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Neurologic Issues in Patients Receiving Extracorporeal Membrane Oxygenation Support

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Abstract

Extracorporeal membrane oxygenation (ECMO) is a well-established therapy for patients experiencing acute severe cardiac and/or respiratory failure. Unfortunately, despite noteworthy improvements in patient selection, technology, and multidisciplinary team management, significant complications are still common. The most dramatic and potentially severe complications are neurologic. However, the incidence of neurologic complications (i.e. embolic stroke, intracerebral hemorrhage, seizures, and anoxic injuries) has not been completely defined. Unfortunately, brain death and neurologic injuries are significant causes of morbidity and mortality for patients requiring an ECMO support. Critical to the management of patients requiring ECMO is a broader understanding of neurologic monitoring along with the clinical assessment and management of neurologic events. It is important to evaluate and potentially intervene early in the event of a neurologic problem to minimize its clinical significance. Hopefully, with a better understanding of the pathophysiology, diagnostic and therapeutic tools, and prevention strategies, the true incidence of neurologic complications can be understood and minimized.

Keywords: ECMO, stroke, neurologic, complications, seizures, brain

1. Introduction

Extracorporeal membrane Oxygenation (ECMO) provides cardiopulmonary support to patients with acute severe refractory cardiac and respiratory failure. In veno-veno (VV) support, blood is drained from the venous system, oxygenated, cleared of carbon dioxide,

and then pumped back into the central venous system (i.e. into the right atrium or cavoatrial junction), is typically used for isolated pulmonary failure. For patients with cardiac failure or combined cardiopulmonary failure, venoarterial (VA) support is typically used. Unlike VV support, in VA support, blood is returned back into the arterial system – often as close to the coronary arteries and/or cerebral arterial system as possible. The specifics, including indications, contraindications, techniques, and outcomes are discussed in other chapters of this text. However, as we will discuss in this chapter, the nuances of arterial vs. venous inflow might potentially affect the management, complications, and outcomes, particularly the risks of cerebral complications of these critically ill and high-risk patients.

Since the initial applications in 1960–70, pediatric patients, neonates, and infants with congenital heart defects or respiratory distress syndrome seem to have been the main recipients of this technique. Better equipment and an exponential increase in the body of knowledge regarding its use have resulted in a dramatic increase in its utilization in the pediatric population. However, more significantly, there has been a tremendous increase in the adult population for both cardiac and respiratory support [1]. ECMO use in adults covers the spectrum of problems ranging from adults who survive cardiopulmonary resuscitation and post-myocardial infarction-associated cardiogenic and septic shock. ECMO is being commonly used for treatment of acute respiratory failure caused by a variety of problems [2–4]. The role of ECMO during the H1N1 pandemic in 2009 is noteworthy, where the use of ECMO resulted in a survival-to-discharge rate of >50–60%; it has been accepted worldwide as an appropriate rescue therapy for these critically ill patients [5]. There is also a growing experience with the use of ECMO as a bridge to heart and/or lung transplantation in highly selected patients in whom end-organ recovery does not occur or is not expected. Conversely, in the world of acute neurocritical care, ECMO has been thought to be of limited use due to the concomitant need for anticoagulation. However, some case reports have successfully utilized this technique in patients who suffered neurogenic pulmonary edema either in the setting of aneurismal subarachnoid hemorrhage (SAH) preceding surgery or traumatic brain injury (TBI), thereby opening the door to speculation regarding the possible future use in these patient populations [6, 7].

Survival rates for patients undergoing ECMO varies dramatically. Results are often a function of the initial primary pathological insult combined with associated comorbidities. As of 2012, the Extracorporeal Life Support Organization (ELSO)—an international organization dedicated to the study of ECMO (including the voluntary collection/reporting of clinical outcomes)—reported survival rate of 50–60% for adult patients with respiratory failure and 39% for cardiac failure patients [8]. However, survival rates in single-center registries have varied from 15% to 59% [4, 9, 10] with some reporting >80% 30-day survival rates [11]. As we will discuss in this chapter, it is also becoming evident that mortality, morbidity, hospital length of stay, patient care cost, and patient discharge to long-term care (LTAC) facilities appear to be closely related to the development of neurological complications. This is particularly true for those who develop intracerebral hemorrhage (ICH), or ischemic stroke (IS), both of which are considered the most frequent complications and had been found in up to nine of 10 brain studies at autopsy for patients who die after ECMO therapy [1, 9, 11]. The incidence of

neurological complications per se vary in the literature and range from 10 to 50% with some investigators speculating as many as 90% of patients treated with ECMO sustain some form of therapy-associated neurologic injury [1, 9, 11]. This huge disparity is a consequence of the lack of structural algorithms for the neurological evaluation of these patients. Most of the outcome data have been obtained from retrospective reviews and are based on clinical exams, imaging, pathology review, or a combination of several diagnostic assessments. Clinically significant events versus imaging or pathological events with no clinical or neurological consequence have also been poorly defined in these case series.

