Chapter

Neurologic Complications and Neuromonitoring on ECMO

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Abstract

Extracorporeal membrane oxygenation is challenged by several potential complications. Adverse neurologic events such as intracranial hemorrhages, strokes, seizures, and brain death are among the most detrimental and even catastrophic of ECMO complications. There are several risk factors related to the patients, their underlying conditions and the therapy itself that predispose these patients to neurologic injuries. In this chapter, we review different types of neurological complications, the identification and management of which can be difficult. We will also discuss some of the currently available technologies for multimodal neurological monitoring as a complement to clinical exam.

Keywords: stroke, hemorrhage, MRI, neuromonitoring, neuroimaging, ECMO

1. Introduction

ECMO is a cardiopulmonary bypass circuit to support patients in severe cardiac and/or respiratory failure. It is an advanced life support therapy for patients at high risk of dying from their respiratory or cardiac disease. Extracorporeal life support, while life-saving in many instances, can pose serious risks and is associated with several neurologic complications. In this chapter, we will review some of the more common neurologic adverse events seen in patients on extracorporeal membrane oxygenation (ECMO), as well as review some of the neuromonitoring modalities available for early recognition of neurologic morbidity. Based on a recent report from the Extracorporeal Life Support Organization (ELSO), the current survival to discharge after ECMO ranges from 28% for adult ECPR patients to 73% for neonatal respiratory ECMO [1]. As survival after ECMO improves with advances in technologies and patient care, there is ever increasing emphasis placed on reducing morbidity experience by survivors.

Majority of the literature on neurologic injuries come from analyses of the ELSO Registry and single center experiences. The ELSO registry currently collects limited information on presence of seizures (clinical or EEG confirmed), central nervous system (CNS) hemorrhages (intraventricular or parenchymal) as determined by ultrasound (US), Computed tomography (CT) or Magnetic Resonance Imaging (MRI); diffuse ischemia or CNS infarction; need for neurosurgical intervention, and brain death on ECMO [2]. In spite of advances in ECMO circuitry, anticoagulation, and clinical management, the rate of occurrence of neurologic injury has not changed in recent times [3].

ECMO was first trialed on a neonate and the success with that patient gradually spread its popularity among the neonatal and eventually pediatric patient

populations [4]. The H1N1 influenza pandemic in 2009 is primarily credited for the adoption of ECMO in many adult centers and its use in adults has grown exponentially since. While most of the early data came from neonates, more recent studies on neurologic injuries in adults are informing care of the ECMO patient. As ECMO is becoming more ubiquitously used, this chapter discusses neurologic complications noted across the age spectrum. However risk factors, types of complications and management often vary by patient population, from neonates to adults. Effort has been made to specify if certain descriptions are only applicable to a certain age group, and information may not be relevant for all ages.

2. Epidemiology

Quantification of the burden of neurologic complications has been difficult due to voluntary and retrospective nature of reporting, variability and lack of consensus on neuromonitoring and heterogeneous populations.

An ELSO registry analysis of neonates on ECMO from 2005 to 2010 showed that 20% had some neurologic complications [5]. Non hemorrhagic complications such as cerebral infarction, brain death and seizures were far less common than intracranial hemorrhage. A look at the subgroup of neonates with congenital heart disease failed to show an association between type of cardiac lesion and CNS injury [6]. The pediatric patient population is more heterogeneous than the neonatal group. A study by Hervey-Jumper et al. looked at children on ECMO from 1990 to 2009 and found that intracranial hemorrhage occurred in 7.4%, cerebral infarction in 5.7% and clinical seizures in 8.4% of all patients [7].

A systematic review of studies from 1990 to 2017 found that intracranial hemorrhage was the most common type of neurologic injury in adults, followed by acute ischemic stroke [8]. Incidence reported varies widely with a range of 2–21% for intracranial hemorrhage and 1–33% for acute ischemic stroke, with a median proportion of 5% of patients experiencing hemorrhages and another 5% with stroke. Seizures had the lowest incidence of about 2%. The study did find that neurologic injury was overall more commonly reported in VA ECMO than VV ECMO. The occurrence of neurologic injury significantly increases the in-hospital mortality with median mortality of 96% for hemorrhages, 84% for ischemic strokes 84, and 40% for seizures.

