Published in final edited form as:

Neurocrit Care. 2020 October ; 33(2): 429–437. doi:10.1007/s12028-019-00892-4.

Association of Cerebral Oximetry with Outcomes after Extracorporeal Membrane Oxygenation

Po-Yang Tsou, MD, MPH¹, Alejandro V. Garcia, MD², Alvin Yiu, BS¹, Dhananjay M. Vaidya, MBBS, MPH, PhD³, Melania M. Bembea, MD, MPH, PhD¹

¹Department of Anesthesiology and Critical Care Medicine, Johns Hopkins University School of Medicine, Baltimore, Maryland ²Department of Surgery, Johns Hopkins University School of Medicine, Baltimore, Maryland ³Department of General Internal Medicine, Johns Hopkins University School of Medicine, Baltimore, Maryland

Abstract

Background: Extracorporeal membrane oxygenation (ECMO) is associated with neurologic morbidity and mortality. We investigated whether cerebral regional oxygen saturation (rSO₂) is associated with neurologic outcomes and survival in children on ECMO.

Methods: This was a retrospective observational study of children ages 1 day to 20 years who underwent ECMO with routine cerebral rSO₂ monitoring in the pediatric intensive care unit at a single academic center between February 2008 and September 2014. We collected all serial rSO₂ values recorded in the electronic medical record during the ECMO course. Favorable outcome was defined as survival with Pediatric Cerebral Performance Category (PCPC) ≥ 2 at hospital discharge or no decline from baseline PCPC.

Results: We reviewed data from 153 patients who underwent 156 ECMO runs. The median age was 12.5 days (interquartile range [IQR], 2 days – 15 months). Ninety-nine (64%) patients survived to hospital discharge, and 82/99 (83%) survivors had favorable neurologic outcome by discharge PCPC. Neuroimaging studies were obtained in 135 (87%) patients, 59 (44%) of which showed abnormal findings. Ninety-two (59%) patients had any rSO₂ $\geq 50\%$, 60 (38%) had any rSO₂ decline $>20\%$ from baseline, and 26 (17%) had any rSO₂ decline $>20\%$ from the reading 1 h prior. Any rSO₂ $\geq 50\%$ and any rSO₂ decline $>20\%$ from baseline were each associated with unfavorable outcome at hospital discharge (multivariable-adjusted odds ratio [OR], 2.82 [95% CI, 1.10–7.25] and 4.52 [95% CI, 1.76–11.58], respectively). rSO₂ decline $>20\%$ from the reading 1 h prior was not significantly associated with the outcomes.

Conclusion: Among children in one institution who underwent routine clinical rSO₂ monitoring during ECMO, rSO₂ decline was associated with unfavorable short-term neurologic outcome and death after adjusting for potential confounders. The effectiveness of initiating early preventative measures in these high-risk patients needs further study.

Corresponding author Melania Bembea, MD, PhD, Department of Anesthesiology and Critical Care Medicine, Johns Hopkins University School of Medicine, 1800 Orleans Street, Suite 6321, Baltimore, MD, United States, 21287, Tel: 410-955-6412, Fax: 410-502-5312, mbembea1@jhmi.edu.

Conflict of interest: The authors report no conflicts of interest.

Keywords

cerebral oximetry; child; extracorporeal membrane oxygenation; extracorporeal life support; outcome assessment; neuromonitoring

Introduction

Extracorporeal life support (ECLS) provides cardiopulmonary support for patients with severe cardiac or respiratory failure that is refractory to conventional treatment¹. The number of neonatal and pediatric ECLS cases reported to the Extracorporeal Life Support Organization (ELSO) registry increased from 2,409 at 157 centers in 2009 to 2,992 at 227 centers in 2015^{2,3}. Neurologic injury is a serious complication among patients supported by ECMO, with an overall incidence of 7%–22%^{3–8}, depending on ECMO mode, age, and etiologies, and is highest among neonates¹. Several pathophysiologic changes associated with ECMO have been hypothesized to trigger neurologic injury, including the disturbance of hemodynamics introduced by ECMO¹, decreased cerebral blood flow after carotid cannulation^{9–11}, and susceptibility of patients' underlying conditions (e.g., neonates with immature cerebral autoregulation)^{10,12–15}. With wider applications of ECMO in larger populations^{2,16}, the disease burden of neurologic complications is expected to increase, prompting a need for appropriate neuromonitoring during the high-risk ECMO course.

Near-infrared spectroscopy (NIRS) is widely used as a continuous and noninvasive method of neuromonitoring that is applicable in both children and adults¹⁷. It offers clinicians real-time information on the regional oxygen saturation (rSO₂) of monitored organs by calculating the ratio of oxyhemoglobin to total hemoglobin using two wavelengths of near-infrared light¹⁸. It has been investigated as a neuromonitoring modality in multiple settings^{19–21}. However, data on its role in patients supported with ECMO are still limited. The aim of this study was to determine whether changes in cerebral rSO₂ are associated with neurologic and survival outcomes in pediatric patients who undergo ECMO.

Material and Methods

Study Design

This was a retrospective observational cohort study of children less than 21 years of age who underwent ECMO for any indication in the pediatric intensive care unit (PICU) of one academic medical center from February 2008 to September 2014. Only the first ECMO run was included for patients with ≥2 ECMO runs during the same hospitalization. We retrospectively reviewed the electronic medical records (EMR) of eligible patients and abstracted clinical, laboratory, imaging, and hospital discharge outcomes data, as well as all consecutive cerebral rSO₂ values recorded in the EMR during the ECMO course. ECMO patients underwent NIRS-based cerebral oximetry monitoring (INVOS; Somanetics, Troy, MI) according to institutional PICU-wide clinical protocols. We excluded from analysis patients who lacked rSO₂ values in the EMR. This study was approved by the Johns Hopkins Institutional Review Board.