Figure 1. CT scan of a 24-year-old female patient with profound hypoxemia and septic shock. Neurologic evaluation was limited by hemodynamic instability and need for pharmacologic paralysis. Once stabilized on ECMO, imaging demonstrated a large hemispheric stroke of unknown etiology. Despite successful weaning from ECMO and recovery of end-organ function, she remained in coma and family withdrew support.

Regarding the spectrum of neurological complications, embolic ischemic strokes, ischemic watershed infarctions, ICH, SAH, seizures, brain death, and diffuse cerebral edema are the most prevalent, followed by unexplained prolonged coma and hypoxic ischemic encephalopathy. Delirium, severe neuropathy, hearing loss, and vocal cord paralysis are also to be included here; some of these may not be directly related to ECMO, but these are secondary to the need for prolonged intubation, mechanical ventilation, possible tracheostomy, and prolonged ICU stays in these extremely ill and complex patients. Acute disseminated encephalomyelitis has also been reported, but its mechanism remains unclear [9].

Adding to the complexity in the determination of true ECMO-associated complications, patients undergoing ECMO may develop neurological complications prior to the initiation of

ECMO, during, or after decannulation. Patients first receive ECMO in emergent circumstances where neurological examinations are rarely performed. Most patients are paralyzed, sedated, and even undergoing mild to moderate hypothermia during the first 24–72 h giving limited value to the bedside clinical examination [10]. Often critical care teams and neurologists are left with the use of laboratory, electrophysiology, and imaging testing as the only tools for detection of acute complications and determination of outcomes [12]. Unfortunately, sometimes definitive imaging and clinical evaluations cannot be determined until the patient is successfully stabilized (**Figure 1**) or weaned from the ECMO support (**Figure 2**).

Figure 2. MRI of a 43-year-old patient who sustained an acute respiratory arrest secondary to severe respiratory failure from seasonal influenza. He was transferred immediately to an ECMO center and required 14 days of veno-veno ECMO support. Despite successful weaning from ECMO with good end-organ function, he remained in a coma. Post-ECMO MRI demonstrated an extensive diffusion defect consistent with severe anoxic brain injury/ischemia. Due to these findings and concerns for a poor long-term neurologic outcome, the family decided to withdraw support.

A basic understanding of the physiology of cerebral blood flow (CBF), metabolism, and the management of complications, particularly in the context of long-term extracorporeal support, will be the focus of this chapter as it is critical to understanding the relationships between extracorporeal support and cerebral protection.

2. Principles of cerebral metabolism and blood flow

Under normal conditions, about 15–20% of cardiac output is devoted solely to the brain. This equates to an average perfusion of 50–55 ml/100 g brain tissue/min, with the more metabol-

ically active areas (i.e., gray matter) receiving higher cerebral blood flow (CBF: 75 ml/100 g brain tissue/min), whereas the white matter exhibits a much lower CBF (i.e. 45 ml/100 g brain tissue/min) [13].

Regulation of CBF in the human brain is exceedingly complex, and although not fully understood, three main regulatory paradigms have been identified thus far, namely *cerebral autoregulation*, *flow-metabolism coupling*, and *neurogenic regulation*. The first mechanism refers to the ability of cerebral arterioles to maintain a constant CBF within a wide range of cerebral perfusion pressures, while a functional hyperemia or coupling between cerebral metabolism in a given area and a matched increase in regional CBF is a well-documented phenomenon. Lastly, the prominent role of *neurovascular units* comprising extensive arborizations of perivascular nerves, endothelial cells, and astrocytes has been increasingly recognized in recent years [14].

Moderate decreases in CBF down to about 30 ml/100 g brain tissue/min are usually well tolerated and do not typically lead to neuronal dysfunction. However, alterations in electrophysiological recordings become apparent once flow drops below 25 ml/100 g brain tissue/min and completely disappear with CBF of ≤ 12 –15 ml/100 g brain tissue/min [15]. The early recognition of hypoperfused but not yet irreversibly injured brain (i.e. penumbra) constitutes one of the main rationales for multimodal brain monitoring of patients undergoing ECMO.