An analysis of the ELSO registry of almost 5000 adult patients on VV ECMO found an overall incidence of neurologic complications in 7.1% of patients [3]. Injuries included hemorrhage in 42.5%, brain death in 23.5%, stroke in 19.9%, and seizures in 14.1%. This study also found that in-hospital mortality was much higher (75.8% versus 37.8%) for patients with neurological injuries. An analysis of the ELSO registry for adult patients on VA ECMO, by the same group, found similar findings in the venoarterial cohort [9]. A decade's review of the Nationwide Inpatient Sample, that included over 23,000 patients, found that adult patients with acute ischemic stroke and intracranial hemorrhage on ECMO had higher rates of discharge to a long term facility and longer length of stay when compared to patients without neurologic injury [10].

A recent international randomized controlled trial, comparing ECMO to conventional mechanical ventilation for severe ARDS, showed a very low rate of ischemic stroke in the ECMO population [11]. Out of 124 patients randomized to receive ECMO, none had ischemic strokes compared to 5% of the patients initially randomized to conventional therapy, although there was the option of crossover to ECMO for refractory ARDS. It is unclear if this is due to a restrictive inclusion criteria of less than 7 days of mechanical ventilation combined with less severe hypoxemia and acidosis from early ECMO cannulation. However, the rates of hemorrhagic stroke were similar in the two groups.

3. Cerebral blood flow and oxygenation on ECMO

Cerebral autoregulation is the term used to describe the ability of cerebral arterioles to maintain steady cerebral blood flow across a wide range of cerebral blood pressure. This is achieved through dilation and constriction of cerebral blood vessels in response to fluctuations in mean arterial pressure. This is a complex process mediated through neurogenic regulation, involving sympathetic and cholinergic mechanisms, myogenic regulation involving smooth muscle tone, and metabolic regulation influenced by local concentration of metabolites [12]. Cerebral autoregulation can become disrupted focally or globally in pathological conditions leading to cerebral ischemia, hemorrhage or edema. These conditions associated with ECMO include vasospasm, severe acidosis, low cardiac output states, hypotension and hypertension, reperfusion injury and absence of pulsatile flow in VA ECMO. Hypercapnia is associated with cerebral vasodilation while hypocapnia causes cerebral vasoconstriction. A rapid decline in paCO2 after initiation of VV ECMO has been associated with central nervous system (CNS) injury [13].

A study by O'Brien using transcranial Doppler (TCD) showed that in patients that did not have neurologic injury, cerebral blood flow velocities on ECMO were much lower than predicted and returned closer to baseline after decannulation. However in patients that did have cerebral hemorrhage on ECMO, supranormal flows were noted in the days preceding the event [14]. A more recent multicenter study by the same author confirmed lower flow velocities on ECMO but did not show a difference in flow velocities in children with cerebral ischemia compared to those without. No patients in this study had cerebral hemorrhage [15].

Cannulation of cervical vessels relies on a competent Circle of Willis to allow for cerebral perfusion of both hemispheres. Occlusion of vessels can cause ipsilateral venous stasis and this venous congestion can lead to venous hypertension and decreased cerebral perfusion. Changes in cerebral blood flow rate and volume can contribute to altered cerebral oxygenation as demonstrated by cerebral oximetry [12]. Impairments in cerebral autoregulation, based on wavelet transform coherence, are associated with findings on neuroimaging and neurologic outcomes [16].

4. Risk factors for neurologic injury

These can be divided into factors prior to initiation of ECMO and factors inherent to ECMO therapy [17]. There are also risk factors for neurological injury after ECMO such as ligation or anastomosis of cervical blood vessels. Because CNS injury is often multifactorial, and lesions are often detected retrospectively on imaging after ECMO, the exact timing of injury can be difficult to determine.

