electroencephalographic suppression ratio (p = 0.014), increased interhemispheric differences in electroencephalographic total power (p = 0.023) and amplitude (p = 0.011), and increased differences in TCD Thrombolysis in Brain Ischemia (TIBI) scores between bilateral middle cerebral arteries (p = 0.049). Best subset model selection identified increased seizure burden (OR = 3.86, partial R-squared 0.40, p = 0.013), increased quantitative electroencephalographic interhemispheric amplitude differences (OR = 2.69, partial R-squared 0.18, p = 0.007), and increased interhemispheric TCD TIBI score differences (OR = 4.97, partial R-squared 0.22, p = 0.005) to be independently predictive toward acute brain injury (AUROC = 0.92).

Conclusions

Increased seizure burden, increased interhemispheric differences in quantitative electroencephalographic amplitude and increased TCD TIBI scores each independently predict acute brain injury in children undergoing ECMO support.

Introduction

Extracorporeal membrane oxygenation (ECMO) provides life-saving support to critically ill patients who experience refractory cardiopulmonary failure¹. The utility of ECMO has increased worldwide² and
despite clear benefit, its use is associated with significant morbidity commonly attributed to acute brain injury\textsuperscript{3–6}. Timely detection of acute brain injury in this population is necessary to mitigate secondary brain injury and improve outcomes. However, frequent use of sedation and neuromuscular blockade limit utilization of neurologic examinations to detect acute brain injury, and neuroimaging is challenging in the setting of hemodynamic instability and transport challenges\textsuperscript{7}. Bedside neuromonitoring may be useful in early detection of acute brain injury which can aid clinicians in management towards either preventing primary brain injury or mitigating resultant secondary brain injury.

Multimodality neuromonitoring (MMM) allows for time synchronized and integrated collection and analysis of high-frequency physiologic data\textsuperscript{8,9}. Retrospective studies investigating the utility of continuous electroencephalography (cEEG), transcranial Doppler ultrasound (TCD), or cerebral regional oximetry (rSO\textsubscript{2}), and their correlations with continuous physiologic parameters in ECMO patients have found associations between altered physiologic parameters and acute brain injury as well as patient outcomes\textsuperscript{10–21}. However, these studies have looked at these neuromonitoring tools in isolation without comparison of each other, with fewer studies describing usefulness or feasibility of combined and integrated MMM in detecting acute brain injury of pediatric ECMO patients in a prospective manner\textsuperscript{15,22}. The primary objective of this study is to prospectively identify biomarkers of acute brain injury using MMM, clinical, and ECMO-circuit characteristics in children during ECMO support.

**Methods**

**Study design, setting and participants**

This study is a single-center prospective observational study conducted at the Phoenix Children's Hospital neonatal, pediatric, and cardiovascular intensive care units (ICUs) that enrolled consecutive ECMO patients aged 0–18 years who underwent multimodality neuromonitoring from June 2019 to April 2022.

Patients were excluded in case of prior known acquired brain injury, sickle cell disease and Moya-Moya disease. This study was approved by Phoenix Children's Hospital Institutional Review Board (No: 19–257; Approval Date 05/16/2019, Institutional Review Board Study Title: Multivariate Prediction of Stroke in Children Requiring Mechanical Circulatory Support). All procedures were followed in accordance with the ethical standards of Institutional Review Board at Phoenix Children's. Written informed consent was obtained from parents or legal guardians for each participant.

**Outcome measures, data sources and data collection**

The primary outcome was the presence of acute brain injury during ECMO support from either neuroradiographic imaging or autopsy findings. All patients were managed according to up-to-date clinical practice guidelines\textsuperscript{23,24}. As standard of care, all patients underwent serial neurological examinations, cerebral regional oximetry, daily head ultrasound for the first 5 days of monitoring if age
appropriate and as requested, and head computed tomography (CT) neuroimaging when clinical concerns for neurologic changes occurred. Surviving patients underwent brain magnetic resonance imaging (MRI) after decannulation, if able. The diagnosis of acute brain injury was made based on neuroanatomic evidence of arterial ischemic stroke (AIS), hemorrhagic stroke (HS) or hypoxic ischemic brain injury (HIBI) from brain MRI, CT or head ultrasounds. We excluded microhemorrhages, extra-axial fluid collections and white matter hyperintensities < 3 mm as biomarkers of acute brain injury. In case of a deceased patient without any neurologic imaging, findings compatible with acute brain injury on autopsy reports were used.

