

REVIEW ARTICLE

Neuromonitoring During ECMO Support in Children



Ryan J. Felling^{1*} , Asavari Kamerkar², Matthew L. Friedman³, Ahmed S. Said⁴, Kerri L. LaRovere⁵, Michael J. Bell⁶ and Melania M. Bembea⁷

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Abstract

Extracorporeal membrane oxygenation is a potentially lifesaving intervention for children with severe cardiac or respiratory failure. It is used with increasing frequency and in increasingly more complex and severe diseases. Neurological injuries are important causes of morbidity and mortality in children treated with extracorporeal membrane oxygenation and include ischemic stroke, intracranial hemorrhage, hypoxic-ischemic injury, and seizures. In this review, we discuss the epidemiology and pathophysiology of neurological injury in patients supported with extracorporeal membrane oxygenation, and we review the current state of knowledge for available modalities of monitoring neurological function in these children. These include structural imaging with computed tomography and ultrasound, cerebral blood flow monitoring with near-infrared spectroscopy and transcranial Doppler ultrasound, and physiological monitoring with electroencephalography and plasma biomarkers. We highlight areas of need and emerging advances that will improve our understanding of neurological injury related to extracorporeal membrane oxygenation and help to reduce the burden of neurological sequelae in these children.

Keywords: Extracorporeal membrane oxygenation, Seizures, Stroke, Intracranial hemorrhage, Electroencephalography, Neuroimaging, Transcranial doppler, Biomarkers

Introduction

Extracorporeal membrane oxygenation (ECMO) is a form of extracorporeal life support that is used to treat patients with severe cardiac or pulmonary failure refractory to conventional interventions. The first child treated with ECMO was a neonate with respiratory failure reported by Dr. Bartlett and colleagues in 1976 [1]. The use of ECMO technology has increased tremendously since then. The Extracorporeal Life Support Organization registry currently contains more than 172,000 ECMO runs in its history, of which approximately 50% are in children [2]. Indications for ECMO include respiratory diseases such as pediatric acute respiratory distress syndrome [3, 4], severe cardiovascular dysfunction with

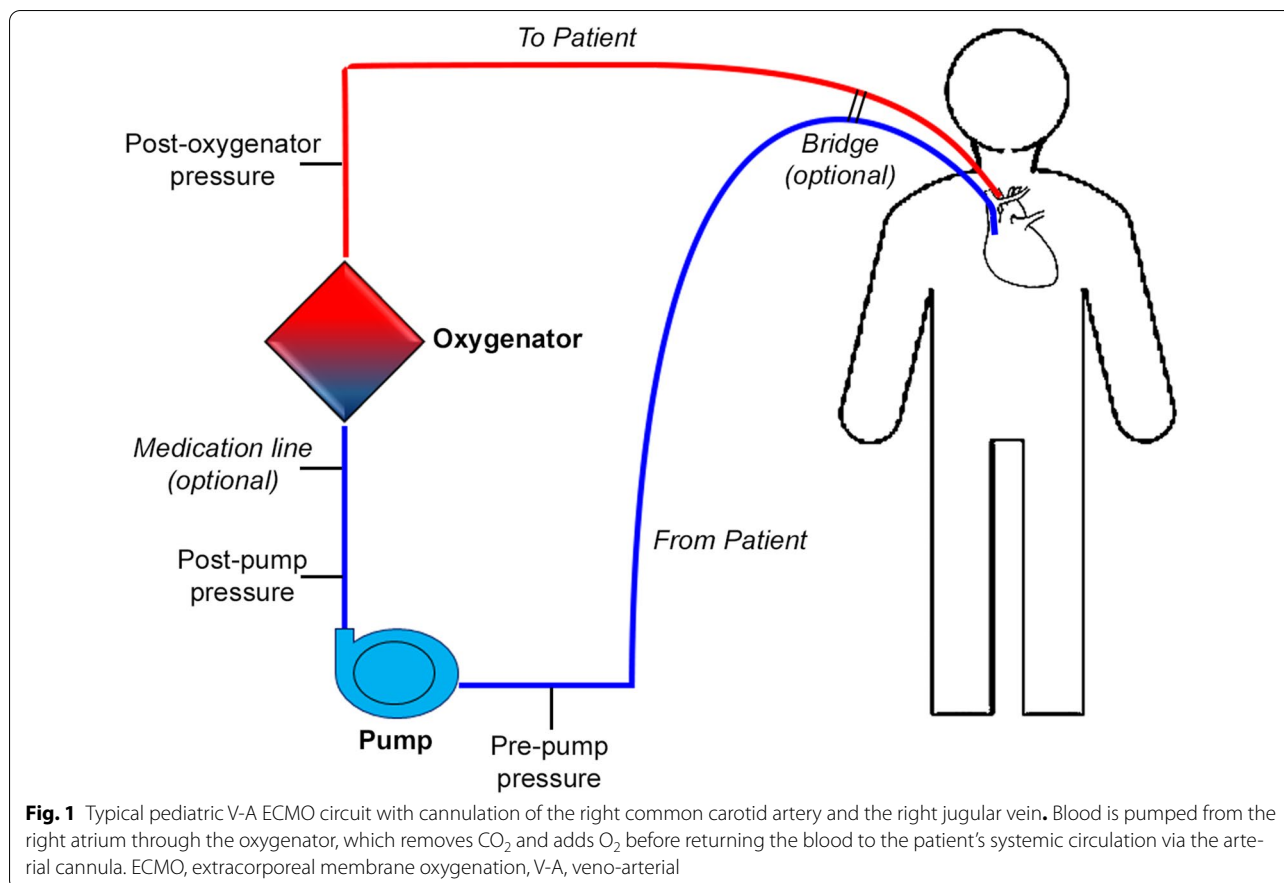
inadequate oxygen delivery in children with congenital heart disease or acquired heart disease [5], or a rapid deployment measure to provide circulatory support in the setting of extracorporeal cardiopulmonary resuscitation (ECPR) [6].