4.1 Pre-ECMO

The underlying physiologic conditions that necessitate ECMO cannulation, such as labile hemodynamics, severe hypoxemia and acidosis, refractory hypotension, etc., leave the patient vulnerable to neurologic insults. These can alter the mechanisms responsible for maintaining cerebral autoregulation and make the vasculature more susceptible to alterations in systemic blood pressure. Prematurity is associated with an increase in intraventricular and intracranial hemorrhage and can be a contraindication for ECMO cannulation. A prior history of neurologic injury puts one at further risk of adverse cerebrovascular events.

4.2 ECMO-related

Animal models have demonstrated the effects of carotid artery and jugular vein cannulation and ligation on cerebral blood flow [18, 19]. Adults with atherosclerosis may develop emboli during arterial cannulation. ECMO cannulae and circuits expose a patient to prothrombotic surfaces and the foreign materials often incite an inflammatory response. Platelets are consumed in the circuit components leading to thrombocytopenia, putting a patient at increased risk of bleeding. Maintaining patency of the circuits requires the use of anticoagulation, which needs to be closely monitored to avoid complications such as bleeding, or thrombosis and embolism. Reperfusion injury is another risk factor after adequate oxygenation and blood flow delivery have been ensured following a period of severe hypoxemia. VA ECMO cannulation for cardiogenic shock is also associated with non-pulsatile flow which is not physiologic. Neurologic exams are often limited for patients on ECMO, confounded by sedation and limited mobility, which can lead to delayed diagnosis and recognition. A precannulation lactate greater than 10 mmol/L was found to be associated with increased odds for ischemic strokes in adults [8]. A history of pre ECMO cardiac arrest, need for renal replacement therapy and elevated bilirubin levels were associated with increased odds of neurologic injury [3]. A study of neonates found that birth weight less than 3 kg, gestational age less than 34 weeks, a history of prior ECMO cannulation and severe acidosis were risk factors for neurologic injury [5].

4.3 Veno-arterial (VA) versus veno-venous (VV)

VA ECMO carries with it the increased risk of embolization as blood is directly pumped into the arterial system, unlike in VV ECMO where the oxygenated blood is returned to the venous system where the lungs can filter thrombi. However, a study by Zahraa found that there was no difference in central nervous system complications between pediatric respiratory failure patients supported on VA versus VV ECMO [20]. Differential hypoxia, where the arterial oxygen tension is lower in the upper half of the body than in the lower half, is a phenomenon occasionally seen in patients supported on peripheral VA ECMO that causes cerebral ischemia [21]. For pediatric patients on VA ECMO, the incidence of stroke was much lower for transthoracic or central cannulation compared to peripheral cannulation [22]. VA ECMO is also unique in that poor cardiac function results in absence of pulsatile flow, with potential implications for cerebral autoregulation and vascular reactivity.

4.4 Carotid repair

The right carotid artery and internal jugular vein are commonly sacrificed during ECMO cannulation. Taylor et al. showed the feasibility of vascular repair with antegrade flow, without increasing the incidence of embolic phenomenon [23]. A larger, more recent study of neonates on VA ECMO, showed over 84% patency of repaired vessels. While 43% of all patients had a severe brain lesion after ECMO, there was no difference in early neurologic outcomes between the groups that underwent carotid repair versus carotid ligation [24].

4.5 Extracorporeal cardiopulmonary resuscitation (ECPR)

ECPR is the rapid deployment of VA ECMO for a patient in cardiac arrest, with ongoing CPR, prior to the return of spontaneous circulation. A systematic review of adult ECPR data showed that a shockable rhythm and duration of CPR were significantly associated with a favorable neurologic outcome [25]. A study of the

ELSO registry looking at pediatric patients that received ECPR found an overall incidence of acute neurologic injury in 22% of patients [26]. The in-hospital mortality was high for these patients at 89%. An analysis of neonatal and pediatric ECPR events from a multicenter, national registry showed that while only 43.7% of patients survived to hospital discharge, the majority of survivors had favorable neurologic outcomes [27]. Another study comparing survivors of ECPR and those with return of circulation after conventional CPR found comparable neurologic outcomes between the two groups, with total duration of cardiac arrest being the only predictor of survival [28].