As part of this study, patients underwent MMM that included cEEG, cerebral rSO₂ and daily TCD of the bilateral middle cerebral arteries (MCA). MMM and systemic hemodynamic monitoring data were integrated through a multimodality neurologic monitoring device (CNS200®; Moberg Intensive Care Unit (ICU) Solutions®, Philadelphia, PA). Intensive Care Monitor Plus (ICM+®) software (Cambridge, UK) was used to visualize and process all MMM data and calculate model-based indices of cerebrovascular pressure reactivity (CVPR) and autonomic function (AF). Physiologic data were collected from ECMO initiation to decannulation. Data with substantial artifacts observed through visual analysis were removed.

Continuous EEG data were captured using institutional clinical hardware (Xltek®; Natus Medical®, Pleasanton CA) under the International 10–20 system. Collected EEG characteristics included maximum hourly electrographic seizure burden, presence of interictal epileptiform discharges, and quantitative features (QEEG) such as amplitude, alpha (8–13 Hz), beta (13–20 Hz), theta (4–7 Hz) and delta power (0–4 Hz), total power (1–20 Hz), alpha-delta power ratio (ADR), and suppression ratio (SR). Interhemispheric differences in QEEG parameters were calculated. Electrographic seizures and maximal hourly seizure burden were defined as previously described²⁵,²⁶. Qualification of all EEG data were confirmed through visual inspection of raw EEG waveforms by a board-certified epileptologist (BA). Qualification of seizures and epileptiform discharges were initially detected by a board-certified epileptologist and later confirmed through standard clinical reports of the clinical epileptologist on service.

Patients underwent TCD evaluations of systolic (Vs), diastolic (Vd) and mean flow velocities (Vm) in bilateral middle cerebral arteries (MCA) within 24 hours of ECMO initiation and daily thereafter. Power-M-mode TCD ultrasound machines (Spencer Technologies® and Novasignal Lucid®) were used which interface with the MMM device, facilitating time-synchronization of TCD waveforms with other physiologic parameters. Transtemporal acoustic windows were identified by patient anatomic landmarks. Flow velocity measurements were collected every 2 millimeters along the entire course of the vessel with maximal velocities collected. The pulsatility index (PI) was derived by the TCD unit for each set measurements according to the equation: PI=(Vs-Vd)/Vm. TCD data on last day of recording were incorporated into acute brain injury prediction models. All TCD measurements were evaluated by a board-certified neurosonologist, and waveform grading was based upon the Thrombolysis in Brain Ischemia
(TIBI) scale when evidence of MCA pulsatility was present on TCD examinations. If patient’s experienced non-pulsatile MCA flow on TCD, they were scored as having non-pulsatile flow.

Continuous cerebral and systemic hemodynamic physiology data were acquired including arterial blood pressure (ABP) central venous pressure (CVP), cerebral regional oxygenation ($rSO_2$) and heart rate (HR). ABP was continuously monitored from an indwelling radial or femoral catheter. Near infrared spectroscopy sensors were placed on the bifrontal forehead and $rSO_2$ was continuously measured (Medtronic INVOS®).

CVPR was investigated using the cerebral oximetry index (COx), which represents a moving Pearson correlation coefficient of ABP and $rSO_2$. COx is calculated within a 5-minute averaging window updated every 60 seconds. COx values approaching 1 are postulated to represent inefficient CVPR, whereas values that are negative or approaching 0 are postulated to represent efficient CVPR. We used previously described methods to evaluate time spent below the lower limit of CVPR (LLA) and above upper limit of CVPR (ULA) as well as optimal values of CVPR (ABPOpt). ABPOpt values were identified using previously described methods of plotting ABP values with COx and identifying the minimum ABP value on a parabolic curve fit to the data with a multiwindow algorithm. ABPOpt values were calculated from every 1 minute from ABP and COx values taken from the moving 4-hour window. Specific details regarding multiwindow algorithm calculation and criteria for value rejection and fitting have been previously described and are summarized in Supplement 1. LLA and ULA were determined for COx as the ABP values at which the curve exceeded COx values of 0.30, as previously described. LLA and ULA were determined as the the lowest and highest ABP value with such thresholds, respectively. The percent time of ABP below and above ABPOpt, LLA and ULA were calculated for each patient during their ECMO course.