ECMO uses either a roller or centrifugal pump to circulate blood back to the patient after it has passively been removed by indwelling catheters with an intervening oxygenator that uses a hollow fiber membrane for gas exchange (Fig. 1). The circuit accesses blood from the patient via a large venous cannula. Blood is pumped through an oxygenator, which supplies O₂ and removes CO₂, and the newly oxygenated blood is returned to the patient in either a vein or artery depending on the mode of ECMO. Although ECMO can provide lifesaving cardiopulmonary support for days to months, it is associated with significant risk of neurological injury. Children supported with ECMO are at risk for seizures, intracranial

*Correspondence: rfelling@jhmi.edu

¹ Department of Neurology, Johns Hopkins University School of Medicine, 200 N. Wolfe Street, Suite 2158, Baltimore, MD, USA

Full list of author information is available at the end of the article



hemorrhage (ICH), and ischemic stroke. These complications are associated with increased mortality as well as long-term morbidity in survivors [7–9]. The most foundational principle when deciding on ECMO eligibility is identifying children with potentially reversible diseases who would otherwise have a high probability of mortality or severe morbidity without ECMO support. Many different factors play into the decision of who is most likely to benefit from ECMO. Predictive models have emerged with reasonable test characteristics for respiratory as well as cardiac ECMO support [10–12].

Modes of ECMO

Extracorporeal membrane oxygenation can be deployed in many configurations and modes based on location of the drainage and reinfusion cannulas. The two most common modes are veno-venous (V-V) and veno-arterial (V-A). V-V ECMO is used primarily for respiratory support and can be accomplished by using a dual lumen cannula or via two single lumen cannulas in different veins. V-A ECMO is used primarily for cardiac support and typically entails the use of two cannulas, one venous drainage cannula and one arterial return cannula.

If cervical (neck) cannulation is used for either V-V or V-A ECMO the internal jugular vein is used, most often on the right side. This may cause some degree of obstruction to venous drainage from the brain and lead to increased intracranial pressure and lower cerebral perfusion pressure [13]. Some centers use a cephalad drain in smaller patients to decompress cerebral venous drainage; however, analysis of this practice has not shown benefit [14].

Of note, the rate of neurological complications is higher in children supported with V-A compared with V-V ECMO [15]. Air or thrombotic emboli from the circuit can obstruct cerebral vessels leading to ischemic stroke. If the arterial cannula is located in the carotid artery, cerebral perfusion will rely on the contralateral carotid artery and the presence of an intact circle of Willis to provide perfusion to the cerebral hemisphere on the side ipsilateral to the arterial cannulation site [16, 17]. It has been shown that carotid artery cannulation is associated with higher rates of neurological complications compared with femoral artery cannulation [18]. At the end of a V-A ECMO course with carotid artery cannulation, the carotid artery may be ligated or repaired. Repair

allows for bilateral carotid flow and recannulation of the same artery should repeat ECMO be needed in the future [19, 20].

Pathophysiology of neurological injury on ECMO

Cerebral Perfusion

The pathophysiology of neurological injury in patients on ECMO is complex and multifactorial. The brain is exquisitely sensitive to perturbations in cerebral blood flow. ECMO disrupts cerebral blood flow in multiple ways. Ligation of the right common carotid artery and right internal jugular vein diminishes anterograde flow through the right carotid artery while increasing flow through the left carotid artery [21]. This also affects venous outflow. Under these circumstances, perfusion of the right hemisphere relies on an intact circle of Willis, but anatomic variations exist that may not support robust collateral flow. Nonpulsatile flow as seen in V-A ECMO has been associated with altered cerebrovascular reactivity and microcirculatory perfusion deficits in both animal models and humans [22–24]. Under physiological conditions, autoregulation of the cerebral arterioles ensures adequate cerebral blood flow over a range of systemic perfusion pressures, but ECMO may impair cerebral autoregulation, rendering the brain vulnerable to ischemic and hemorrhagic injury [25].

In infants undergoing ECMO, transcranial Doppler (TCD) provided some of the earliest observations of altered cerebral hemodynamics. These early studies found that the mean pulsatility index (PI) decreased with ECMO initiation and over time at high ECMO flows but actually increased at low ECMO flow [26, 27]. The investigators postulated that this increase in PI correlated with increased cerebral blood flow (CBF) that could lead to ICH. In contrary though, other studies have demonstrated significantly lower CBF velocities (CBFVs) in children on ECMO compared with healthy or other critically ill children, as well as age-related variability [28, 29]. These findings may in part be related to reduced cerebral metabolic demand secondary to sedation frequently used in pediatric patients on ECMO.

Inflammation

In addition to directly altering CBF, ECMO is associated with a profound inflammatory response. The extensive exposure of a patient's blood to foreign surfaces of the circuit induces a cascade akin to systemic inflammatory response syndrome, compounding the inflammatory response to critical illness that is already present preceding cannulation [30]. On ECMO initiation, interaction between blood and the surfaces of the ECMO circuit activates the complement system, with early elevations of activated C3 and tumor necrosis factor- α [31, 32].