Cerebral Oximetry Categories

We abstracted all bifrontal EMR rSO₂ recordings during the ECMO course. Based on previously published literature^{22–24}, we defined *a priori* the following rSO₂ cutoffs for absolute values and percent decline: 1) any rSO₂ < 40% or < 50% during the ECMO course, 2) a reduction >20% from baseline (defined as the first rSO₂ recorded after ECMO cannulation), and 3) a reduction >20% from the rSO₂ recorded 1 h prior. Additionally, we divided the cumulative time spent with rSO₂ lower than these cutoffs by the duration of ECMO support to obtain the time percentage. We used mid-rSO₂ and min-rSO₂ to represent median and minimum of each patient's rSO₂ during cerebral oximetry monitoring, respectively.

Outcome Measures

The primary outcome was neurologic status at hospital discharge based on the Pediatric Cerebral Performance Category (PCPC)^{25,26}. Favorable neurologic outcome was defined *a priori* as survival with PCPC of 1 or 2 at hospital discharge, or no decline from baseline PCPC. The PCPC scale was developed to assess changes in cognitive abilities in pediatric intensive care^{24,25}. The six PCPC categories are 1) normal, age-appropriate neurodevelopmental functioning, 2) mild cerebral disability, 3) moderate cerebral disability, 4) severe cerebral disability, 5) coma or vegetative state, and 6) brain death^{25,26}. The secondary outcomes were mortality prior to hospital discharge and abnormal neuroimaging, defined as new (if pre-ECMO imaging was available) intracranial hemorrhage, thromboembolic stroke, or postasphyxial injury. We reviewed clinical reports of neuroimaging studies that had been obtained for clinical purposes, including daily cranial ultrasounds during ECMO in infants with open anterior fontanel, and brain computed tomography (CT) or magnetic resonance imaging (MRI) obtained by clinical providers during ECMO or up to 6 weeks after the ECMO course.

Statistical Analysis

We conducted exploratory data analysis to describe patient, ECMO course characteristics, to determine the proportion of patients in whom serial rSO₂ was recorded, and to describe the distribution of rSO₂ values. We compared groups of patients with favorable and unfavorable outcomes at hospital discharge using the Wilcoxon rank-sum test, t-test, or chi-square test, as appropriate, for non-normally distributed continuous variables, normally distributed continuous variables, and categorical variables, respectively.

We performed multivariable regression analyses to assess the independent association between rSO₂ during the ECMO course and unfavorable outcomes, controlling for potential pre- and on-ECMO confounders: age, gender, pre-existing neurologic disease, chromosomal defect, pre-ECMO inotrope use, pre-ECMO cardiac arrest, primary ECMO indication, ECMO mode, ECMO pump flow (recorded hourly), seizures during ECMO, and ECMO duration. Multivariable logistic regression models included variables determined based on prior work^{7,27,28}, or associated with the outcome in univariate analysis at a significance level of $p < 0.1$. Analyses were conducted with and without ECMO duration, which was considered a potential mediator. We treated rSO₂ as a binary variable using pre-defined categories as noted above, as well as a continuous variable representing the percentage of

ECMO time spent at rSO_2 below each cutoff. Statistical analysis was conducted using Stata 12.0 (Stata Corp, College Station, TX).

Results

Patient and ECMO Characteristics

During the study period, ECMO was utilized 182 times, of which we included 156 ECMO runs from 153 patients based on the inclusion and exclusion criteria (Figure 1). The median patient age was 12.5 days (interquartile range [IQR]: 2 days – 15 months). Eighty-four patients (53.9%) were neonates, and 81 (51.9%) were male. The indications for ECMO were primary respiratory failure, 65/156 (41.7%); primary cardiac failure, 51/156 (32.7%); extracorporeal cardiopulmonary resuscitation (ECPR), 30/156 (19.2%); and sepsis, 10/156 (6.4%). Most patients, 137/156 (87.8%), were supported by venoarterial ECMO. Additional patient and ECMO course characteristics are presented in Tables 1 and 2.

The median duration of ECMO was 5.2 days (IQR, 3.3–11.1). The median duration of cerebral oximetry monitoring was 4.75 days (IQR, 2.9–10.1), representing 99.2% (IQR, 97.5%–100%) of the time on ECMO. An rSO_2 40% was recorded in 61/156 (39.1%) ECMO runs, an rSO_2 50% was recorded in 92/156 (59.0%) patients, and an rSO_2 reduction >20% from baseline was recorded in 60/156 (38.5%) patients (Table 2 and Supplemental Figures 1–3). An rSO_2 reduction >20% from the value 1 h prior was recorded in 26/156 (16.7%) patients. The median rSO_2 values before and after the >20% decline in 1 h were 79% (IQR, 69–89) and 53% (IQR, 36–62), respectively.

Primary Outcome

Seventy-four (47.4%) patients had unfavorable outcome at hospital discharge: 57/74 (77%) died prior to discharge and 17/74 (23%) survived with PCPC >2. The proportions of patients with any rSO_2 40%, any rSO_2 50%, any decline >20% from baseline, and any decline >20% from 1 h prior, were significantly higher in patients with unfavorable outcome than in those with favorable outcome at hospital discharge (Table 2).