During ECMO support, a number of investigations have shown a significant decrease in cerebral blood flow, with mean flow velocities on transcranial Doppler sonography about half of those predicted for age and gender and a flow pattern characterized by decreased systolic upstroke, lack of dichrotic notch, and continuous diastolic flow [16]. This consistent decrement in CBF with near normalization following decannulation has been ascribed to metabolism-flow coupling secondary to decreased cerebral metabolic rate (i.e. due to the use of sedative agents), cerebral venous congestion secondary to jugular vein ligation (in pediatric and neonatal cases), and left ventricular dysfunction, particularly in patients with venoarterial ECMO [17].

Interestingly, patients who develop intracerebral hemorrhage as a complication of ECMO seem to experience reactive hyperemia with resultant increases in CBF an average of 2–6 days prior to clinical recognition of the acute neurologic injury, likely due to uncoupling of the flow-metabolism regulatory mechanism. In such patients, recent ischemic injury and the use of anticoagulants likely contribute to the elevated risk of cerebral hemorrhage [18].

2.1. Causes of neurological complications during ECMO

As previously mentioned, some of the neurological complications detected during ECMO may be the consequence of the insult that led to the need for ECMO to begin with. The extent of this pre-ECMO injury is impossible to predict prospectively in most cases. These patients are either hypoxic or hypotensive before ECMO and represent a wide range of circumstances, from cardiac arrest to severe respiratory failure and sepsis, thereby making it impossible to

identify common denominators as predictors of outcome in the front end. Data suggest that pre-ECMO lactic acidosis levels >10 mmol/L are associated with poor outcomes as well as the presence of hyperpyrexia, hyperglycemia, and metabolic acidosis. Other potential contributors to the overall injury to the central nervous system prior and during ECMO that may be considered as independent predictors of poor outcome include high ventilatory pressures, disseminated septic embolism, and air embolism.

In children, the ECMO cannulation approach represents a significant risk by altering blood flow after ligation of the internal jugular vein and common carotid arteries. In adults with extensive aortic atherosclerotic disease, arterial cannulation might result in retrograde disruption of debris from the high pressure and flow and result in diffuse microvascular embolic events. Cases of retrograde aortic (and carotid) dissection have also been discussed as the potential causes of acute catastrophic injuries during cannulation and therapy. Other similar procedures that require vascular access complications may include currently reported causes of embolic neurologic system to oxygenate, development of pump head thrombus, and intracardiac thrombus are among the currently reported causes of embolic neurologic [18, 19].

All patients undergoing ECMO should be systemically anticoagulated. Exposure of blood to non-biological surfaces leads to a chain of biological reactions, increased inflammatory response, and increase in acute-phase reactants. This results in hypercoagulability and potential thrombotic events. This may occur acutely within 24–48 h after initiation of the circuit and can lead to ischemic complications including stroke. Embolic areas that become ischemic are subsequently prone to associated hemorrhagic transformation and intra-cranial bleeding complication. Similarly, these biological reactions, which can increase the bleeding risk via thrombocytopenia, impaired platelet function, and consumption of clotting factors as well as fibrinolysis associated with the therapeutic anticoagulation, increase dramatically the risk for hemorrhagic complications, among which ICH is the most feared [20].

Different considerations for neurologic risk are based upon VA versus VV cannulation. This is particularly true in neonates where VV ECMO has a significantly lower risk for neurologic complications when comparing with VA ECMO [11]. However, the same findings have not been consistently replicated in adult population. It is important to recognize that neurologic complications increase the risk of a poor outcome, but such events are not inherently futile [21]. In the absence of a specific diagnosis of brain death, clinically significant neurologic events are often used for justification to withdraw support on patients requiring ECMO. In one study of 87 patients treated with ECMO (for all indications), 65 experienced a neurologic event. Of these 66, 25 survived to discharge, 25 had support withdrawn, and 16 died. The distinction between the 16 patients who were listed as having “died” versus the 25 who had “support withdrawn” and presumed to have died remained unclear [11]. Given the potential implications and link between neurologic events and clinical outcomes, without a doubt, a better understanding, definitions, and management protocols are necessary.