Activated C3 is one of the effector molecules of the complement cascade, collectively termed "anaphylotoxins," that result in vasodilation, recruitment of immune cells, and triggering of other proinflammatory responses [33]. Elevations in many cytokines, including tumor necrosis factor- α , interleukin-6, and interleukin-8, have been demonstrated in children on ECMO [34–37]. In addition to these inflammatory mediators, ECMO also results in activation of the contact pathway through activation of factor XII, thus bridging inflammatory and coagulation cascades [38].

Thrombophilia

Nonhemorrhagic brain injury in patients on ECMO is associated with a particularly poor prognosis and warrants special attention [39]. ECMO induces a procoagulant state due to extensive exposure of the blood to artificial materials. Platelet activation, tissue factor release, and activation of the contact system shift the homeostatic balance toward clotting and an increased risk of thrombosis [40–43]. Thrombosis in the circuit can lead to oxygenator dysfunction, circuit failure, and circuit-induced disseminated intravascular coagulopathy (DIC). Circuit DIC often leads to patient DIC and bleeding complications. Thrombosis in the circuit distal to the oxygenator is particularly worrisome because clots can embolize into the patient's arterial circulation if on V-A ECMO. There is a need for anticoagulation in ECMO because of the prothrombotic nature of the circuit. The optimal strategy for anticoagulation on ECMO is still unknown; the best drug, dose, method of monitoring, and thresholds for transfusions of blood products are not clear [41, 44]. Unfractionated heparin infusion with activated clotting time and, more recently, antifactor Xa monitoring has become standard practice. Bivalirudin infusion with activated partial thromboplastin time monitoring has emerged as an alternative to unfractionated heparin.

Epidemiology of Acute Brain Injury on ECMO

Children on ECMO are at risk for neurological injury due to pre-ECMO events (e.g., hypoxia, hypotension, acidosis, cardiac arrest), comorbidities, and factors associated with ECMO itself. The incidence of neurological injury is reported as high as 25% [45–49]. The most commonly reported neurological complications of ECMO are seizures, intracranial hemorrhage (ICH), and ischemic stroke (Table 1).

Seizures

It is common for children to develop seizures while on ECMO, with reported rates varying widely from about 6% up to 23% [2, 8, 46, 48–53]. Some of the variability

Table 1 Adverse neurological events associated with ECMO

Parameter	Incidence	Contributing factors	Monitoring strategies ^a	References
Seizure	11–23%	Preexisting conditions, ischemic or hemorrhagic injury, metabolic disturbances	Clinical examination, EEG, plasma biomarkers	[2, 8, 42, 44–50]
Intracranial hemorrhage	4–16%	Blood pressure, anticoagulation, ischemic injury	Clinical examination, neuroimaging, EEG, TCD, cerebral oximetry, plasma biomarkers	[5, 9, 51–54]
Ischemic injury (including arterial ischemic stroke and global hypoxic-ischemic injury)	2–17%	Preexisting conditions, blood pressure, inflammation, hypercoagulability	Clinical examination, neuroimaging, EEG, TCD, cerebral oximetry, plasma biomarkers	[9, 45, 55–58]

ECMO, extracorporeal membrane oxygenation, EEG, electroencephalography, TCD, transcranial Doppler

^a Neuromonitoring modalities that have potential for identifying these adverse events or raising suspicion for them. They do not necessarily have established clinical roles at present

in seizure incidence may be due to differing monitoring standards at different institutions. Lower rates of seizures of 7% to 8.4%, depending on indication and age group, are reported in the Extracorporeal Life Support Organization registry [2]. Conversely, in single center studies conducted at institutions with extensive video electroencephalography (EEG) monitoring programs, the rate of electrographic and electroclinical seizures was higher, 11% to 23% [8, 50–52]. Subclinical seizures in these studies were common, occurring in up to 83% of patients with seizures, suggesting that subclinical seizures are likely underdiagnosed clinically and highlighting the need for neuromonitoring during ECMO [51].

Most seizures started within the first 48 h of ECMO with the first seizure rarely occurring after 72 h on ECMO [8, 51, 52]. Across multiple studies about half of the patients who developed seizures had status epilepticus. Risk factors for the development of seizures in children on ECMO include cardiac indications, ECPR, pre-ECMO cardiac arrest, hypoplastic left heart syndrome, ischemic stroke, and lactic acidosis [8, 9, 51, 54].

The causes of seizures in children on ECMO are multiple. It is common for seizure onset to be the first sign that a structural injury such as ICH or ischemic stroke has occurred. Seizures are also commonly associated with poorer outcomes in children on ECMO, although these studies typically did not adjust for the concomitant presence of structural brain injury [8, 51, 54].

Intracranial Hemorrhage

Anticoagulation is necessary for patients treated with ECMO, and ICH is one of the most feared complications, with a reported incidence of 4–16% [5, 55]. The occurrence of ICH in children on ECMO presents difficult decisions regarding interrupting anticoagulation or adjusting anticoagulation goals, prognosis, and whether to continue ECMO support. There is no standard practice for neuroimaging, leading to variability in detection

of ICH [56]. When detected acutely, ICH is often symptomatic and catastrophic, with survival as low as 20% [9, 57]. This low survival, however, may be in part due to a self-fulfilling prophecy, as the historical teaching was that large ICHs would require discontinuation of ECMO support and redirection of care if the child was not able to survive off ECMO. On the other hand, intracranial microbleeds have been shown to be very common in ECMO survivors when assessed by magnetic resonance imaging (MRI) and have unclear clinical significance [58]. Further prospective studies to detect subclinical ICH in children treated with ECMO would provide better prognostic information to inform clinical decisions.