5. Types of neurological complications and their management

There is a wide variety of neurological injuries that are noted after ECMO including embolic strokes, hypoxic-ischemic encephalopathy, cerebral infarction, intracranial and subarachnoid hemorrhages, seizures, cerebral edema and even brain death. Other complications, such as critical illness myopathy, neuropathies, delirium, hearing loss, vocal cord paralysis etc. are related to prolonged hospitalization and ICU stays, need for prolonged mechanical ventilation or tracheostomy, prolonged exposure to sedation, and limited mobility that often accompany ECMO runs. In this section of the chapter, we will look at some of the more common neurologic complications experienced by patients treated with ECMO.

5.1 Hemorrhagic complications

Intracranial hemorrhage (ICH) is one of the most common adverse neurologic events on ECMO, carrying a high mortality rate. It can occur as intraparenchymal, intraventricular or subarachnoid hemorrhages. Gestational age at time of ECMO cannulation, severe acidosis needing correction, sepsis, need for epinephrine, therapeutic hypothermia and need for cardiopulmonary resuscitation (CPR) have been associated with intracranial hemorrhage in neonates [29–31]. A longer duration of ECMO, higher activated clotting times (ACTs), presence of bleeding at other sites, pre-admission antithrombotic therapy, and low platelet counts were associated with hemorrhage in adults [32, 33]. Rapid PaCO2 decrease/correction of hypercapnia and renal failure at ICU admission were associated with increased intracranial hemorrhage in one adult study [13]. In order to detect intracranial hemorrhage while on ECMO, cranial ultrasounds are used in neonates while CT imaging is used in children and adults. In one observational study, 42% of the cohort underwent withdrawal of life sustaining therapy, 18% did not require any intervention and 40% were treated. Treatments included hemostatic interventions, ICP management and surgical interventions with 14% of the cohort uneventfully decannulated [34]. Patients that have clinically significant bleeds, with progression of brain injury and little to no improvement on ECMO ultimately end up with withdrawal of life sustaining therapies due to poor prognosis and risk of progression of the bleed. Patients with very small or clinically insignificant hemorrhages can continue their ECMO courses with close neurological monitoring, decannulation at the earliest feasible time and possibly lowering of anticoagulation parameters while balancing thrombotic risks. Platelets and anti-fibrinolytics may need to be administered. Occasionally ECMO circuits can be trialed without any anticoagulation keeping a close eye on the circuit for clots and fibrin deposition. Life-threatening hemorrhage can be severe enough to warrant a craniotomy [7, 35]. Hematoma evacuation on ECMO is high risk and carries a high mortality although there are reports of patients who survived [34]. There is heterogeneity in practice with drugs used for anticoagulation (heparin versus bivalirudin), tests to assess for anticoagulation (TEG,

ROTEM, activated clotting time, PT/PTT, heparin assays) and therapeutic targets for titration. Further research is needed to help develop guidelines and consensus on best practice to minimize and treat bleeding complications on ECMO.

5.2 Ischemic complications

It occurs in about 5–6% of children and adults [8, 36], and is best identified on MR imaging. Due to multifactorial etiology for ischemic strokes such as hypotension, large vessel occlusion, thromboembolism, septic embolism, etc. it is difficult to characterize lesions anatomically or to prognosticate based on imaging. Timing of injury is also difficult to ascertain. There are conflicting reports on laterality of lesions [37] but seem to occur in the middle cerebral artery vascular territory. A single center pediatric study found that majority of strokes were bilateral, a few were unilateral right sided lesions and no patients had unilateral left sided strokes; majority of the lesions were in the anterior cerebral circulation distribution [22]. Ischemic lesions are associated with electrographic seizures and decreased survival [38]. Asymmetry in regional cerebral saturation or on continuous EEG monitoring might be suggestive of focal ischemia. Once detected, hemodynamics should be optimized through adequate pump flows on VA ECMO, vasoactives can be used if needed, and further neurologic injury should be minimized by avoiding hyperoxia and treating seizures.