In multivariable logistic regression models adjusted for age, gender, ECMO indication, pre-ECMO cardiac arrest, ECMO duration, clinical seizures during ECMO, and ECMO pump flow, any rSO_2 50% (adjusted OR, 2.82; 95% CI, 1.10–7.25) and rSO_2 decline >20% from baseline (adjusted OR, 4.52; 95% CI, 1.76–11.58) were significantly associated with unfavorable outcome at hospital discharge (Table 3, Supplemental Tables 1 and 2). Given that ECMO duration could be a potential mediator between rSO_2 decline and unfavorable outcome, we conducted sensitivity analyses that excluded ECMO duration in the multivariable logistic regression. Any rSO_2 50% (adjusted OR, 3.37; 95% CI, 1.35–8.43) and rSO_2 decline >20% from baseline (adjusted OR, 5.04; 95% CI, 2.02–12.60) remained significantly associated with unfavorable outcome at hospital discharge. Any rSO_2 40% (adjusted OR, 2.93; 95% CI, 1.19–7.22) and any rSO_2 decline >20% from 1 h prior (adjusted OR, 3.94; 95% CI, 1.29–11.98) shifted from having a marginally significant association with unfavorable outcome to significant association.

Secondary Outcomes

Fifty-seven patients died prior to hospital discharge. Of the 156 patients in the study, 135 (86.5%) had neuroimaging studies obtained for clinical purposes, and 59 of those (43.7%) had abnormal findings (Table 2). Abnormal neuroimaging included arterial ischemic stroke (n=22), venous sinus thrombosis (n=1), global postasphyxial injury (n=10), watershed infarctions (n=4), deep gray matter injury (n=4), leukomalacia (n=1), intracranial hemorrhage (intraparenchymal hemorrhage [n=17], subdural hemorrhage [n=20], subarachnoid hemorrhage [n=3], intraventricular hemorrhage [n=18], punctate white matter hemorrhage [n=7], diffuse intraparenchymal microhemorrhages [n=3]). The aforementioned n represent the number of imaging studies with abnormal findings, as one patient could have 1 type of injury. Patients who died before hospital discharge had significantly lower median and minimum recorded rSO₂ than patients who were alive at hospital discharge, as well as higher proportions of any rSO₂ < 50%, any rSO₂ < 40%, any rSO₂ decline >20% from baseline, and percent of ECMO time spent at lower rSO₂, as detailed in Supplemental Table 3. Among patients with neuroimaging studies available, those with abnormal neuroimaging findings did not have significantly lower rSO₂ than those without abnormal neuroimaging findings except for any rSO₂ < 50% (Supplemental Table 4). Logistic regression model results for the two secondary outcomes are presented in Supplemental Table 5. After adjusting for potential confounders, any rSO₂ < 50% and any rSO₂ decline >20% from baseline were significantly associated with the outcome of abnormal neuroimaging, and any rSO₂ decline >20% from baseline was associated with mortality prior to hospital discharge.

Discussion

To our knowledge, this is the largest cohort study to investigate the association between the decline in cerebral rSO₂ and neurologic outcomes and mortality among children on ECMO. This study showed that the degree of change in cerebral rSO₂ as well as the duration of significant rSO₂ decline during the ECMO course, were associated with unfavorable outcome at hospital discharge, abnormal neuroimaging, and mortality prior to hospital discharge. In this study, we defined *a priori* rSO₂ cutoffs for absolute values and percent decline. Any rSO₂ < 40% or < 50% during the ECMO course, and reduction >20% from baseline were selected based on previously published studies showing that cerebral rSO₂ crossing these thresholds is associated with unfavorable outcomes such as multiorgan dysfunction, cognitive dysfunction, stroke, postoperative delirium, or mortality^{23,24,38}. Some have proposed the cutoff of absolute rSO₂ < 50% as an “intervention threshold” and rSO₂ < 40% as a “critical threshold”²⁴. Given the retrospective nature of our study, we could not evaluate the effect of interventions by clinicians. However, our findings suggest that, when applied to the pediatric ECMO population, these previously proposed rSO₂ thresholds are associated with mortality and unfavorable neurologic outcomes in bivariate as well as multivariable logistic regression analyses. Further prospective studies are needed to refine clinically-relevant rSO₂ thresholds or trajectories over time, and to investigate real-time causes for and potential interventions to correct cerebral oximetry decrements in ECMO patients.

