Neurologic Complications of Extracorporeal Cardiopulmonary Resuscitation in Neonates and Infants

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Abstract
Objective: Extracorporeal membrane oxygenation (ECMO) is a lifesaving measure for patients in cardiac or respiratory failure. Extracorporeal cardiopulmonary resuscitation (ECPR) is emergent ECMO cannulation during cardiac arrest. All ECMO patients are at high risk for neurologic complications, but the degree of risk of ECPR relative to ECMO without CPR in progress (non-ECPR ECMO) is not well documented in infants. The goal of the present study is to compare neurologic complication rates between infants who underwent ECPR and those who underwent non-ECPR ECMO. Methods: We performed a retrospective chart review on all patients admitted between 2009 and 2020 to the neonatal intensive care unit (NICU) in our quaternary children’s hospital. We separated patients by ECPR vs. non-ECPR ECMO cannulation. We compared rates of death and used neuroimaging and video electroencephalogram (vEEG) to determine incidence of stroke, intracranial hemorrhage, and seizure. Chi-square and Fisher’s exact tests were used to compare these categorical variables among groups. Results: A total of 181 infants were cannulated onto ECMO. Of these, 40 received ECPR, 56 received non-ECPR ECMO for a cardiac indication, and 85 received non-ECPR ECMO for a respiratory indication. After excluding patients currently admitted (n=1, ECPR), 180 patients were subjected to analysis. ECPR patients were less likely to survive to hospital discharge than patients who underwent non-ECPR ECMO for respiratory indications, and less likely to survive without any neurologic complication compared with infants who underwent non-ECPR ECMO for cardiac or respiratory indications. Interpretation: Significantly fewer ECPR patients survived without experiencing a neurologic complication, compared with non-ECPR ECMO patients. Keywords electroencephalography, extracorporeal membrane oxygenation, extracorporeal cardiopulmonary resuscitation, neonatal, neurologic outcomes

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Introduction
Extracorporeal membrane oxygenation (ECMO) is a lifesaving measure for patients in cardiac or respiratory failure. The most common perinatal cardiac indications for ECMO include congenital defects, cardiogenic shock, cardiomyopathies, and myocarditis, while the most common perinatal respiratory indications include congenital diaphragmatic hernia, meconium aspiration syndrome, persistent pulmonary hypertension of the newborn, and sepsis.1–3 Extracorporeal cardiopulmonary resuscitation (ECPR) refers to ECMO cannulation in the setting of sudden cardiac arrest of any etiology. ECPR has been shown

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to increase survival to discharge when compared to conventional resuscitation in pediatric cardiac arrest.4

ECMO carries a high risk of neurologic harm. A 2019 study demonstrated radiologic evidence of CNS injury in 44% of pediatric ECMO patients cannulated for cardiac indications in the peri-ECMO period, and cardiac ECMO survivors were found to have significant delays in several neurodevelopmental domains compared to age-matched controls with congenital heart disease who had not undergone ECMO.5 In our previous study of 70 neonatal and pediatric patients cannulated onto ECMO, 23% had electrographic evidence of seizure, with 50% of these seizures occurring within the first 24 h of ECMO. Patients who experienced seizures were significantly less likely to survive to hospital discharge.6 Another recently published cohort of 110 pediatric ECMO patients was found to have an 18% incidence of seizure, with a trend towards increased survival to discharge in patients without seizure.7

Long-term neurodevelopmental impairment among survivors of pediatric ECMO has also been described in multiple studies. ECMO survivors tend to have poorer performance on neuropsychological testing and decreased ability in specific performance domains such as motor and language relative to their age matched, non-ECMO counterparts when assessed in early childhood and young school age.8–13 EPCR also presents high risk of neurologic complications, but the impact of these complications is unknown. Kramer et al demonstrated in 2020 that while only 36% of EPCR patients survived to discharge, of those who survived, up to 77% were considered to have a “favorable” neurologic outcome, defined as a change in the Pediatric Cerebral Performance Category score (scores range from 1-6, with 1 being normal neurologic function and 6 being brain death) of less than 1 (ΔPCPC <1) before and after ECMO.14 Although multiple studies report the incidence of immediate and long-term neurologic complications in pediatric ECMO patients, a paucity of data exists comparing outcomes for EPCR versus non-ECPR ECMO patients. Direct comparison of these outcomes between EPCR and ECMO without CPR in progress, or non-ECPR ECMO, has not been reported in infants.