Ischemic Injury

Ischemic injury on ECMO has multiple causes, but two general patterns are seen: global hypoxic-ischemic injury from a low perfusion state, and focal arterial ischemic stroke due to thromboembolic mechanisms (e.g., in situ thrombus formation with artery-to-artery embolus, emboli from the ECMO circuit). Children on ECMO who suffer an ischemic injury have higher mortality, with about 25% lower survival rate compared with those who do not suffer an ischemic stroke [9].

Ischemic injury has been documented in 2% to 17% of children supported on ECMO [9, 49, 59]. The true rate may very well be higher given the lack of standardized protocols for neuroimaging in patients on ECMO and a lower sensitivity for detecting ischemic injury with computed tomography (CT) and ultrasound modalities compared with MRI [9]. Prospective studies using standardized, universal imaging would be helpful for understanding the true incidence but are challenging, given the inherent risks of transporting critically ill patients and the lack of widely available portable technologies.

In a 10-year retrospective study of 81 neonates who underwent routine brain MRI following ECMO, 6% had infarctions primarily in arterial vascular territories,

with no difference in infarction rate between V-A and V-V ECMO recipients [60]. In an 8-year retrospective review of 878 adult patients on V-A ECMO, ECMO-related neurological injury was diagnosed in nearly 8% of patients, with 5% suffering ischemic strokes [61]. In a large retrospective cohort of 677 neonates, ischemic stroke occurred in 5%, including 30 patients with arterial ischemic stroke and 4 patients with venous sinus thrombosis [62]. In another institutional study of 179 patients on ECMO, 82 underwent at least one CT scan and 49 exhibited brain injury with 27 of these being ischemic [9]. Of these patients, 41% had bilateral infarctions whereas 15% had isolated right side and 15% had isolated left side infarctions [9]. Distribution of ischemic injury in patients on ECMO has been variable in reported case series, and hypothesized factors influencing this include the site of cannulation and the presence of a complete circle of Willis, which may influence venous pressure and cerebral perfusion.

Outcomes

Children with severe respiratory or cardiac failure supported with ECMO have a substantially higher risk of mortality than the general intensive care unit population. Survival to hospital discharge varies by age and indication; it is lowest for neonatal and pediatric ECPR (42%) and highest for neonatal respiratory ECMO (73%) [2].

Children supported on ECMO who survive to hospital discharge frequently suffer from long-term deficits due to neurological injuries acquired during hospitalization for ECMO [63]. Cognitive deficits, behavioral problems, motor impairments, and lower health-related quality of life have been described in 10% to as many as 60% of survivors of critical illness requiring ECMO support [63]. Improving neurological monitoring of children supported on ECMO could lead to identification of at-risk physiological states and earlier detection of neurological injury. The next step would be to then identify interventions directed toward modifying those states to reduce morbidity and improve neurological outcome.

Neuromonitoring in Patients on ECMO Neurological Examination

Although the neurological examination is the gold standard of determining neurological function, a reliable examination is often not available in patients treated with ECMO. Sedation and paralysis may be required to protect the patient and catheter safety while on the ECMO circuit, particularly in children. Even if awake, reversible alterations in mental status including encephalopathy and delirium due to metabolic

derangements and intensive care unit environment frequently confound the clinical assessment of the patient. Highlighting the importance of the neurological examination, some centers advocate for sedation holidays or “neurologic wake up tests.” While providing the ability to directly assess the patient’s neurological function, there are potential concerns with this practice, including increasing patient distress and pain as well as increasing intracranial pressure and cerebral perfusion pressure, although evidence suggests that this does not necessarily translate to alterations of energy metabolism and oxygenation in patients with brain injury [64–66]. Neurologic wake up tests can only be performed intermittently, and there certainly may be times when a patient’s condition precludes weaning of sedation to any significant degree. For this reason, clinicians often rely on ancillary assessments of neurological function through a variety of modalities [67].

Quantitative Pupillometry

Although the neurological examination is often limited in patients during ECMO treatment, the pupillary reflex remains accessible, and automated pupillometry is being more widely used and studied in neurocritical care patients. Quantitative pupillometry reliably and sensitively assesses both static and dynamic aspects of the pupillary reflex, with normative data established in pediatric patients [68, 69]. A study of 28 pediatric patients with acute brain injury or encephalopathy included 1,171 measurements of intracranial pressure (ICP) and found that the Neurological Pupil index (NPi), a proprietary algorithm combining measures of pupil reactivity, percent change in pupil size, constriction velocity, and dilation velocity were all lower when intracranial pressure was elevated (greater than or equal to 20 mm Hg) [70]. Although pupil reactivity had an inverse correlation with concurrent ICP measurements, the NPi was not consistently predictive of patients who, with normal ICP at enrollment, would go on to develop increased ICP [70]. When evaluated within the first 72 h, the abnormal NPi (less than 3) has also been associated with poor neurological outcome in adult patients with severe brain injury [71]. In a study of 100 consecutive adult patients treated with VA-ECMO, an NPi less than 3 at any time from 24 to 72 h from ECMO initiation was 100% specific for 90 day mortality [72]. Other emerging uses for quantitative pupillometry include assessment of pain in sedated children [73], but further research is still necessary to understand all the factors that influence pupil reactivity in these patient populations who frequently have numerous potential

confounders such as pharmacologic treatments and metabolic conditions [74].