5.3 Seizures

Although less common than intracranial hemorrhage and stroke, seizures can be difficult to recognize if they are nonconvulsive or subclinical. A study of children and neonates undergoing ECMO revealed that 18% of patients had electrographic seizures, with 61% of those patients having electrographic status epilepticus and 83% having exclusively electrographic seizures [39]. Another recent study of neonatal and pediatric patients found electrographic seizures in 23% of their patients, especially within the first 24 hours of ECMO [40]. Patients with seizures had decreased survival to discharge (44% versus 74%). Older studies that reported lower incidence of seizures may have missed patients if only clinical seizures were reported, as the routine use of continuous EEG monitoring for patients is not yet a widespread practice, although recent recommendations advocate for its use in ECMO. Given that patients on ECMO are a high risk population, seizures should be treated with the help of neurologists.

5.4 Sensorineural hearing loss

Sensorineural hearing loss has been reported in neonatal ECMO graduates with a frequency of 3–21% [41]. Diagnosis of congenital diaphragmatic hernia, duration of ECMO, and aminoglycoside antibiotic use were associated with hearing loss [42]. A follow-up study found that even children diagnosed with hearing loss after ECMO can go on to have normal language development [43].

5.5 Myopathy

Prolonged immobilization, sedation and paralytics, hemodynamic instability, all contribute to neuromuscular weakness in ECMO patients. Studies have proved that active physiotherapy, with early mobilization, is feasible and safe in ECMO patients when performed with an experienced, multidisciplinary team [44, 45]. It may also shorten hospital duration and improve functional outcomes for patients [46].

5.6 Delirium

A small study of pediatric cardiac ECMO patients diagnosed delirium in all their patients, in 21% of coma-free ECMO days [47]. Use of validated delirium screening tools can aid in early recognition and management of delirium. The move to liberate ICU patients should include patients on ECMO whenever feasible, with an emphasis on delirium prevention.

5.7 Brain death on ECMO

Progressive cerebral edema and large hemorrhages, whether from insults prior to cannulation or secondary to complications from ECMO, can ultimately lead to brain death in patients supported on ECMO. Diagnosis of brain death can be challenging on ECMO, but is important to determine as it is medically and ethically unreasonable to continue ECMO for a patient who has met criteria for brain death.

5.7.1 Determination of brain death

The American Academy of Neurology issued guidelines on the determination of brain death in adults, most recently revised in 2010 [48]. Similarly the Society of Critical care Medicine, American Academy of pediatrics and the Child Neurology Society jointly published guidelines for the determination of brain death in children and infants in 2011 [49]. The following general criteria apply to all patients undergoing brain death testing, although the specifics may vary by institutional policies. Patients should be relatively normothermic, and electrolytes and glucose should be within acceptable ranges. Any medications that may interfere with respiratory drive and neurologic function must be discontinued, with drug levels obtained if needed. The patient must demonstrate absence of all motor function and lack of responsiveness to stimuli, except spinal reflexes. Cranial nerve testing should reveal absence of pupillary reflexes, corneal reflexes, oculovestibular and oculocephalic reflexes, absence of cough and gag reflexes and absent brain stem reflexes.