To evaluate for autonomic function, we investigated baroreflex sensitivity (BRs) and three measures of heart rate variability (HRV): standard deviation of heart rate (HRsd), root-mean-square of successive differences in heart rate (HRrmssd) and low-high frequency ratio (LHF). Methods of calculating these parameters have been previously described and are summarized in Supplement 2.

In addition to continuous physiologic data, demographic data collected included age, sex, race and indication for ECMO support. ECMO-circuit characteristics investigated include type of circuit initiated (veno-arterial [VA] or veno-venous [VV]), arterial cannulation site (carotid vs. aorta vs. femoral), venous cannulation site (e.g., femoral vs. right atrial vs. internal jugular vein), arterial and venous catheter sizes, duration of ECMO course, and minimal and maximal anti-Xa levels, pump flow rates, and sweep FiO$_2$ and oxygenation rates.

**Statistical analysis**

Descriptive characteristics were summarized by using median and interquartile range (IQR) or counts and percentages as appropriate. Univariate logistic regression modeling was used to identify risk factors or
features that were associated with acute brain injury. The strength of univariate associations was summarized using odds ratios and their corresponding 95% confidence intervals (95% CI) and p-values. All risk factors with p-value less than 0.20 were entered in a multivariable logistic regression model using a guided stepwise method and the Akaike Information Criterion (AIC) to identify combined characteristics best discriminating risk toward acute brain injury using the area under the receiver operating characteristic curve (AUROC). In the multivariable model, the contribution of each predictor was summarized using the partial R-squared for generalized linear models\textsuperscript{31}. Univariate logistic regression was also applied to explore factors associated with AIS, HS or HIBI. Statistical analyses were performed using the statistical software packages SAS 9.4 (SAS Institute, Cary, NC) and R Studio Version 3.4.1.

Results

Basic characteristics of the study population

Demographic data and ECMO circuit characteristics are summarized in Table 1 and enrollment is summarized in Fig. 1. One hundred twenty-three patients were screened and identified undergoing ECMO support from June 2019 to April 2022. Seventy-five such patients (61.0%) were prospectively enrolled and underwent MMM. One patient (1.0%) was determined ineligible due to age criteria and one patient (1.0%) was deemed ineligible due to a prior arterial ischemic stroke. Five patients (4.1%) did not provide consent. Forty-one patients (33.3%) were not consented due to logistic reasons (see Supplement 3). The median age was 1.1 [IQR 0.2–10.3] years with thirty-seven females (49.3%). Common indications for ECMO included acute respiratory failure (36%) followed by cardiogenic shock (29%) and cardiac arrest (17%). Fifty-three (70.7%) patients underwent VA-ECMO, twenty-one (28.0%) underwent VV-ECMO, and one (1.3%) underwent both VV-ECMO later converted to VA-ECMO. Arterial cannulation occurred in the carotid artery for fifty patients (66.7%), aorta for eighteen patients (24.0%), and femoral artery for four patients (5.3%). Venous cannulation occurred in the internal jugular vein for forty-six patients (61.3%), femoral vein for eight patients (10.7%), and right atrium for eighteen patients (24.0%). Median length of hospital stay was 35 (IQR [21–83]) days. Median length of ECMO duration was 7 (IQR [3–13]) days.
<table>
<thead>
<tr>
<th>Characteristic (n = 75)</th>
<th>n</th>
<th>N%</th>
</tr>
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<tbody>
<tr>
<td>Female sex,</td>
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<tr>
<td>Ethnicity</td>
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<tr>
<td>Caucasian</td>
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<td>Native American</td>
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<td>9.3</td>
</tr>
<tr>
<td>African American</td>
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<td>9.3</td>
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<tr>
<td>Asian American</td>
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<td>2.7</td>
</tr>
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<td>Acute Brain Injury</td>
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<td>25.3</td>
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<tr>
<td>AIS</td>
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<td>10.7</td>
</tr>
<tr>
<td>HS</td>
<td>4</td>
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<tr>
<td>HIBI</td>
<td>8</td>
<td>10.7</td>
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<tr>
<td>VA ECMO</td>
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</tr>
<tr>
<td>VV ECMO</td>
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<tr>
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<td>1.3</td>
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<tr>
<td>Arterial Cannulation</td>
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<td>Carotid artery</td>
<td>50</td>
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<tr>
<td>Aorta</td>
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<td>24.0</td>
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<tr>
<td>Femoral artery</td>
<td>4</td>
<td>5.3</td>
</tr>
<tr>
<td>Venous Cannulation</td>
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<td></td>
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<tr>
<td>Internal jugular vein</td>
<td>46</td>
<td>61.3</td>
</tr>
<tr>
<td>Right atrium</td>
<td>18</td>
<td>24.0</td>
</tr>
<tr>
<td>Femoral vein</td>
<td>8</td>
<td>10.7</td>
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<table>
<thead>
<tr>
<th></th>
<th>Median (IQR)</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (year)</td>
<td>1.1 (0.2, 10.3)</td>
<td>0–18</td>
</tr>
<tr>
<td>Arterial catheter size (mm)</td>
<td>12.0 (10.0, 16.0)</td>
<td>8–25</td>
</tr>
</tbody>
</table>