Structural Imaging

Ultrasound

Cranial ultrasound is currently the most common portable, noninvasive imaging technique for children supported on ECMO and as such has become part of the routine neuromonitoring techniques in clinical practice. The current Extracorporeal Life Support Organization neuromonitoring guidelines recommend cranial ultrasound on a regular cadence; daily for the first 3–5 days followed by variable intervals based on clinical concerns such as new onset seizures or sudden decline in hemoglobin [75, 76]. Despite their appeal, cranial ultrasounds have several limitations including age limitation given the need for an open anterior fontanelle in addition to field of view limitations and variability in diagnostic criteria [77]. Secondly, to date, cranial ultrasound abnormalities have shown limited associations with long-term neurodevelopmental outcomes in survivors and are typically predictive only with severe lesions [78, 79]. Evaluation of 50 post-ECMO neonatal brain MRI studies showed inconsistency between MRI and ultrasound findings, with half of the patients with normal ultrasound findings noted to have MRI abnormalities [15]. As such, cranial ultrasounds continue to be utilized as primarily neuroimaging screening modalities with the need for confirmatory testing with CT or post-ECMO MRI.

Abnormalities detected on cranial ultrasound can be categorized as vessel occlusion abnormalities including arterial ischemic strokes or sinus venous thrombosis, primary hemorrhage including parenchymal, extracerebral and choroid plexus, and other abnormalities including focal dysplasia, hydrocephalus, evolving hematoma, periventricular leukomalacia, cortical laminar necrosis, lenticulostriate vasculopathy, and diffuse hypoxic-ischemic encephalopathy [62, 77]. Spectral Doppler flow assessments also allow evaluation of the resistance in intracranial vessels, resistive index, including the internal carotid and basilar arteries, the circle of Willis as well as the superior sagittal sinus, vein of Galen, and straight sinus. There is preliminary evidence that a greater than 10% variability in the resistive index with gentle compression of the anterior fontanelle is associated with neurological complications on ECMO [80].

CT

Head CT continues to be the imaging modality of choice on ECMO for older children in whom cranial ultrasound cannot be obtained. CT provides a full detailed view of the brain with the ability to identify ICH with high sensitivity and minimal interoperator variability (Fig. 2a).

CT however is less sensitive at identifying early ischemic injury (Fig. 2b) [9]. There is evidence for higher detection of these abnormalities with more CT use, with associated concern for underreporting of intracranial complications occurring during the ECMO course [81]. Detection of these abnormalities, depending on their severity, has the potential to significantly impact patient care with alterations in anticoagulation management or even efforts to discontinue extracorporeal support [82].

In the absence of portable CT, one of the major limitations of head CT is the need for intrahospital transport and the associated potential complications, thus limiting its use to clinical suspicion of an acute neurological injury [83]. Additionally, CT is associated with the risk of radiation exposure, another factor weighed in the decision making of obtaining head CT on ECMO. While contrast-enhanced CT can be used for studying blood flow through angiography and perfusion imaging, the altered hemodynamics in patients on ECMO can significantly impact the accuracy and interpretation of such imaging [84].

CBF Monitoring

TCD Sonography

Transcranial Doppler sonography provides a noninvasive, portable, and inexpensive means of monitoring CBFV in real time. Insonation through different acoustic windows can provide measurements of CBFV and PI in all the large cerebral arteries around the circle of Willis. PI reflects downstream vascular resistance and may be altered by impaired cerebral perfusion or autoregulation, intracranial hypertension/poor brain compliance, or distal stenosis [85]. General applications of TCD include assessment of intracranial pressure, measurement of cerebrovascular autoregulation, evaluation of vasospasm, and detection of cerebral embolization or large vessel occlusion. ECMO produces predictable alterations in TCD waveforms, but these applications remain investigational in patients undergoing ECMO therapy.

Variable associations have been identified between CBFVs and neurological injury in children treated with ECMO, likely reflecting small patient numbers in most of these case series [28, 86]. In one study of 27 patients, there was no statistically significant association between CBFVs and neurological injury, defined as focal deficits on clinical exam, seizures, or severe EEG abnormalities [28]. In contrast another study of 18 children found elevated CBFVs in patients who suffered intracerebral hemorrhage, with the increased velocities occurring 2–6 days prior to recognition of the injury.

In addition to providing information about cerebral hemodynamics in children on ECMO, TCD has the potential to be used in real time to rapidly identify