3. Specific complications

3.1. Intracranial hemorrhage (ICH)

ICH is most frequently reported in neonates due to easy detection using transcranial Doppler (TCD), with the incidence varying between 26% and 52% and also the cerebellum being the most common location at this age. Independent of the use of ECMO, the overall mortality from ICH is 60–70% [2, 22, 23]. This contrasts dramatically with lower incidence reported in adult population, with 2–19% patients developing ICH. The range in incidence varies depending on the variability in the use of computed tomography (CT) scanning for diagnosis or postmortem pathology data [10, 11, 20]. Conversely, the most common location in adult patients is supratentorial [11]. The existence of proven independent risk factors for ICH is limited at this time. While the duration of ECMO support and site of cannulation did not seem to affect the rates of ICH in adults, a correlation has been noted between female gender, thrombocytopenia, acute renal failure ($\text{Cr} > 2.6$ or the need for dialysis). Being female with thrombocytopenia ($<50,000$) is the most important predictor. In the case of infants, prematurity, venous cannulation, carotid artery ligation, sepsis, and acidosis carried an increased risk [20]. In adults, outcomes after ICH while on ECMO are felt to be catastrophic with mortality as high as 92.3% [24], but successful outcomes are not uncommon [25] (**Figure 3**).

Figure 3. CT scan of a 25-year-old male patient who sustained a motor vehicle accident. He presented with hypothermia and refractory hypoxemia from severe pulmonary contusions. Despite intraventricular hemorrhage, he was supported on veno-veno ECMO for 4 days, 2 days without the use of systemic heparin. He was successfully weaned from ECMO, extubated, and discharged to a rehabilitation facility 21 days postinjury (see text for reference).

3.2. Stroke

Ischemic strokes are among the most common complications in patients on ECMO; however, the true incidence is not known. Data currently available do not differentiate among the mechanism of stroke, characteristics of the infarctions (for example, large vessel occlusions versus microembolization) or the timing of the infarction with regard to outcomes. Events caused by hypoperfusion that may have occurred during CPR leading to watershed infarctions are thought to have completely different presentations, mechanisms, and outcomes as cardioembolic events in patients with CHF, septic embolization, thrombosis caused by hypercoagulability; however, these are lump together at the time of discussing incidence and outcomes. It is therefore impossible to generalize the prediction of the prognosis of ischemic strokes in patients with ECMO, which should be considered in a case-to-case bases, rather than assuming that the presence of ischemic stroke equals poor prognosis.

Limited information exists regarding the true incidence of stroke as mentioned before. The work by Omar HR et al. [26] is worth mentioning, wherein a retrospective review of all ECMO patients at the Tampa General Hospital from 2004 to 2014 has been reviewed for detection of incidence of radiologically proven ischemic stroke. Detecting a 5.8 % of incidence, however in the report, they recognize the limitation of the study based on the lack of systematic studies with the possibility of a falsely low incidence due to underreported events. In this report, the presence of high lactic acid of >10 mmol/L prior to ECMO appeared related to an increased incidence of stroke. Literature review has associated stroke with an increased morbidity of up to 14% [11]. However, unfortunately, most of the adult studies tend to combine mortality for both ischemic and hemorrhagic cases. No stroke correlation has been proven with the duration of ECMO treatment; however, the association with high levels of lactic acid suggests that systemic post-anoxic events is more common than ischemic strokes caused by cardiac embolization. While cannula embolization or air or atherothrombotic embolisms as mechanism are far more common with venoarterial therapies in which abnormal or high pressure (and often retrograde) flows in the arterial system might predispose to this complication. Unless air is iatrogenically introduced into the system, post-oxygenator, the intrinsic filtering of modern oxygenators has virtually eliminated the risk of ECMO circuit-induced embolic complication [27]. Nevertheless, there is clearly much to learn in this specific area of neurologic complications [21].

3.3. Seizures

Post-anoxic encephalopathy, stroke, and ICH are all associated with an increased risk for development of seizures. Therefore, it is not surprising that ECMO patients also have an increased risk. Fever, metabolic changes, and medications all contribute to this risk. Their presentation may vary from post-anoxic myoclonus, focal, generalized seizures to subclinical seizures. Any indication of abnormal motor function, especially while under heavy sedation, or concern should prompt a formal evaluation. Unrecognized seizure activity, if left untreated, can result in catastrophic neuronal ischemia/anoxic injury. Formal recommendations for the systematic use of electroencephalography in this patients do not exist, thereby resulting in a potentially under reported incidence and therefore poor understanding of the role that this

entity plays in the overall outcome. Continuous EEG recording could assist with the detection of not only seizure activity but also focal suppression of the background that could indirectly herald the presence of a structural abnormality.