NIRS has been used for neuromonitoring and for guiding interventions in several clinical settings. The intraoperative use of cerebral oximetry has been studied in adult and pediatric cardiac surgery and is associated with improved short-term outcomes and long-term neurodevelopment^{19–21}. Its use to assess regional oxygenation of targeted organs has been associated with less organ failure and lower mortality in patients with trauma or shock^{29,30}. NIRS might be associated with neurologic complications, particularly among neonates^{31–33}. In ECMO, relevant studies have focused on rSO₂ changes at cannulation or the association between rSO₂ changes and vital parameters during ECMO (e.g., mean arterial blood pressure, ECMO flow)^{9,10,34–37}. The prognostic value of cerebral oximetry for adverse outcomes has been descriptively addressed in two small ECMO studies^{22,38}. In an observational study of 34 infants <3 months supported with ECMO, Clair et al.³⁸ showed that the mean rSO₂ and the duration of rSO₂ desaturation, using either rSO₂ <50% or rSO₂ decline >20% from baseline as cutoffs, were significantly different between survivors without brain injury and those who had brain injury or died, where brain injury was evaluated by brain MRI in survivors only. In our study, rSO₂ decline was associated with abnormal neuroimaging for any rSO₂ <50% in univariate analyses, and for any rSO₂ <50% and reduction >20% from baseline in multivariable analyses. Two key differences exist between the Clair et al study and this study. First, the evaluation of the outcome of abnormal neuroimaging in our study was not contingent on survival and thus on the ability to obtain a brain MRI post-ECMO. It included routine daily cranial ultrasound in all infants, whether they eventually survived or not. Second, the larger sample size in our study allowed for adjustment for potential confounders of the association between cerebral rSO₂ and abnormal neuroimaging, which was not possible in the Clair et al study (n=34). Another study of adults supported with ECMO (n=20) by Wong et al.²² suggested that patients (n=4) with persistent rSO₂ desaturation (rSO₂ <40% or rSO₂ decline >25% from baseline) refractory to hemodynamic interventions were all subsequently found to have had a cerebrovascular accident. Compared to previous studies, we utilized a significantly larger sample size (n=156), included children only, and controlled for confounding effects through statistical modeling that allows for more objective quantification of the association between rSO₂ decline and unfavorable outcomes.

This single-center pediatric population had an in-hospital mortality rate (36.5%) comparable to other large cohorts, and a similar distribution in the indications for ECMO support³. The proportion of children with abnormal neuroimaging (43.7%) was higher than that reported by ELSO³, but similar to other single center studies that also employed an all-inclusive definition for abnormal neuroimaging³⁹.

ECMO support lays on a continuum of care of children who may have suffered serial neurologic insults and periods of hypoxia or hypoperfusion pre-ECMO. In this cohort, 19% of children underwent ECPR, and a total of 43% suffered a cardiac arrest pre-ECMO (including ECPR). Hypoxic brain injury after cardiac arrest may influence the unfavorable outcome of patients undergoing venoarterial ECMO post-arrest. While we adjusted for pre-ECMO cardiac arrest status in our multivariable models, there might be residual confounding related to the duration of arrest and quality of resuscitation that need to be addressed in future prospective studies. An observation worth noting is that ECMO duration is a potential mediator of the causal pathway from inadequate cerebral blood perfusion to

adverse outcomes. We investigated the influence by comparing the effect estimates of significant rSO₂ decline in the multivariable logistic models with and without including ECMO duration. However, whether ECMO duration is independently associated with adverse events remains unsettled because the risk does not increase linearly with ECMO duration.

Another intriguing finding was that neither rSO₂ decline >20% from the value an hour prior nor the percentage of time that rSO₂ was reduced based on pre-defined criteria was significantly associated with primary or secondary outcomes on multivariable analysis. A combination of factors may have contributed to this result. Our analyses did not account for interventions via drugs or ECMO settings that could immediately affect patients' hemodynamics and cerebral blood perfusion. Such interventions could mask the potentially significant rSO₂ decline within an hour, and cumulatively decrease the amount of rSO₂ decline time during ECMO, resulting in false negatives. Second, rSO₂ was not documented continuously in the EMR system, but was recorded approximately hourly. Hence, significant cerebral oxygenation changes would not be captured in-between recordings. When recordings were less frequent than hourly, we conducted sensitivity analyses with the carry-forward method to impute missing data using the next available rSO₂ reading based on the assumption that no changes occurred in the interval. This analysis did not show any significant change in the effect estimate in the multivariable regression model.

The results of this study should be interpreted in light of its strengths and limitations. To the best of our knowledge, this work is the largest study to summarize the associations of cerebral rSO₂ and outcomes in pediatric patients on ECMO. The sample size allowed us to include patients of different age categories and ECMO indications and to increase the generalizability of the results. Our work showed that both the presence and duration of rSO₂ decline during ECMO were independently associated with neurologic morbidity and mortality after adjustment for potential confounding effects.

However, the study bears several limitations. First, the intensivists in our study were not blinded to the results of cerebral oximetry. Interventions given based on cerebral oximetry changes might not only affect the cerebral blood perfusion but also mitigate the development of neurologic morbidity or mortality. Such interventions would decrease the duration of significant rSO₂ decline and partially explain the marginally significant associations between adverse outcomes and predictors. The fact that the association between any rSO₂ decline and neurologic morbidity and mortality remained significant despite potential misclassification bias introduced by interventions suggests that the association may be even stronger than it appeared. During the study period, assessments generally triggered in our center for significant decline in rSO₂ were: examination for equipment failure (e.g., NIRS probe position, ECMO cannula position), review of hemodynamic status (e.g., mean arterial pressure), oxygen delivery and extraction (e.g., hemoglobin, SvO₂), with interventions including red blood cell transfusion, increasing ECMO flows or sweep gas inlet oxygen fraction, neuroimaging in the form of cranial ultrasound for infants or brain CT in older children, if stable for transport to CT. Second, we could not establish whether cerebral oximetry changes preceded or resulted from adverse outcomes. From a clinical perspective, either would require immediate intervention and, therefore, would not affect the clinical