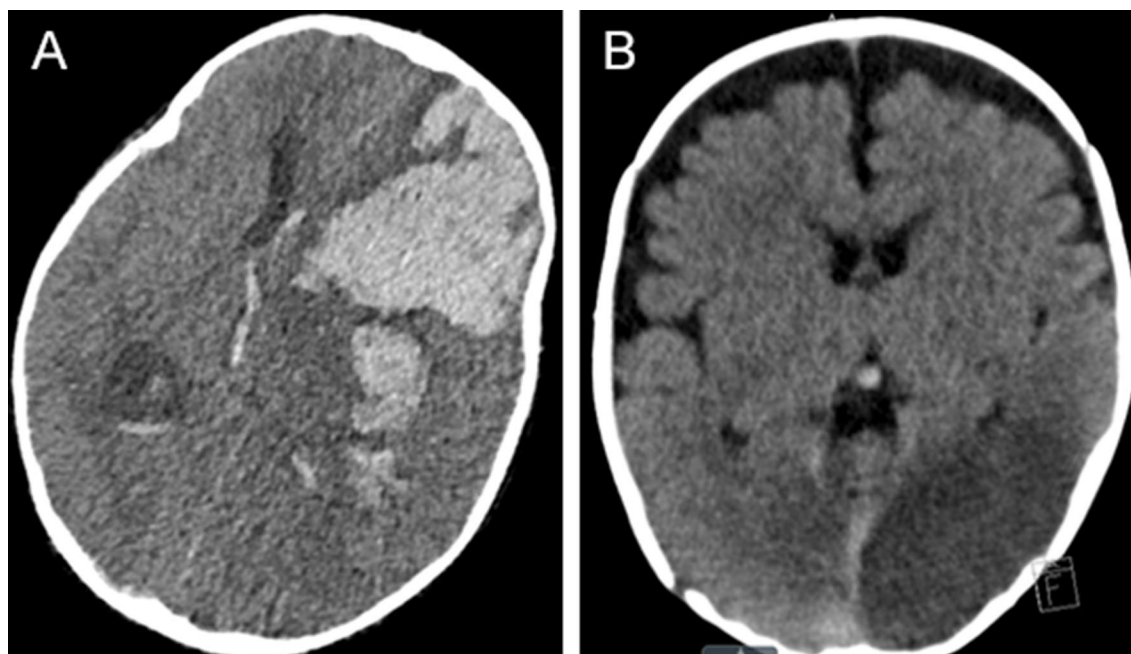


Fig. 2 Examples of head CT abnormalities on ECMO. **a** Head CT of a 4-year-old patient with failed Fontan physiology on ECMO day 3 following cardiac arrest showing large predominantly intraparenchymal hemorrhage centered in the left frontal and left parietal lobes. There is spillage into both lateral ventricles and small volume subarachnoid hemorrhage surrounding the large intraparenchymal hemorrhage. **b** Head CT image of a 6-month-old patient with dilated cardiomyopathy on day 26 of ECMO with evidence of bilateral posterior cerebral artery territory infarcts, larger and more well-defined on the left without evidence of mass effect or midline shift. CT, computed tomography, ECMO, extracorporeal membrane oxygenation

causes of neurological injury that may be amenable to intervention, such as emboli leading to stroke (Fig. 3) [87, 88]. TCD has several limitations. About 10–20% of patients will not have adequate acoustic windows for reliable insonation. Performance of this technique relies on skilled operators and thus is limited by their availability. These characteristics make TCD more suitable to intermittent evaluation rather than continuous monitoring.

Microvascular Imaging

Microvascular imaging is an emerging Doppler sonography technique that can provide high-resolution visualization of microvasculature in both deep and superficial brain structures in infants with an open fontanelle [90]. This method can identify tortuosity in the vessels, perfusion heterogeneity or asymmetry, and vascular engorgement [91]. A study of 30 patients demonstrated the feasibility of this technique, and while there was no association of basal ganglia abnormalities with neurological outcome, white matter vascular engorgement showed a statistically significant association with poor neurological outcome defined as death, seizure, or cerebrovascular injury [92].

Physiological Monitoring

Cerebral Oximetry

Near-infrared spectroscopy (NIRS) offers a means to continuously monitor regional cerebral oxygen saturation ($crSO_2$). In infants and children, NIRS has demonstrated reductions in the concentration of oxyhemoglobin and concomitant increases in the concentration of deoxyhemoglobin immediately after cannulation onto ECMO, with return to baseline or even over the first hour [93, 94]. Recent studies have analyzed the association between NIRS monitoring and neurologic outcome. In a series of 34 neonates, $crSO_2 < 50\%$ and a change of at least 20% from baseline ($\Delta crSO_2$) were associated with death or brain injury [95]. This was confirmed in the largest study to date of 153 infants and children at a single academic center, in which both criteria were again associated with poor outcome at hospital discharge (either death or survival with Pediatric Cerebral Performance Category [PCPC] score > 2 at discharge, with decline from baseline PCPC) [96]. Another study of 63 patients found similar associations using a slightly different outcome definition that included any evident neurological injury, providing positive predictive values of 78% and 80% for $crSO_2 < 50\%$ and $\Delta rScO_2 > 20\%$, respectively [97].