4. General brain edema/brain death

The presence of generalized brain edema is clinically heralded by either persistent coma or physical examination findings suggestive of brain death. Systemic conditions resulting in severe hypoxia or hypotension will result in a global decrease in cerebral blood flow or cerebral oxygenation, which if sustained and above what the cerebral autoregulation or metabolic coupling can compensate for, the result can be general brain edema neuronal cell death. Many of these patients are diagnosed with general brain edema within 3 days of cannulation for ECMO [11]. This would suggest that is the brain insult suffered during the condition that led to the need for ECMO what cause the injury and subsequent edema. Brain death occurred in 7–21% of the ECMO patients treated in academic centers [28–30].

In one recent series, 295 adult patients treated with ECMO, 21% of patients were given a diagnosis of brain death [24]. Unfortunately, given the retrospective nature of this voluntary registry data, no specific criteria were given to validate the method for making the diagnosis.

Brain death is a formal diagnosis for which there can be little margin of error in assessment. Once these diagnostic criteria are met, the diagnosis is established, which thereby provides both medical and legal grounds for terminating any and all care. Prolongation of therapies after the establishment of brain death is unethical and potentially illegal with grounds for litigation. Because many of the physiologic criteria and responses to bedside testing used for the assessment of cerebral and brainstem function can be influenced by the physiologic benefits of ECMO, the diagnosis of brain death while on ECMO can be challenging. In addition, while several authors have advocated criteria for determining brain death in a patient supported by ECMO, formal guidelines to assist in the making of such a critical, life-ending, diagnosis are lacking. This topic will be further discussed below.

4.1. Neurological monitoring during ECMO

The role of the ongoing neurological assessment while patients are on ECMO support is of particular importance in this patient population due to the high incidence of neurological complications [1, 11, 31, 32]. Findings from neurological monitoring either physical exam, laboratory, electrophysiological, or neuroimaging data have a high probability to result in a change in care plan or goals of care that may definitely lead to change in outcomes and potentially prevent further deterioration. There is no consensus regarding minimal recommended neurological assessment either prior, during, or after ECMO. Nevertheless, to the extent possible, all patients on ECMO – even when heavily sedated and pharmacologically paralyzed – require very close and frequent neurologic assessment consistent with routine ICU clinical monitoring. Given the high risk and incidence for adverse neurologic complications, as discussed, any and all neurologic changes in patients undergoing ECMO therapy require

early and aggressive evaluation and management. Limited data exist regarding the predictive value of the different monitoring modalities and in particular physical examination prior and during treatment on ECMO outcomes.

4.2. Physical exam

As itor response to noxious stimulation. Most of this could be continued during ECMO support, limited only by sedation and paralysis, in which case, only pupillary studies may be followed. The latest can be done using an automatic computerized measure to avoid examiner variability (**Figure 4**). As with any critical care patient, we suggest the establishment of sedation vacation protocols that would facilitate clinical examination whenever possible. Identification of changes in physical exam findings has been followed traditionally by a need in cranial imaging.

Figure 4. The NPi-200 Pupillometer (Neuroptics Inc, Irvine CA, USA, <http://www.neuroptics.com>) uses quantitative infrared technology that objectively and accurately measures and trends the pupillary size and reactivity in critically ill patients. Eliminating inaccuracies caused by interpreter reliability. Measurement of NPi, (Neurologic pupillary index), maximal diameter at rest and maximal constriction as well as calculating % change and latency time between initiation of stimulation and onset of constriction. MCV, (maximum constriction velocities, mm/sec) is also calculated in each eye.

4.3. Imaging

Choices for imaging techniques are also limited during ECMO. While in infants, transcranial Doppler (TCD) provides extraordinary bedside imaging data prior to the closure of the fontanels; in adults, cranial computed tomography (CT) is preferred and TCD is limited to assessment of cerebral blood flow dynamics, detection of increase in ICP, and detection of microembolism [33]. Due to the ferrous properties of the ECMO pump and circuit, magnetic resonance imaging while on ECMO is obviously contraindicated.

4.4. Cranial computed tomography (CT)

Transportation of these patients outside of the ICU is not only technically and physically difficult but also potentially dangerous [34]. For the most part, presumably, only a few patients undergo CT during actual ECMO and most are tested after decannulation. Up to 95 % of the complications found in infants and 85 % in pediatric and adult patients are found in the first 3–4 days on ECMO support, undelaying the need of imaging technique protocols during ECMO [9, 18]. The availability of portable CT scans is of particular use in the ECMO centers. With wider availability of portable CT scanning or easier transport of patient due to more compact ECMO circuit design, the hope is that closer monitoring or more frequent imaging might improve the overall understanding of ECMO therapies on clinical neurologic events and outcomes. Clearly, more comprehensive, and potentially prospective data and studies, are required in this area.