implication of the findings. Third, neuroimaging performed at the discretion of clinicians might have failed to capture all neurologic injuries and might have given rise to false negative cases. Cranial ultrasounds were obtained daily and findings of territorial stroke and postasphyxial injury were confirmed on subsequent CT or MRI, if available, or labeled as such only via cranial ultrasound when subsequent CT or MRI studies were not available. Cranial ultrasounds are operator-dependent, affected by the positioning of the patients, and have low sensitivity to detect acute hemorrhagic or ischemic lesions compared to CT or MRI. NIRS cannot detect tissues with compromised oxygenation outside the pathway between near-infrared light emitter and detector or deeper than 2 cm below the scalp¹⁸. Therefore, NIRS may have limited power to detect focal lesions located further from the bifrontal area. These factors may have collectively yielded misclassification bias that resulted in the non-significant associations between rSO₂ decline and abnormal neuroimaging. Forth, as this was a retrospective study based on electronic medical record data, we were not able to investigate NIRS-derived cerebral blood flow or cerebrovascular autoregulation, which could be altered during ECMO. Lastly, as this was an observational study, unmeasured confounders might not have been accounted for.

Conclusions

Our study showed that presence of any rSO₂ 50% or any rSO₂ decline >20% from baseline is significantly associated with unfavorable outcome and mortality prior to hospital discharge in pediatric patients supported by ECMO. The results reconfirm that use of NIRS in pediatric neurocritical care can help clinicians to identify patients at risk of poor short-term neurologic outcome and death, allowing them to initiate preventative measures early. Additional work is needed to validate the real-time diagnostic utility of cerebral oximetry in large, prospectively collected data sets.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgment

The authors are thankful to Claire Levine, MS, ELS, Department of Anesthesiology and Critical Care Medicine, Johns Hopkins University School of Medicine, Baltimore, Maryland, USA, for the final editing of the text.

Sources of funding: Research reported in this publication was supported by the National Institute of Neurological Disorders and Stroke of the National Institutes of Health under Award Number K23NS076674 (MMB). The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

References

1. Makdisi G, Wang IW. Extra Corporeal Membrane Oxygenation (ECMO) review of a lifesaving technology. *J Thorac Dis* 2015;7:E166–76. [PubMed: 26380745]
2. Thiagarajan RR, Barbaro RP, Rycus PT, et al. Extracorporeal Life Support Organization Registry International Report 2016. *ASAIO J* 2017;63:60–7. [PubMed: 27984321]
3. Barbaro RP, Paden ML, Guner YS, et al. Pediatric Extracorporeal Life Support Organization Registry International Report 2016. *ASAIO J* 2017;63:456–63. [PubMed: 28557863]

4. Polito A, Barrett CS, Wypij D, et al. Neurologic complications in neonates supported with extracorporeal membrane oxygenation. An analysis of ELSO registry data. *Intensive Care Med* 2013;39:1594–601. [PubMed: 23749154]
5. Thiagarajan RR, Laussen PC, Rycus PT, Bartlett RH, Bratton SL. Extracorporeal membrane oxygenation to aid cardiopulmonary resuscitation in infants and children. *Circulation* 2007;116:1693–700. [PubMed: 17893278]
6. Barrett CS, Bratton SL, Salvin JW, Laussen PC, Rycus PT, Thiagarajan RR. Neurological injury after extracorporeal membrane oxygenation use to aid pediatric cardiopulmonary resuscitation. *Pediatr Crit Care Med* 2009;10:445–51. [PubMed: 19451851]
7. Cengiz P, Seidel K, Rycus PT, Brogan TV, Roberts JS. Central nervous system complications during pediatric extracorporeal life support: incidence and risk factors. *Crit Care Med* 2005;33:2817–24. [PubMed: 16352965]
8. Weber TR, Kountzman B. Extracorporeal membrane oxygenation for nonneonatal pulmonary and multiple-organ failure. *J Pediatr Surg* 1998;33:1605–9. [PubMed: 9856876]
9. Fenik JC, Rais-Bahrami K. Neonatal cerebral oximetry monitoring during ECMO cannulation. *J Perinatol* 2009;29:376–81. [PubMed: 19158806]
10. Liem KD, Hopman JC, Oeseburg B, de Haan AF, Festen C, Kollee LA. Cerebral oxygenation and hemodynamics during induction of extracorporeal membrane oxygenation as investigated by near infrared spectrophotometry. *Pediatrics* 1995;95:555–61. [PubMed: 7700758]
11. Van Heijst A, Liem D, Hopman J, Van Der Staak F, Sengers R. Oxygenation and hemodynamics in left and right cerebral hemispheres during induction of veno-arterial extracorporeal membrane oxygenation. *J Pediatr* 2004;144:223–8. [PubMed: 14760266]
12. Tweed A, Cote J, Lou H, Gregory G, Wade J. Impairment of cerebral blood flow autoregulation in the newborn lamb by hypoxia. *Pediatr Res* 1986;20:516–9. [PubMed: 3714361]
13. Short BL, Walker LK, Traystman RJ. Impaired cerebral autoregulation in the newborn lamb during recovery from severe, prolonged hypoxia, combined with carotid artery and jugular vein ligation. *Crit Care Med* 1994;22:1262–8. [PubMed: 8045146]
14. Short BL, Walker LK, Bender KS, Traystman RJ. Impairment of cerebral autoregulation during extracorporeal membrane oxygenation in newborn lambs. *Pediatr Res* 1993;33:289–94. [PubMed: 8460067]
15. Salen P, Melniker L, Chooljian C, et al. Does the presence or absence of sonographically identified cardiac activity predict resuscitation outcomes of cardiac arrest patients? *American Journal of Emergency Medicine* 2005;23:459–62.
16. Paden ML, Conrad SA, Rycus PT, Thiagarajan RR, Registry E. Extracorporeal Life Support Organization Registry Report 2012. *ASAIO J* 2013;59:202–10. [PubMed: 23644605]
17. Maldonado Y, Singh S, Taylor MA. Cerebral near-infrared spectroscopy in perioperative management of left ventricular assist device and extracorporeal membrane oxygenation patients. *Curr Opin Anaesthesiol* 2014;27:81–8. [PubMed: 24366053]
18. Yu Y, Lu Y, Meng L, Han R. Monitoring cerebral ischemia using cerebral oximetry: pros and cons. *J Biomed Res* 2015;30.
19. Goldman S, Sutter F, Ferdinand F, Trace C. Optimizing intraoperative cerebral oxygen delivery using noninvasive cerebral oximetry decreases the incidence of stroke for cardiac surgical patients. *Heart Surg Forum* 2004;7:E376–81. [PubMed: 15799908]
20. Murkin JM, Adams SJ, Novick RJ, et al. Monitoring brain oxygen saturation during coronary bypass surgery: a randomized, prospective study. *Anesth Analg* 2007;104:51–8. [PubMed: 17179242]
21. Sood ED, Benzaquen JS, Davies RR, Woodford E, Pizarro C. Predictive value of perioperative near-infrared spectroscopy for neurodevelopmental outcomes after cardiac surgery in infancy. *J Thorac Cardiovasc Surg* 2013;145:438–45 e1; discussion 44–5. [PubMed: 23219333]
22. Wong JK, Smith TN, Pitcher HT, Hirose H, Cavarocchi NC. Cerebral and lower limb near-infrared spectroscopy in adults on extracorporeal membrane oxygenation. *Artif Organs* 2012;36:659–67. [PubMed: 22817780]
23. Kurth CD, Steven JM, Nicolson SC. Cerebral oxygenation during pediatric cardiac surgery using deep hypothermic circulatory arrest. *Anesthesiology* 1995;82:74–82. [PubMed: 7832338]