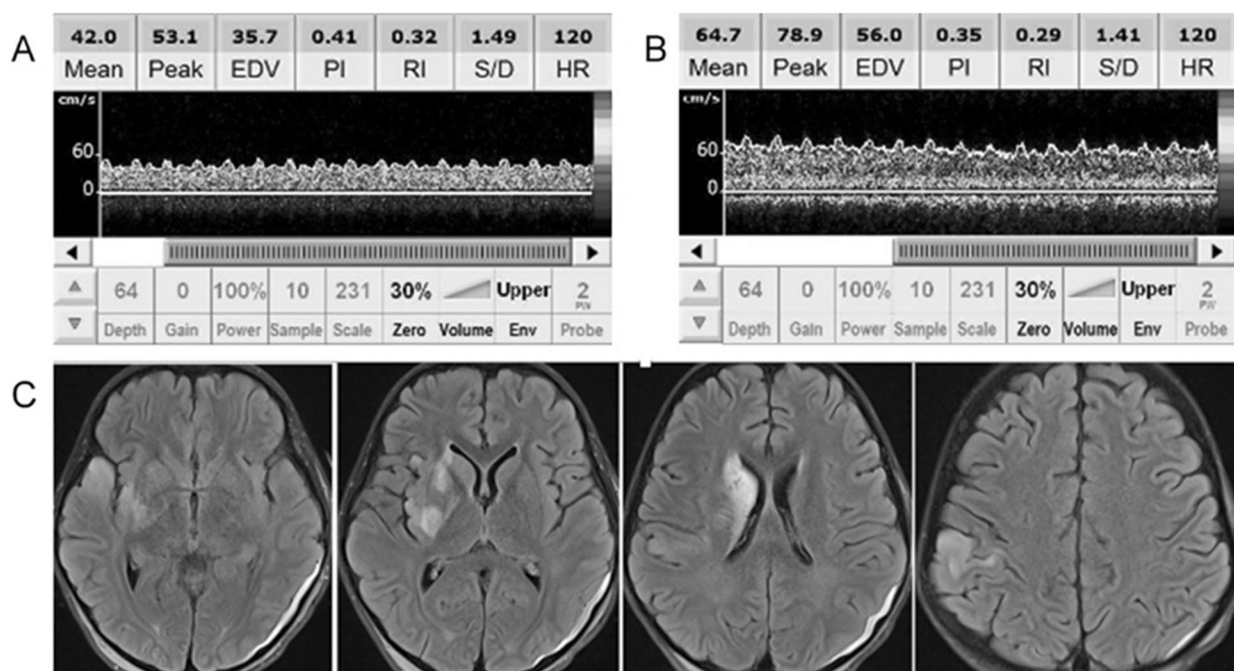


Fig. 3 Elementary school aged boy presented with fever and purpura fulminans due to Staphylococcal toxic shock syndrome and developed refractory shock requiring V-A ECMO. TCD study of the left (a) and right (b) MCA showed mean CBFVs that were 6 and 3 standard deviations below normal for age [89], respectively. There is a 35% side-to-side asymmetry in mean CBFV, with relatively increased mean, peak systolic, and end-diastolic velocity in the right MCA. Neurologic examination 10 days after decannulation off sedation was notable for left upper extremity plegia. Brain MRI (c) the following day showed patchy edema (partially facilitated, partially restricted in diffusion) in the right insula, right superior temporal gyrus, right basal ganglia, and inferior right parietal lobe consistent with subacute infarctions in the right MCA. CBFV, cerebral blood flow velocity, ECMO, extracorporeal membrane oxygenation, EDV, HR, MCA, xxx, MRI, magnetic resonance imaging, PI, pulsatility index, RI, resistive index, S/D, xxx, TCD, transcranial Doppler, V-A, veno-arterial

Another active area of investigation and promise for cerebral oximetry measures is in the determination of cerebral autoregulation. In six newborns on V-A ECMO, decreasing ECMO flows were associated with loss of cerebrovascular autoregulation demonstrated by wavelet cross-correlation between multisite oxyhemoglobin concentration and mean arterial blood pressure [98]. A more recent pilot study of 29 children treated with either V-A or V-V ECMO demonstrated feasibility of continuous assessment of cerebral autoregulation. The investigators found that children with acute neurological events while on ECMO had both a higher mean cerebral oxygenation reactivity index and a greater percentage of time with impaired autoregulation, indicated by cerebral oxygenation reactivity index greater than 0.3 [99].

Measuring cerebral oximetry with NIRS has the distinct benefit of providing continuous monitoring that can easily be integrated into multimodal monitoring systems. The limitations of NIRS include the highly restricted area that is monitored, namely the frontal lobes. Thus, NIRS provides only a regional measure of cerebral oxygen saturation. While the utility of continuous monitoring of

cerebral oxygenation and autoregulation is promising, further work is needed to determine whether interventions based upon these measures can influence outcome.

EEG

Electroencephalography provides direct information regarding brain physiology through the measurement of cortical electrical activity. It has become more widely used in critically ill children, providing the benefit of continuous noninvasive monitoring. Unlike regional information provided by cerebral oximetry, full EEG electrode arrays provide information about global cortical function. In addition to demonstrating electrographic seizures, EEG background can provide indirect information about CBF. As cerebral perfusion decreases, the EEG initially shows loss of faster frequencies, followed by an increase in slow frequency activity, and ultimately suppression of activity [100]. These changes are detectable even in states of critical illness, when the baseline EEG tracing is already abnormal due to sedation and other factors [101].

One of the largest case series of EEG monitoring studied 112 children on ECMO, of whom 99 received

continuous video EEG (cEEG) monitoring for at least 1 day, identifying seizures in 16% of patients. Of the patients who had seizures, most were only electrographic-without clinical correlate, and more than half exhibited electrographic status epilepticus [51]. In this cohort, mortality and poor neurologic outcome were more common in patients with electrographic seizures. Another study of 70 children on ECMO who received cEEG monitoring identified electrographic seizures in 23%, with electrographic status epilepticus in 7% [52]. A third smaller case series of 19 patients further supported these findings with 21% of patients having electrographic seizures, all of which were subclinical [102]. In these studies, the majority of seizures were detected within the first 48 h of ECMO initiation.

Changes in EEG background may also be predictive of neurological injury. Lin et al. identified focal background abnormalities in 12% of patients on ECMO, most of which correlated to acute neuroimaging abnormalities [51]. Focal slowing and focal attenuation of the EEG signal were also commonly associated with injury on neuroimaging in a study by Piantino et al. [102]. In all studies the occurrence of seizures was also highly correlated to subsequent detection of neurological injury [51, 52, 102].

Amplitude-integrated EEG is a simpler method to monitor the brain's electrical activity. It uses a reduced montage of electrodes to provide a time-compressed EEG tracing. Most commonly used in neonates, it has become a standard of care in monitoring during hypothermia for neonatal hypoxic-ischemic encephalopathy [103–108]. One study found that a background score of >17 (out of 32) for the first 24 h of aEEG was highly predictive of poor outcome (positive predictive value 95%) [109]. Although the reduced electrode montage of aEEG reduces the sensitivity and ability to localize abnormalities, the relative simplicity and ease of use and interpretability make this an appealing alternative to full montage cEEG.