We sought to quantify, characterize, and compare the neurologic complication rates at our institution in infants who underwent EPCR and those who underwent ECMO without CPR in progress, or non-ECPR ECMO. Given the additional premorbid stress associated with cardiac arrest in patients who undergo EPCR, we hypothesized that patients undergoing EPCR would have an increased risk of death and an increased risk of neurologic morbidity, including seizure, stroke, and intracranial hemorrhage, compared with patients undergoing non-ECPR ECMO.

Patients and Methods

We performed a retrospective chart review of all patients admitted to the general neonatal intensive care unit (NICU) and the infant cardiac unit in our quaternary children’s hospital between 2009 and 2020 treated with EPCR or non-ECPR ECMO. We did not include patients admitted to the PICU, of any age. Therefore, all patients included in this study were cannulated in the setting of a perinatal disease process. Of note, this NICU cohort included both neonates (<28 days old) and infants (<1 year old). From this point forward we will refer to patients in the present study as infants, denoting inclusion of all NICU patients. Baseline characteristics including sex and age (in days) at cannulation were collected, as well as survival data, reports from video electroencephalogram (vEEG), and radiology reports from head ultrasound, computerized tomography scan (CT), and magnetic resonance imaging (MRI) studies when available.

The neuromonitoring protocol while on ECMO at our institution includes daily head ultrasound throughout cannulation for patients with an open anterior fontanel, and vEEG for at least the first 48 h of cannulation. Video EEG is continued if the patient is medically paralyzed (which rarely occurs in neonates) or has known uncontrolled seizure activity. CT scan is obtained if there is suspicion for acute cerebral insult based on changes in vEEG monitoring, concerning findings on head ultrasound, or alteration in mental status or neurologic exam. Ideally neuroimaging with MRI is obtained after successful ECMO decannulation to establish a new neuroimaging baseline, though this does not universally occur.

We used the above reports (head ultrasound, head CT, MRI brain, and vEEG) when available to collect neuromonitoring data in our infant ECMO cohort. Statistical analysis was performed using Chi-Square test and Fisher’s Exact test. We compared rates of death prior to discharge between each study group, and then each neurologic complication (seizure, intracranial hemorrhage, ischemic stroke) separately. We then performed a composite outcome analysis where we compared the following three outcomes, 1) Survived with NO Neurologic Complication, 2) Survived with Neurologic Complication, and 3) Death Prior to Discharge among the three study groups. Neurologic Complication was defined as having any stroke, intracranial hemorrhage, or electrographic seizure.

Results

There were 187 total NICU ECMO runs at our institution between 2009 and 2020. Six patients experienced two separate ECMO runs. In these cases, only the first run was studied and used to assign the patient to one of the three study groups, though neuroimaging at any time point after the conclusion of the first run was included, including imaging which occurred after the conclusion of the second run. In total, 181 patients were subject to analysis, of which 40 were treated with EPCR, 56 with non-ECPR ECMO for a cardiac indication, and 85 with non-ECPR ECMO for a respiratory indication. One EPCR patient was excluded from analysis because as of this writing, the patient is still admitted to the hospital, leaving 39 EPCR patients. (Figure 1).