24. Zheng F, Sheinberg R, Yee MS, Ono M, Zheng Y, Hogue CW. Cerebral near-infrared spectroscopy monitoring and neurologic outcomes in adult cardiac surgery patients: a systematic review. *Anesth Analg* 2013;116:663–76. [PubMed: 23267000]
25. Fiser DH. Assessing the outcome of pediatric intensive care. *J Pediatr* 1992;121:68–74. [PubMed: 1625096]
26. Fiser DH, Long N, Roberson PK, Hefley G, Zolten K, Brodie-Fowler M. Relationship of pediatric overall performance category and pediatric cerebral performance category scores at pediatric intensive care unit discharge with outcome measures collected at hospital discharge and 1- and 6-month follow-up assessments. *Crit Care Med* 2000;28:2616–20. [PubMed: 10921604]
27. Cashen K, Reeder R, Dalton HJ, et al. Functional Status of Neonatal and Pediatric Patients After Extracorporeal Membrane Oxygenation. *Pediatr Crit Care Med* 2017;18:561–70. [PubMed: 28419061]
28. Lin JJ, Banwell BL, Berg RA, et al. Electrographic Seizures in Children and Neonates Undergoing Extracorporeal Membrane Oxygenation. *Pediatr Crit Care Med* 2017;18:249–57. [PubMed: 28099234]
29. Cohn SM, Nathens AB, Moore FA, et al. Tissue oxygen saturation predicts the development of organ dysfunction during traumatic shock resuscitation. *J Trauma* 2007;62:44–54; discussion –5. [PubMed: 17215732]
30. Lima A, van Bommel J, Jansen TC, Ince C, Bakker J. Low tissue oxygen saturation at the end of early goal-directed therapy is associated with worse outcome in critically ill patients. *Critical care* 2009;13 Suppl 5:S13.
31. Storm C, Leithner C, Krannich A, et al. Regional cerebral oxygen saturation after cardiac arrest in 60 patients—a prospective outcome study. *Resuscitation* 2014;85:1037–41. [PubMed: 24795284]
32. Tsuji M, Saul JP, du Plessis A, et al. Cerebral intravascular oxygenation correlates with mean arterial pressure in critically ill premature infants. *Pediatrics* 2000;106:625–32. [PubMed: 11015501]
33. Muehlschlegel S, Selb J, Patel M, et al. Feasibility of NIRS in the neurointensive care unit: a pilot study in stroke using physiological oscillations. *Neurocrit Care* 2009;11:288–95. [PubMed: 19649749]
34. Liem KD, Hopman JC, Kollee LA, Oeseburg B. Assessment of cerebral oxygenation and hemodynamics by near infrared spectrophotometry during induction of ECMO: preliminary results. The ECMO Research Group. *Adv Exp Med Biol* 1992;317:841–6. [PubMed: 1288211]
35. Ejike JC, Schenkman KA, Seidel K, Ramamoorthy C, Roberts JS. Cerebral oxygenation in neonatal and pediatric patients during veno-arterial extracorporeal life support. *Pediatr Crit Care Med* 2006;7:154–8. [PubMed: 16446597]
36. Papademetriou MD, Tachtsidis I, Elliot MJ, Hoskote A, Elwell CE. Multichannel near infrared spectroscopy indicates regional variations in cerebral autoregulation in infants supported on extracorporeal membrane oxygenation. *J Biomed Opt* 2012;17:067008.
37. Papademetriou MD, Tachtsidis I, Leung TS, Elliott MJ, Hoskote A, Elwell CE. Cerebral and peripheral tissue oxygenation in children supported on ECMO for cardio-respiratory failure. *Adv Exp Med Biol* 2010;662:447–53. [PubMed: 20204828]
38. Clair MP, Rambaud J, Flahault A, et al. Prognostic value of cerebral tissue oxygen saturation during neonatal extracorporeal membrane oxygenation. *PLoS One* 2017;12:e0172991.
39. Mateen FJ, Muralidharan R, Shinohara RT, Parisi JE, Scheers GJ, Wijdicks EF. Neurological injury in adults treated with extracorporeal membrane oxygenation. *Arch Neurol* 2011;68:1543–9. [PubMed: 21825216]
40. Hervey-Jumper SL, Annich GM, Yancon AR, Garton HJ, Muraszko KM, Maher CO. Neurological complications of extracorporeal membrane oxygenation in children. *J Neurosurg Pediatr* 2011;7:338–44. [PubMed: 21456903]