Abbreviations: AIS, arterial ischemic stroke; FiO₂, Fractionated inspired oxygenation; HIBI, hypoxic ischemic brain injury; HS, hemorrhagic stroke; lpm, liters per minute; mm, millimeters; % percent.
<table>
<thead>
<tr>
<th>Characteristic (n = 75)</th>
<th>n</th>
<th>N%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Venous catheter size (mm)</td>
<td>15.0 (12.0, 23.0)</td>
<td>8–31</td>
</tr>
<tr>
<td>Pump flow rate, max (lpm)</td>
<td>1.18 (0.55, 3.67)</td>
<td>0.30–5.50</td>
</tr>
<tr>
<td>Pump flow rate, min (lpm)</td>
<td>0.48 (0.25, 1.77)</td>
<td>0.00–3.97</td>
</tr>
<tr>
<td>Sweep O2, max (lpm)</td>
<td>2.00 (0.50, 5.00)</td>
<td>0.30–14.0</td>
</tr>
<tr>
<td>Sweep O2, min (lpm)</td>
<td>0.10 (0.10, 0.50)</td>
<td>0.00–8.00</td>
</tr>
<tr>
<td>Sweep FiO2, max (%)</td>
<td>75.0 (60.0, 100.0)</td>
<td>40.0–100.0</td>
</tr>
<tr>
<td>Sweep FiO2, min (%)</td>
<td>35.0 (12.0, 45.0)</td>
<td>0.0–90.0</td>
</tr>
<tr>
<td>ECMO duration (days)</td>
<td>7.0 (3.0, 13.0)</td>
<td>1.0–36.0</td>
</tr>
<tr>
<td>Hospital length (days)</td>
<td>35.0 (21.0, 83.0)</td>
<td>1.0–424.0</td>
</tr>
</tbody>
</table>

Abbreviations: AIS, arterial ischemic stroke; FiO2, Fractionated inspired oxygenation; HIBI, hypoxic ischemic brain injury; HS, hemorrhagic stroke; lpm, liters per minute; mm, millimeters; % percent.

At least one neuroimaging modality was utilized in sixty of seventy-five (80%) patients. Four patients did not have neuroimaging due to hemodynamic instability and eventually expired while on ECMO. Autopsy was declined by their families. None of the fifteen patients without neuroimaging demonstrated clear evidence toward neurological complications (e.g., seizures, neurologic exam changes).

In total, nineteen patients suffered acute brain injury (25.3%), including seven (36.8%) with AIS, four (21.1%) with HS, seven with HIBI (36.9%) and one (5.3%) with both AIS and HIBI. Acute brain injury was recognized on CT neuroimaging in eleven patients (57.9%), MRI neuroimaging in five (26.3%), head US in four (21.1%) and postmortem autopsy examinations in two patients (10.5%).

**Physiologic Features Predicting Brain Injury**

Univariate logistic regression demonstrated that acute brain injury was associated with maximal hourly seizure burden (OR = 3.17 [95% CI, 1.15–8.79], p = 0.026), interictal epileptiform discharges (OR = 6.31 [1.38–33.93], p = 0.020), QEEG suppression ratio (SR) (OR = 1.06 [1.01–1.11], p = 0.014), increased interhemispheric differences in QEEG total power (OR = 1.76 [1.08–2.85], p = 0.023) and amplitude (OR = 2.13 [1.19–3.81], p = 0.011), and increased differences in TCD TIBI scores between bilateral middle cerebral artery (MCA) territories (OR = 2.84, [1.00–8.00], p = 0.049) (Supplement 4). Multivariate best subset model selection identified that maximal hourly seizure burden (OR = 3.86 [1.33–11.23], partial R-squared 0.40, p = 0.013), interhemispheric amplitude differences (OR = 2.69 [1.31–5.49], partial R-squared 0.18, p = 0.007), and differences in MCA TIBI scores (OR = 4.97 [1.61–15.30], partial R-squared 0.22, p = 0.005) each independently predicted acute brain injury (AUROC = 0.92) (Table 2). We did not identify any
demographic or ECMO-circuit characteristics that were associated with acute brain injury, including for AIS, HS and HIBI (Supplement 4).