Continuous EEG offers tremendous promise for neuromonitoring during ECMO, but it is not without challenges. Most cEEG monitoring is recorded continuously but analyzed intermittently, thus detecting changes in real time is not always realistic. The vast array of equipment in a critical care setting can create electrical artifacts in the recordings which requires troubleshooting. Lead attachment and maintenance can also be difficult in these children, particularly given poor perfusion states and edema. Thus, while cEEG provides extremely valuable information, obtaining a reliable study requires skilled and experienced technicians.

Plasma Biomarkers

Plasma biomarkers have been extensively studied in critical illness, and data are beginning to emerge in pediatric patients on ECMO, as well. Prospective studies of 22 and 80 children in one pediatric intensive care unit identified associations between peak levels of GFAP, MCP1, NSE, and S100b and unfavorable outcome (death or survival with neurological disability determined by PCPC) [37, 110]. A two-center observational cohort did not identify any associations between inflammatory biomarkers and long-term neurobehavioral outcome, but levels of interleukin-6 and plasminogen activator inhibitor-1 were elevated in children who died compared with those who survived to discharge [36].

Plasma biomarkers offer the advantage of specifically probing pathophysiological cascades, and the potential to identify modifiable factors that may improve outcome after ECMO. Differentiating between central nervous system and systemic contributions to peripherally measured biomarkers remains a confounder in determining the specific relevance to neurological injury versus critical illness in general. Also measuring peripheral biomarkers relies on disruption of the blood brain barrier, a pathophysiological process that occurs with injury but may not be directly correlated with severity and may not be consistent from patient to patient. Further studies of plasma biomarkers in this population will help to clarify some of these issues.

Knowledge Gaps and Future Directions

Increasing use of neuromonitoring strategies has provided a deeper understanding of the physiological changes that occur on ECMO and predispose to neurological injury. This has mostly been applied to determining predictors of neurologic outcome, but with further refinement neuromonitoring strategies have the potential to allow precision medicine in patients on ECMO, tailoring our care to provide individually optimized cerebral perfusion and reduce the incidence of neurological injury. For instance, significant decrease in the arterial partial pressure of CO_2 at ECMO initiation has been consistently associated with adverse neurological events and mortality [111–113]. Arterial partial pressure of CO_2 has important cerebrovascular effects, and technical modifications in the ECMO circuit such as adjusting flow rates or sweep to change the amount of CO_2 removed from the blood may offer a means to proactively alter CBF for neuroprotective purposes [114]. Neuromonitoring data could also be used to target blood pressures within the range of autoregulation [99, 115]. Modifications to add pulsatility to ECMO flow may also be a means of

improving hemodynamics and reducing microcirculatory damage [116].

One step toward achieving these goals will be developing more continuous monitoring strategies. Of the current widely used technologies, NIRS and EEG allow for continuous monitoring, though both are typically continuously recorded but only intermittently evaluated. The development of automated algorithms that can detect important changes in these neuromonitoring modalities will be useful in furthering this cause. Quantitative EEG is one example of this, extracting trends from the background of the EEG to provide prognostic values. Given significant limitations to the clinical neurological examination in patients on ECMO, we also rely on imaging studies to confirm acute injury. Transport of patients on ECMO is not a trivial endeavor, and further optimization and adoption of portable bedside imaging modalities may facilitate the ability to detect acute injury. To date clinicians have had to rely on CT scan or ultrasound for brain imaging, modalities that have limited temporal and spatial resolution for detecting acute injury. Evolving technologies including MRI that is portable and compatible with the ECMO circuit may eventually further enhance our capability for detecting neurological injury [117].

Conclusions

Extracorporeal membrane oxygenation is a lifesaving procedure for children with catastrophic cardiorespiratory failure, but neurological injury remains a significant complication that negatively impacts long-term outcome. Multiple factors including, but not limited to, critical illness and the need for sedation limit the ability to clinically monitor for neurological injury or deterioration. As we have reviewed here, there are numerous modalities available for neuromonitoring in these patients, each with their own uses and limitations. Increasing the systematic use of such technologies will continue to further our understanding of neurological injury that occurs in patients on ECMO, provide the ability to predict such injury, and ultimately tailor therapeutic strategies to improve outcome.

Author details

¹ Department of Neurology, Johns Hopkins University School of Medicine, 200 N. Wolfe Street, Suite 2158, Baltimore, MD, USA. ² Department of Anesthesia Critical Care Medicine, Children's Hospital Los Angeles, Los Angeles, CA, USA. ³ Division of Pediatric Critical Care, Indiana School of Medicine, Indianapolis, IN, USA. ⁴ Division of Pediatric Critical Care, Department of Pediatrics, Washington University in St. Louis School of Medicine, St. Louis, MO, USA. ⁵ Department of Neurology, Boston Children's Hospital and Harvard Medical School, Boston, MA, USA. ⁶ Division of Critical Care Medicine, Department of Pediatrics, Children's National Medical Center, Washington, DC, USA. ⁷ Department of Anesthesiology and Critical Care Medicine, Johns Hopkins University School of Medicine, Baltimore, MD, USA.

Author contributions

All listed authors have met the requirements for authorship, including the following: substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; drafting the work or revising it critically for important intellectual content; final approval of the version to be published; and agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Conflict of interest

The authors declare that they have no other conflict of interest.

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