The apnea test is an important component of brain death testing without which ancillary studies such as cerebral angiography, nuclear scanning for cerebral blood flow, electroencephalography, transcranial Doppler etc. are required to demonstrate absence of blood flow to the brain. The apnea test is performed to demonstrate absence of spontaneous respiratory drive in the presence of rising paCO2 levels in the blood. The patient is pre-oxygenated with 100% FiO2 and ventilated to achieve normocarbia, if possible. A baseline blood gas analysis is obtained. The patient is then disconnected from the ventilator and oxygenated via a T-piece or flow-inflating anesthesia bag. The patient is closely observed for signs of spontaneous respiration or chest rise. Serial blood gases are obtained at every few minute intervals. A rise in paCO2 > 60 mmHg and > 20 mmHg above baseline is conclusive of absence of respiratory drive. If the patient were to become hypoxic or hemodynamically unstable the apnea test should be discontinued and ancillary studies obtained.

5.7.2 Apnea testing on ECMO

While clinical criteria of absence of cortical function and brain stem reflexes can be assessed in the usual manner, apnea testing can be difficult on ECMO. A proposed method for apnea testing is oxygenating the patient by use of continuous positive airway pressure (CPAP) or T-piece or by placing the patient on a self-inflating anesthesia bag with a PEEP valve, while watching for spontaneous respirations. The oxygenator on the circuit can then be capped. Alternatively, the sweep

gas is decreased to 0.5 –1 L/minute and oxygen increased to 100% FiO2 through the circuit, without any changes to extracorporeal blood flow [50, 51]. In-line gas monitoring on the ECMO circuit can be used to trend venous paCO2, but serial arterial blood gas analysis should be used to confirm the lack of ventilation secondary to central apnea. For patients on VA ECMO, hemodynamics should be maintained through circuit flows and use of vasoactive medications as needed. Patients found to be brain dead on ECMO can be considered as candidates for organ donation.

6. Neurological monitoring

There are currently no consensus guidelines for neuromonitoring on ECMO, with variations in practice at different institutions. Neuromonitoring may include assessment of brain structure or morphology via imaging, assessment of brain function via EEG or SSEPs, assessment of cerebral perfusion via cerebral oximetry or transcranial doppler, and assessment for neurological injury via biomarkers. Bembea and colleagues performed a systematic review of the literature; 39 observational and case-control studies met inclusion criteria, with most of the literature coming from neonatal studies [52]. There was very little data in pediatric and adult cohorts, and the study found limited data on the use and effectiveness of monitoring technologies. A recent review by Lin et al. discusses neuromonitoring in the neonatal ECMO patient [53].

6.1 Exam

Neuromonitoring of the ECMO patient should begin with daily neurologic assessments that are documented in the patients chart. These are limited by reliability when performed by multiple providers from different disciplines, however are useful for obtaining a daily baseline that can be suggestive of injury when a change is noted. This would also require daily sedation holidays for accurate assessments as well as using the least amount of sedation to keep the patient safe and comfortable. Use of neuromuscular blockade should be reserved for extremely ill patients and those whose movement limits ECMO flows. A change in neurologic exam is often the trigger for seeking additional information such as through neuroimaging.

6.2 Neuroimaging

Cranial or head ultrasound (HUS) is a mode of imaging limited to neonates and infants with open fontanelles. Ultrasound uses high frequency sound waves transmitted via a probe that are reflected back based on the tissue's composition as well as distance from the probe. Changes in tissue density from hemorrhage or ischemia will reflect back sound waves differently from surrounding tissue. Cranial ultrasounds are portable, easy to use, relatively inexpensive, and do not carry radiation risks. Most neonatal ECMO programs will obtain a HUS prior to ECMO cannulation as well as daily HUS for the 1st few days on ECMO. While it is best for detecting hemorrhages, ischemic changes are harder to interpret on HUS [54]. HUS can also give information on changes in ventricular size that would be seen in hydrocephalus. It is not as sensitive as other imaging techniques and a study showed that MRI was significantly more sensitive for detection of CNS lesions than HUS alone [55, 56]. The quality of images depends on the skill level of the ultrasound technician and interpretation of acquired images can be subjective and variable. HUS findings have not consistently correlated with neurodevelopmental outcomes and should not be used for predicting outcomes in neonatal ECMO survivors [37, 56].