<table>
<thead>
<tr>
<th>Variables</th>
<th>OR (95% CI)</th>
<th>p value</th>
<th>Partial R-squared</th>
<th>AUROC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Differences in MCA TIBI scores</td>
<td>4.97 (1.61–15.30)</td>
<td>0.005</td>
<td>0.22</td>
<td>0.92</td>
</tr>
<tr>
<td>Seizure burden</td>
<td>3.86 (1.33–11.23)</td>
<td>0.013</td>
<td>0.40</td>
<td></td>
</tr>
<tr>
<td>Amplitude difference</td>
<td>2.69 (1.31–5.49)</td>
<td>0.007</td>
<td>0.18</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: TIBI, Thrombolysis in Brain Ischemia Grading Score; AUROC, area under the receiver operating characteristic curve.

Physiologic Features Associated with Arterial Ischemic Stroke

Univariate analysis identified that interictal epileptiform discharges (OR = 50.00 [3.92–637.44], p = 0.003) and differences in bilateral MCA TIBI scores (OR = 4.98 [1.61–15.38], p = 0.005) were significantly associated with AIS (Supplement 5).

Physiologic Features Associated with Hemorrhagic Stroke

Univariate analysis identified that interhemispheric differences in QEEG alpha power (OR = 81.76 [1.18–5689.00], p = 0.042), total power (OR = 2.60 [1.36–4.98], p = 0.004) and amplitude (OR = 3.65 [1.46–9.10], p = 0.006) and reduced rSO₂ (OR = 0.94 [0.88-1.00], p = 0.044) were associated with HS (Supplement 5).

Physiologic Features Associated with Hypoxic Ischemic Brain Injury

Univariate analysis identified increased SR on QEEG (OR = 1.07 [1.02–1.13], p = 0.006), maximal hourly seizure burden (OR = 1.35 [1.07–1.71], p = 0.012), and increased time of ABP below ABPOpt (OR = 1.10 [1.01–1.20], p = 0.034) were associated with HIBI (Supplement 5).

Discussion

This study reviewed MMM data from a prospective cohort of pediatric patients who were treated with ECMO. Acute brain injury was common with a 25.3% incidence in accordance with prior
literature\textsuperscript{3,5,6,16,32−34}. Multivariable analysis revealed that increased maximal hourly seizure burden on cEEG, interhemispheric amplitude differences on QEEG, and differences in MCA TIBI scores using TCD independently predicted acute brain injury with high accuracy. To our knowledge, this is the first prospective to demonstrate the utility of combining cEEG, QEEG and TCD monitoring for recognition of acute brain injury in pediatric ECMO patients.

cEEG has been previously utilized by various centers to predict outcomes in ECMO patients. In a study by Huang et al., investigators found that electrographic or electro-clinical seizures were identified in 40\% of patients and were associated with brain injury in infants undergoing ECMO\textsuperscript{13}. Electrographic seizure incidence was found to be 18\% in another pediatric study\textsuperscript{35}. Another retrospective study of 201 pediatric ECMO patients examined EEG features associated with brain injury and found that severely abnormal cEEG background activity and higher electroencephalographic seizure burden was associated with mortality. They also reported that the type of ECMO arterial cannulation site (right carotid vs. aorta) correlated with side of focal cerebral injury which in 33\% is associated with electrographic seizures\textsuperscript{18}. QEEG features have not yet been examined as predictive biomarkers of acute brain injury in ECMO patients, and our study results suggest that QEEG differences in interhemispheric amplitude may be useful in acute brain injury detection.