The most common cardiac indications were hypoplastic left heart syndrome (n = 11), transposition of the great arteries (n = 8), severe sepsis (n = 6), and Tetralogy of Fallot (n = 5). The
The most common respiratory indications were congenital diaphragmatic hernia (n = 31), meconium aspiration syndrome (n = 19), and persistent pulmonary hypertension of the newborn (n = 18). The non-ECPR respiratory group had a greater proportion of males relative to non-ECPR cardiac patients (68% (58/85) versus 44% (25/56) for cardiac, P = .005) (Figure 2). Non-ECPR respiratory patients were significantly younger at the time of cannulation compared with both non-ECPR cardiac and ECPR patients. The mean age (days) at cannulation for each group was 36.3 for ECPR, 21.6 for cardiac, and 5.2 for respiratory (SD 40.8, 33.1, and 12.4, respectively; one-way ANOVA allowing for unequal variance, P < .0001). Significantly fewer ECPR patients survived to hospital discharge compared with non-ECPR respiratory ECMO patients (33% (13/39) for ECPR versus 67% (57/85) for respiratory patients, P < .001). There was no significant difference in survival to hospital discharge for ECPR patients compared with non-ECPR cardiac ECMO patients (52% (29/56) for cardiac, P = .075) (Figure 3). Cause of death in the ECPR group was most commonly due to cardiac or cardiopulmonary arrest (n = 11), heart failure (n = 2), respiratory failure (n = 2), and cardiopulmonary failure (n = 2), with one patient terminally decannulated for poor prognosis after intracranial hemorrhage. Cause of death in the non-ECPR cardiac group was most commonly cardiac or cardiopulmonary arrest (n = 7), heart failure (n = 5), cardiorespiratory failure (n = 4), and sepsis (n = 3), with one patient terminally decannulated for poor prognosis after subdural hemorrhage and multiple intracranial infarcts. Cause of death in the non-ECPR respiratory group was most commonly respiratory failure (n = 7), cardiorespiratory failure (n = 5), cardiac or cardiopulmonary arrest (n = 4), intracranial hemorrhage followed by terminal decannulation for poor prognosis (n = 3), and heart failure (n = 2).

All neuroimaging during or after ECMO was included for analysis. Abnormal imaging findings either occurred while patients were on ECMO or any length of time after the ECMO run. The time between decannulation and abnormal imaging findings ranged from zero days after decannulation to a maximum of four years later, with most patients having imaging between zero- and 30-days post-cannulation. Of the six patients who underwent >1 ECMO run, two had evidence of ischemic stroke that was found after the conclusion of the second run.

174 patients (96%) underwent head ultrasound while on ECMO; 83 (46%) had either CT or MRI during or after ECMO, and 105 patients (58%) had EEG while on ECMO (Figure 1). There were seven patients who lacked all three modalities of neuroimaging as well as vEEG, because death occurred within the first 24h after cannulation and so neuromonitoring was not pursued. These included two cardiac patients, one respiratory patient, and four ECPR patients.

When comparing among the three study groups (ECPR, respiratory, cardiac), there was no significant difference in rates of intracranial hemorrhage, ischemic stroke, and electrographic

**Figure 1.** Pediatric ECMO Runs and Inclusion/Exclusion Criteria: Total number of pediatric extracorporeal membrane oxygenation (ECMO) cannulations between 2009 and 2020. Non-infants were excluded from analysis as well as six ECMO runs that were not the first run for the patient. Of the 181 first-time ECMO runs, 40 were extracorporeal cardiopulmonary resuscitation (ECPR), 56 were for a non-ECPR cardiac indication, and 85 were for a non-ECPR respiratory indication.
Figure 2. Comparison of sex distribution among the three study groups: extracorporeal cardiopulmonary resuscitation (ECPR), extracorporeal membrane oxygenation (ECMO) for a cardiac indication without CPR in progress, ECMO for a respiratory indication without CPR in progress. *P*-values calculated using Chi-Square Test. **P-value < .01.