Computed tomography (CT) is a diagnostic imaging modality that utilizes X-Rays directed at the patient that are picked up by a detector and sent to a computer to create thin 2D image slices, at different tissue depths. Multiple images can then be stacked to create a 3D picture. It is the most frequently used imaging modality for diagnosis of acute intracranial injury for patients on ECMO. A CT scan can be quickly obtained and has better sensitivity and specificity for detecting intracranial hemorrhage that might lead to clinical changes in management [53]. A disadvantage is exposure to radiation and its associated risks. Transporting a patient on ECMO to a CT scanner in the radiology department can be challenging in the absence of a portable scanner that can be brought to bedside. ELSO currently recommends a CT scan prior to hospital discharge for patients less than 4 years of age and if there is an abnormal neurologic exam for patients older than 4 years of age as part of post-ECMO follow up [57].

Magnetic Resonance Imaging (MRI) is a non-invasive technology that creates 3D anatomic images without exposing the patient to radiation. A strong magnetic field is used to force protons in the body into alignment. Then a brief radiofrequency pulse stimulates protons causing a change in alignment. The scanner can detect electromagnetic energy transmitted as the protons realign. It is reserved for patients after decannulation from ECMO, due to MRI incompatible materials in the cannulae and circuits. MRI is the most sensitive and specific imaging technique available. However it takes much longer time to obtain the study compared to a CT and is more expensive. While diffusion-restriction can be seen up to 10 days after acute ischemic injury, the optimal timing for obtaining an MRI after ECMO remains unclear [53].

6.3 Electroencephalography (EEG)

While neuroimaging provides information on the structure of the brain, EEG provides real-time information on the electrical activity of the brain. Information is obtained via electrodes placed on the scalp, connected to a monitor, with very little burden to the patient that would include scalp abrasions. Continuous EEG (cEEG) monitoring requires technicians to set up the electrodes as well as neurologists to read the EEGs, which can be time consuming. Amplitude-integrated EEG (aEEG) compresses the raw EEG data from 1 to 2 leads, is easier to set up and interpret, but due to lower sensitivity, can be used as a screening tool or in resource limited settings [53]. Ischemic and hemorrhagic injuries can predispose a patient to seizures that require prompt treatment. Continuous EEG monitoring is important for early identification and treatment of subclinical seizures or electrical status epilepticus that may not be otherwise detected, although studies are needed to show its benefit in improving long term outcomes. EEG monitoring is especially useful in paralyzed patients in whom a neurological exam cannot be elicited. EEG can be used to detect early cerebral ischemia through loss of fast alpha and beta frequencies to slowing and even suppression of all electrical activity as might be seen in an infarct. In 2011, the American Clinical Neurophysiology Society deemed ECMO as a high risk clinical scenario in neonates that would warrant long term EEG monitoring due to cardiac or pulmonary risks for acute brain injury and clinical encephalopathy [58]. This recommendation is supported by ELSO in their guidelines for management of neonatal respiratory failure [59]. In their 2015 consensus statement on continuous EEG in critically ill adults and children, the American Clinical Neurophysiology Society recommended continuous EEG monitoring for patients treated with pharmacologic paralysis, including patients on ECMO [60].

6.4 Transcranial doppler ultrasound (TCD)

This is a non-invasive, portable test that is based on the Doppler effect. A Doppler probe is used to emit high frequency sound waves through the cranium that are reflected

back by moving red blood cells in the blood vessels. The difference in frequencies of emitted and reflected waves is proportional to the cerebral blood flow. Studies have found that TCD velocities (TCDV) are much lower for pediatric patients on ECMO when compared to normative values for healthy and critically-ill children [15, 61]. While there was no significant association between global TCDV (systolic flow velocity, diastolic flow velocity, mean flow velocity) and neurologic injury, increased pulsatility index and regional increases in velocities or asymmetries might be predictive of neurologic injury.