Only a few studies have investigated the role of TCD for detecting acute brain injury in pediatric ECMO patients, with none to date demonstrating significant features that are predictive in nature. An observational study in the pediatric ECMO population showed that flow velocities during ECMO deviated from age-specific normal values in all major cerebral vessels and across different age groups. This study also reported that global or regional elevations and asymmetries in flow velocity may suggest impending neurologic injury, although statistical significance was not achieved\textsuperscript{21}. A multi-center study on TCD evaluation of cerebrovascular physiology in ECMO supported children found that MCA flow velocities were significantly lower than normative values for critically ill children\textsuperscript{20}. However, in accordance with our findings, no significant difference was detected in systolic, diastolic, or mean flow velocities between pediatric patients with or without ischemic injury. Investigators found that increased PI may be a marker for ischemic injury in young infants on ECMO\textsuperscript{20}. We evaluated MCA TIBI grades as a method of extracting MCA waveform analysis, identifying those differences in TIBI grade between each MCA territory independently predicted acute brain injury in pediatric ECMO patients. Our finding is consistent with previously published literature which revealed a strong association with TIBI grades and brain injury severity among patients with arterial ischemic stroke\textsuperscript{28}.

Regarding model-based indices of CVPR identified from MMM, prior retrospective work reported that ABP was below LLA and above ULA over longer time in patients with acute neurologic events (ANE) compared to patients without ANE\textsuperscript{15}. We did not observe the same findings in our cohort, although we observed at the univariate level that increased time below ABPOpt was associated with HIBI. Prior work has suggested that greater burden of ABP below ABPOpt (otherwise described as ‘MAPopt’) is associated
with unfavorable outcomes after pediatric cardiac arrest\textsuperscript{28}. Further work is needed to understand whether optimizing ABP toward efficient CVPR may be neuroprotective in nature.

This study is one of few to date investigating the role of combined and integrated MMM toward detection of acute brain injury among pediatric ECMO patients. Previous studies focused on identifying clinical and laboratory predictors of acute brain injury in ECMO patients\textsuperscript{32}, or evaluated specific neuromonitoring modalities without comparison of alternative strategies. We note that we did not identify any clinical or ECMO-circuit characteristic as predictive of acute brain injury, highlighting the value of MMM monitoring integrating cEEG, QEEG and TCD.

Our study carried limitations. Sedative agents used in the ICUs at our institution include dexmedetomidine, fentanyl, midazolam and morphine which might have some influence on EEG, ABP and rSO\textsubscript{2} recordings. Challenges in acquiring neuroimaging for all enrolled patients limited comprehensive and timely detection of acute brain injury. While MMM provides information in real-time, it is not possible to identify the precise occurrence of acute brain injury. Our sample size was insufficient for age-stratification of our multivariable model or for multivariable analysis of specific causes of acute brain injury including AIS, HS and HIBI. A larger sample size arising from a multicenter cohort may be helpful for such investigations.

\textbf{Conclusions}

Acute brain injury is a common complication in pediatric patients undergoing ECMO support. Higher seizure burden, interhemispheric QEEG amplitude differences, and TCD MCA TIBI score differences independently predict acute brain injury in children requiring ECMO. Detection of acute brain injury through MMM that incorporates cEEG, QEEG and TCD may provide a window of opportunity for the recognition of injury with potential opportunities to offer neuroprotective strategies of care.

\textbf{Declarations}

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Authorship: BA provided substantial contributions to the conception and design of the study, acquisition, and analysis of data, and drafting significant portions of the manuscript. DH, MT, KH, EM, and ZG provided substantial contributions to acquisition and analysis of data and drafting significant portions of the manuscript. All authors provide final approval of the version to be published.

Conflicts of interest: Dr. Appavu, report a completed research grant from Moberg ICU Solutions as well as a research grant from the United States Department of Defense Congressionally Directed Medical
Research Programs Epilepsy Research Program (W81XWH-19-1-0514), both outside the scope of this work. Dr. Appavu also received speaking honoraria from Natus® for two webinar presentations.

References


Figures

123 Patients were screened for eligibility

75 Were screened for eligibility

19 Were found to have BI
  8 had HIBI
  8 had AIS
  4 had HS

56 Were found not to have BI

48 Were excluded
  41 had logistical reasons
  5 did not provide consent
  1 did not meet age criteria
  1 had a prior neurologic injury
Figure 1

Patient Enrollment

Abbreviations: BI, brain injury; HIBI, hypoxic ischemic brain injury; AIS, arterial ischemic stroke; HS, hemorrhagic stroke.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- Supplement.docx