Figure 1.
Flow diagram for patient inclusion. ECMO, extracorporeal membrane oxygenation; rSO₂, cerebral regional oxygen saturation.

Table 1.

Patient characteristics overall and by primary outcome at hospital discharge^a

Variable	All ECMO ^b (n=156)	Favorable outcome ^c (n=82)	Unfavorable outcome (n=74)	p-value
Age group, n (%)				
Neonate, <1m	84 (53.9)	58 (70.7)	26 (35.1)	
Infant, 1m-<1y	29 (18.6)	7 (8.5)	22 (29.7)	<0.001
Child, 1y-12y	27 (17.3)	11 (13.4)	16 (21.6)	
Adolescent, >12y	16 (10.3)	6 (7.3)	10 (13.5)	
Male, n (%)	81 (51.9)	49 (59.8)	32 (43.2)	0.04
Weight (kg), median (IQR)	4.1 (3.3, 12.2)	3.9 (3.3, 5.0)	5.4 (3.3, 15.0)	0.09
Race, n (%)				
Caucasian	70 (44.9)	37 (45.1)	33 (44.6)	
African-American	58 (37.2)	30 (36.6)	28 (37.8)	0.99
Other/Unknown	28 (17.9)	15 (18.3)	13 (17.6)	
PRISM III score, median (IQR)	25 (20, 32)	26 (21, 32)	24 (18, 33)	0.58
Gestational age (weeks), n=84 (neonates), n (%)	39 (38, 39)	39 (38, 40)	39 (37, 39)	0.04
Apgar score at 1 minute, median (IQR)	6 (2, 8)	6 (2, 8)	7 (2, 8)	0.37
Apgar score at 5 minutes, median (IQR)	8 (6, 9)	8 (6, 9)	8 (6, 9)	0.94
Chromosomal defect, n (%)	15 (9.6)	5 (6.1)	10 (13.5)	0.12
Preexisting neurologic disease, n (%)	20 (12.8)	7 (8.5)	13 (17.6)	0.09
Pre-ECMO inotrope use, n (%)	131 (84.0)	72 (87.8)	59 (79.7)	0.17
Pre-ECMO cardiac arrest, n (%)	68 (43.6)	26 (31.7)	42 (56.8)	0.002
Primary indication for ECMO, n (%)				
Respiratory failure	65 (41.7)	46 (56.1)	19 (25.7)	
Cardiac failure	51 (32.7)	26 (31.7)	25 (33.8)	<0.001
ECPR	30 (19.2)	5 (6.1)	25 (33.8)	
Sepsis	10 (6.4)	5 (6.1)	5 (6.8)	

^aCategorical variables are presented as counts (frequencies) and continuous variables as median (interquartile range).^bThere were 156 ECMO runs in 153 patients; for patients with two ECMO runs, they took place in separate hospitalizations.^cFavorable outcome defined as Pediatric Cerebral Performance Category at discharge 2 or no decline from baseline

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

ECMO, extracorporeal membrane oxygenation; IQR, interquartile range; m, month; y, year; PRISM III, Pediatric Risk of Mortality III, ECPR, extracorporeal cardiopulmonary resuscitation

Table 2.

Extracorporeal membrane oxygenation course characteristics overall and by outcome at hospital discharge^a