Figure 3. Comparison of death prior to discharge, incidence of stroke, incidence of intracranial hemorrhage, and seizure detected on video electroencephalogram (vEEG) among the three study groups: extracorporeal cardiopulmonary resuscitation (ECPR), extracorporeal membrane oxygenation (ECMO) for a cardiac indication without CPR in progress, ECMO for a respiratory indication without CPR in progress. P-values for comparison of stroke calculated using Fisher’s Exact Test. All other P-values calculated using Chi-Square Test. ***P-value < .001.
seizure (Figure 3). In the ECPR group, 2/39 (5%) survived to hospital discharge and did not experience any neurologic complications, 11/39 (28%) survived to hospital discharge but experienced at least one neurologic complication, and 26/39 (67%) died prior to discharge. Fewer ECPR patients survived without neurologic complication compared with both groups of non-ECPR ECMO patients (2/39 or 5% for ECPR vs 13/56 or 24% for cardiac vs 31/85 or 36% for respiratory, see Figure 4). The proportion of survivors who experienced at least one neurologic complication was similar among the three groups (28% or 11/39 for ECPR, 29% or 16/56 for non-ECPR cardiac, and 31% or 26/85 for non-ECPR respiratory). Among patients who survived ECPR, a large proportion (11/13 or 85%) experienced a neurologic complication, compared with 16/29 (55%) for non-ECPR cardiac ECMO survivors and 31/57 (54%) non-ECPR respiratory survivors (Figure 4).

Discussion

To our knowledge, this is the first study to compare rates of short-term neurologic complications between ECPR and non-ECPR ECMO patients in the infant population. The aim of this study was to determine whether infants who undergo ECMO cannulation in the setting of cardiopulmonary resuscitation are at increased risk of poor neurologic outcomes than are infants cannulated onto ECMO in a non-ECPR setting.

We found a significantly increased risk of death in those sustained by ECPR in contrast to ECMO in the setting of a non-ECPR respiratory indication, but no significant difference in death prior to discharge between ECPR and non-ECPR cardiac ECMO. The finding that ECPR patients are less likely to survive to discharge and less likely to survive without a neurologic complication when compared with their non-ECPR counterparts supports our hypothesis that ECPR patients are at greater risk for poor outcome, including death or neurologic complication, when compared with non-ECPR patients. This difference is most pronounced between ECPR patients and non-ECPR respiratory ECMO patients. Only 2/39 (5%) of ECPR patients survived without experiencing a neurologic complication, and 11/13 survivors had at least one neurologic complication. In the event of ECPR, the patient has already arrested, requiring chest compressions, thereby suggesting that these patients are sicker at the time of cannulation compared with patients for whom ECMO cannulation is a planned event (ie before onset of cardiac arrest). In addition, cannulation in the setting of an active resuscitation attempt is less controlled, more emergent and could happen at any time of day or night, with varying availability of resources.

Overall, only 58% (105/181) of patients in this study had vEEG. However, this can be explained by a change in

**Figure 4.** Composite outcome: (1) patients who died prior to discharge, regardless of whether they had any neurologic complications, (2) patients who survived to discharge but experienced any of the neurologic complications studied (intracranial hemorrhage, ischemic stroke, or electrographic seizure) either during or any length of time after the ECMO run, (3) patients who survived to discharge and never had a neurologic complication, compared among the three study groups: extracorporeal cardiopulmonary resuscitation (ECPR), extracorporeal membrane oxygenation (ECMO) for a cardiac indication without CPR in progress, and ECMO for a respiratory indication without CPR in progress. P-values calculated using Chi-Square Test. *** denotes $P < .001$ and * denotes $P < .05$. Schmaedick et al. 5
institutional protocol in 2014, to include vEEG monitoring in the first 48h of ECMO for all patients. A greater proportion of patients in each group have vEEG reports available after 2014. In the respiratory group, 43 patients were cannulated prior to 2014, of which 28% (12/43) had vEEG monitoring, compared with 69% (29/42) of patients cannulated 2014 or later. In the cardiac group, 14 patients were cannulated prior to 2014, of which 14% (2/14) had vEEG monitoring, compared with 76% (34/45) of patients cannulated 2014 or later. In the ECPR group, only 7 patients were cannulated prior to 2014, of which 3/7 or 43% had vEEG monitoring, compared with 88% (29/33) of patients cannulated 2014 or later. Similarly, CT head or MRI brain would ideally be obtained for all patients after successful decannulation from ECMO, to establish whether the patient has evidence of central nervous system insult that was not detected during the ECMO course. Of those who survived to decannulation, only 54% (73/134) received the recommended imaging. Even after decannulation, many patients remain critically ill, and obtaining imaging, which often requires transport, in the immediate post-ECMO period would be unsafe.