6.5 Cerebral near infra-red spectroscopy (NIRS)

NIRS monitoring is a non-invasive technology that uses near-infrared wavelength of light that penetrates brain tissue via a scalp electrode. It provides a continuous measurement of regional tissue oxygen saturation (rSO2), which is a marker of the balance between oxygen delivery and demand in the tissues. When the probe is placed on the forehead, it measures cerebral oximetry. An analysis of adult patients on VA ECMO showed that cerebral desaturation was common and mortality higher for patients with cerebral desaturation compared to those without [21]. A sudden decrease in cerebral saturation can be associated with an acute neurological event, prompting further investigation. It can also serve as an early predictor of inadequate oxygenation and cardiac output especially peri-cannulation [62]. It can influence management by prompting a need for increased flows in VA ECMO or alternate cannulation strategies if there is differential hypoxia. A very high rSO2 could also be suggestive of very poor oxygen extraction and poor neurologic outcomes.

6.6 Biomarkers

Several plasma proteins have been evaluated as potential markers for brain injury [63]. These biomarkers include substances associated with glial injury (glial fibrillary acidic protein and s-100b), neuronal injury (neuron-specific enolase and brain-derived neurotrophic factor) and neuro-inflammation (intercellular adhesion molecue-5). Unfavorable neurologic outcomes have been associated with higher biomarker concentrations [64], with combinations of biomarkers providing higher sensitivities and specificities for detection of neurologic injury. These tests are more expensive and require laboratory equipment and processing availability. While not currently a routine component of neuromonitoring on ECMO in most institutions, there is potential for further research and applicability if these results can be obtained in real time to influence management.

6.7 Somato-sensory evoked potentials (SSEPs)

SSEPs measure electrical signals in the somatosensory cortex after a peripheral stimulus, assessing the pathway of neuronal conduction from the peripheral nerve to the cortex. They are assessed as normal, abnormal (increased latency) or absent. ECMO cannulation is not thought to alter the ability to assess SSEPs from the hemispheres [65]. Small studies have shown an association between abnormal SSEPs and poor neurologic outcome after ECMO [66], but the predictive value of evoked potentials remains to be determined. In one study, absence of bilateral SSEPs was associated with progression to brain death for patients treated with ECPR [67].

6.8 Optic nerve sheath diameter (ONSD)

It is a simple bedside test used to detect elevated intracranial pressure. A cut-off of 5.2 mm is sensitive and specific for intracranial hypertension [68]. Its use in

ECMO management is still in its infancy, although a study showed that higher ONSD was associated with poor neurological outcome after ECPR [69].

7. Therapeutic hypothermia

Therapeutic hypothermia has been shown to be neuroprotective for term neonates at risk of hypoxic ischemic encephalopathy secondary to perinatal asphyxia. However a randomized controlled study out of the United Kingdom did not show an improvement in outcomes for neonates on ECMO treated with mild hypothermia [70]. On the other hand, therapeutic hypothermia has been associated as a risk factor for intracranial hemorrhage and should be avoided [30]. In 2015, the American Heart Association recommended targeted temperature management of 32–36°C for comatose patients with return of spontaneous circulation after cardiac arrest [71]. This was also applied to patients who suffered in- hospital cardiac arrest leading to ECPR. A more recent large, multicenter, randomized control trial failed to show a benefit in survival with favorable neurological outcome for children with in-hospital cardiac arrest. There is no data to support routine therapeutic hypothermia for children undergoing ECPR although maintaining normothermia is still encouraged.

8. Conclusion

Neurologic complications contribute to significant morbidity and mortality for patients on ECMO, who constitute a high risk population. There are many modalities currently available for neuromonitoring, and as we gain more experience and information through more frequent use, we will be able to develop consensus guidelines and protocols to provide better care. A multimodal approach to active surveillance, early recognition and prompt management of neurologic injuries as they arise, may improve outcomes for patients on ECMO.

Conflict of interest

The author has no "conflict of interest" to disclose.

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