Variable	All ECMO ^b (n=156)	Favorable outcome ^c (n=82)	Unfavorable outcome (n=74)	p-value
ECMO mode, n (%)				0.32
Venoarterial	137 (87.8)	70 (85.4)	67 (90.5)	
Venovenous	19 (12.2)	12 (14.6)	7 (9.5)	
Venovenous to venoarterial, n=19	4 (21.1)	2 (16.7)	2 (28.6)	0.54
Duration of ECMO support (days), median (IQR)	5.2 (3.3, 11.1)	4.7 (3.3, 7.1)	6.3 (3.4, 18.0)	0.04
Pump flow (ml/kg/min), median (IQR)	83 (64, 103)	79 (64, 96)	90 (65, 108)	0.06
Clinical seizures during ECMO, n (%)	13 (8.3)	2 (2.4)	11 (14.9)	0.005
Neuroimaging during or within 6 weeks post-ECMO, n=135, n (%)	135 (86.5)	71 (86.6)	64 (86.5)	0.99
Daily cranial ultrasound only	46 (34.1)	27 (38.0)	19 (29.7)	0.31
Cranial ultrasound and brain CT or MRI	71 (52.6)	38 (53.5)	33 (51.6)	0.82
Brain CT or MRI only	18 (13.3)	6 (8.5)	12 (18.8)	0.08
Abnormal neuroimaging findings ^d , n=135, n (%)	59 (43.7)	20 (28.2)	39 (60.9)	<0.001
Cerebral infarction/ischemic injury	34 (25.2)	7 (9.9)	27 (42.2)	<0.001
Intracranial hemorrhage	45 (33.3)	18 (25.4)	27 (42.2)	0.04
Cerebral oximetry monitoring during ECMO, median (IQR)				
Percent ECMO time with rSO ₂ monitoring	99.2 (97.5, 100)	98.9 (95.5, 100)	99.4 (97.8, 99.9)	0.39
Median rSO ₂ (%) regardless of side	72 (64, 80)	75 (68, 82)	69 (59, 76)	<0.001
Median right rSO ₂ (%)	71 (62, 79)	75 (66, 82)	69 (57, 75)	<0.001
Median left rSO ₂ (%)	73 (64, 81)	76 (69, 83)	70 (58, 76)	<0.001
Any rSO ₂ 40%	61 (39.1)	20 (24.4)	41 (55.4)	<0.001
Percent ECMO time spent at rSO ₂ 40%, median (range)	0.0 (0.0, 63.3)	0.0 (0.0, 18.0)	0.0 (0.0, 63.3)	<0.001
Any rSO ₂ 50%	92 (59.0)	34 (41.5)	58 (78.4)	<0.001
Percent ECMO time spent at rSO ₂ 50%, median (range)	2.4 (0.0, 67.5)	0.0 (0.0, 61.9)	1.4 (0.0, 67.5)	<0.001
Any decline >20% from baseline	60 (38.5)	22 (26.8)	38 (51.4)	0.002
Percent ECMO time spent at rSO ₂ >20% below baseline, median (range)	0.0 (0.0, 61.6)	0.0 (0.0, 28.6)	0.0 (0.0, 61.6)	0.008
Any rSO ₂ decline >20% from 1h prior	26 (16.7)	9 (11.0)	17 (23.0)	0.04
Percent time rSO ₂ drop >20% from 1h prior during ECMO, median (range)	0.0 (0.0, 5.0)	0.0 (0.0, 3.8)	0.0 (0.0, 5.0)	0.11

ECMO, extracorporeal membrane oxygenation; EEG, electroencephalography; CT, computed tomography; MRI, magnetic resonance imaging; rSO₂, regional cerebral oxygen saturation

^aCategorical variables are presented as counts (frequencies) and continuous variables as median (interquartile range), unless otherwise specified.

^bThere were 156 ECMO runs in 153 patients; for patients with two ECMO runs, they took place in separate hospitalizations.

^cFavorable outcome defined as Pediatric Cerebral Performance Category at discharge 2 or no decline from baseline

^dAbnormal neuroimaging included arterial ischemic stroke (n=22), venous sinus thrombosis (n=1), global postasphyxial injury (n=10), watershed infarctions (n=4), deep gray matter injury (n=4), leukomalacia (n=1), intracranial hemorrhage (intraparenchymal hemorrhage [n=17], subdural hemorrhage [n=20], subarachnoid hemorrhage [n=3], intraventricular hemorrhage [n=18], punctate white matter hemorrhage [n=7], diffuse intraparenchymal microhemorrhages [n=3]). The aforementioned n represent the number of imaging studies with abnormal findings, as one patient could have 1 type of injury.

Table 3.The association between reduction in rSO₂ and unfavorable outcome of ECMO patients

	Unfavorable outcome ^b
Any rSO ₂ < 40%, n (%)	41/61 (67.2)
All rSO ₂ >40%, n (%)	33/95 (34.7)
Unadjusted OR (95% CI)	3.85 (1.95 – 7.61)^c
Adjusted OR (95% CI)	2.32 (0.90 – 5.99)
Any rSO ₂ < 50%, n (%)	58/92 (63.0)
All rSO ₂ >50%, n (%)	16/64 (25.0)
Unadjusted OR (95% CI)	5.12 (2.52 – 10.37)^c
Adjusted OR (95% CI)	2.82 (1.10 – 7.25)^c
rSO ₂ decline >20% from 1h prior, n (%)	17/26 (65.4)
No rSO ₂ decline >20% from 1h prior, n (%)	57/130 (43.8)
Unadjusted OR (95% CI)	2.42 (1.00 – 5.83)
Adjusted OR (95% CI)	3.13 (0.98 – 10.05)
rSO ₂ decline >20% from baseline rSO ₂ , n (%)	38/60 (63.3)
No rSO ₂ decline >20% from baseline rSO ₂ , n (%)	36/96 (37.5)
Unadjusted OR (95% CI)	2.88 (1.48 – 5.62)^c
Adjusted OR (95% CI)	4.52 (1.76 – 11.58)^c

^aVariables adjusted in multivariable logistic regression: age category, gender, ECMO indication, pre-ECMO cardiac arrest, ECMO duration, clinical seizures during ECMO, ECMO pump flow.

^bData from 156 patients.

^cp<0.05

OR, odds ratio; CI, confidence interval; rSO₂, regional cerebral oxygen saturation; ECMO, extracorporeal membrane oxygenation