Interestingly, a study of 80 pediatric patients, with a median age of 150 days, found that children with isolated heart disease who required ECPR had improved survival compared with children who experienced a cardiac arrest of a different etiology requiring ECPR. The authors attribute this to the fact that patients with isolated heart disease generally lack significant dysfunction of other organ systems, in contrast to children who experience cardiac arrest as a complication of other medical disease. Since the present study only included general NICU and infant cardiac unit patients, the vast majority of ECPR patients in this study had underlying congenital heart disease. Because of the limitation to the neonatal/infant units (rather than readmitted neonates/infants treated in the PICU), our ECPR population is mostly a cardiac population. Future studies should attempt to compare ECPR outcomes among patients with and without congenital heart disease, which may require broadening the scope to include PICU, as opposed to strictly NICU/Infant Cardiac Unit, patients.

The strengths of this study include the relatively large sample size for a single institution ECPR study, especially in infants. Our institution sees a high volume of ECMO patients each year, and this is reflected in the large cohort available for this study. However, the study is underpowered to detect a difference in the discrete outcomes (stroke, hemorrhage, and seizure) when tested alone. Only the composite outcome is adequately powered given our sample size. In addition, there is significant variation in the neuroimaging studies available for patients. Obtaining CT or MRI neuroimaging in the hospital requires the patient to be stable enough for transport. In most cases this occurs after decannulation due to the risk and logistic difficulty inherent in transporting these patients. In contrast, head ultrasound occurs at the bedside, and the standard of care at our institution is daily head ultrasounds for patients with an open anterior fontanel, for the duration of the ECMO run. Head ultrasound is sensitive for detecting hemorrhage, but less sensitive for detecting ischemic stroke. Ideally, every patient would have CT or MRI imaging immediately after decannulation to determine a new neurologic “baseline” after ECMO. Some patients take months to stabilize resulting in delayed imaging and the inability to directly attribute new lesions to the ECMO run. Lastly, a major limitation of this study is that it is a retrospective study, as opposed to a randomized, controlled, prospective study. Because ECMO, and in particular ECPR, is a last-resort therapy to prevent death in the setting of cardiac arrest, with inadequate response to conventional CPR measures, one could not ever perform a prospective study with random assignment to ECPR or non-ECPR groups. The aim of this type of work is to provide clinicians—and ultimately, patients’ families—with realistic expectations for potential complications, the likelihood of these complications, and eventually the long-term ramifications of these complications if and when they occur.

It is important to note that there may be an element of historical bias in this study with regards to comparison of ECPR with non-ECPR ECMO. We included ECMO patients as early as 2009, but the earliest ECPR patient was in 2011, and ECPR was not regularly done until 2013. Therefore, the timespan of ECPR patients and non-ECPR patients is not identical. ECPR is a lifesaving option for patients in cardiac arrest refractory to conventional resuscitative measures, but the potential neurologic consequences have not been fully quantified. As indications for ECMO in the infant population continue to expand, understanding the potential neurological complications of ECMO and ECPR will be critical for surgeons (and collaborative teams) in their triage of offering ECMO cannulations, as well as to families and researchers. Future studies should seek to elucidate whether a true difference in each individual neurologic complication exists and should clarify the subtypes and severity of central nervous system injury in each ECMO type. Even more importantly, many parents and caregivers want to know what to expect beyond the acute phase, with a better understanding of the long-term consequences of neurologic complications that occur after ECMO and ECPR.

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Declaration of Conflicting Interests
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**Ethics Approval**
Ethical approval to perform this study was obtained from the Columbia University IRB, protocol #AAAR1368.

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**Patient Consent**
This study qualifies for a waiver or alteration of consent as the following criteria are met: 1) the research involves no more than minimal risk to the subjects, 2) the waiver or alteration will not adversely affect the rights and welfare of the subjects, 3) the research could not practically be carried out without the waiver or alteration, and 4) whenever appropriate, the subjects will be provided with additional pertinent information after participation.

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