In a study by Marika K et al., 37% of patients who underwent cranial CT scanning during ECMO were found to have either ICH, IS, or generalized brain edema. Imaging findings were not always associated with clinical findings proving underreporting of neurological complications based on clinical exam alone, but the results of CT had a significant impact in clinical management, change in goals of care, and surgical indications [9, 11].

5. Electrophysiological monitoring

5.1. Somatosensory-evoked potentials (SSEPs)

Evoked potentials are electrical signals generated by the nervous system in response to sensory stimuli. In SSEPs, an electrical stimulus is applied to the median nerve at the wrist, the common peroneal nerve at the knee, or the posterior tibial nerve at the ankle, while electrodes are placed along the neuraxis measure latency and amplitude. The median nerve is the most commonly stimulated site and scalp electrodes overlying the contralateral somatosensory cortex record the so-called N20 component of the evoked potential.

The cortical generators of the N20 component are located in the territory of the middle cerebral artery and various studies have correlated decreased N20 amplitude (by >50%) with cerebral hypoperfusion in this vascular distribution [35, 36]. Furthermore, the absence of SSEPs in the setting of cardiac arrest and global cerebral ischemia strongly correlates with poor neurologic outcome, while its presence is not sensitive enough to predict a favorable one [37].

In patients undergoing ECMO, SSEP responses can be asymmetric between right and left hemispheres in up to 15% of cases [38]. Abnormalities (or absence) of the N20 component following median nerve stimulation seem to have a prognostic value for poor neurologic outcome, similar to other instances of global cerebral ischemia [39]. Future studies are warranted to further refine its role in ECMO patients.

5.2. Electroencephalography (EEG)

In major medical centers, frequent or even continuous EEG monitoring of patients with devastating neurologic injuries is becoming commonplace, and patients undergoing ECMO support should not be an exception to this rule. Akin to cardiac telemetry, this form of monitoring (“neurotelemetry”) can assist in the identification and early treatment of reversible conditions, which could then lead to improved neurologic outcomes in this patient population. With this in mind, EEG monitoring can serve three main purposes: early identification of cerebral ischemia, recognition of seizure activity, and assisting with prognostication. While a review of the complexities of EEG testing and interpretation are beyond the scope of this chapter, an understanding of the basics – particularly as applied to ECMO patients – is important to clinical management (**Figure 5a and b**).

Figure 5. (a) Initial EEG in a 40-year-old, status post cardiopulmonary arrest and initiation of ECMO therapy for acute respiratory failure. CPR had been conducted on and off for over 60 min, at home, during transport to hospital and then during salvage cardiac catheterization. A 16-channel digital EEG recording 1 h after arrival to the ICU demonstrating low amplitude and severe suppression of the background rhythms with superimposed drug effect. No evidence of asymmetry or paroxysmal discharges. (b) Follow-up EEG (approximately 1 week later). A 16-channel digital EEG recording of the same patient with clinical examination concerning persistent coma off sedation and after discontinuation of ECMO. EEG demonstrates generalized suppression, which however has improved in amplitudes. No paroxysmal or asymmetric patterns were detected, despite concern for an asymmetric tone of limbs in the clinical exam. Patient recovered consciousness 48 h, following this EEG and was discharged 2 weeks later with no neurological deficits.

Following decreased CBF and ensuing cerebral ischemia, EEG changes progress from the loss of faster frequencies (i.e. beta and alpha) to slowing, first with excess theta and, as ischemia worsens, with excess delta waves. Finally, suppression of all frequencies usually indicates neuronal cell death and infarction. Periodic lateralized epileptiform discharges (PLEDs), stimulus-induced periodic rhythmic or ictal discharges (SIRPIDs), unilateral attenuations, and asymmetric triphasic waves can all be seen in patients with cerebral ischemia and aid in early recognition and prevention of irreversible injury [40].

The relatively high risk of both ischemic and hemorrhagic stroke during ECMO support leading to irreversible brain injury can in turn elevate the risk of clinical as well as non-convulsive seizures (as mentioned above). The incidence of clinical seizures during ECMO ranges from 2 to 10%, with somewhat higher rates in younger children [41]. However, the rates of subclinical seizures have been reported to be as high as 17%, including 11% with non-convulsive status epilepticus [42]. Furthermore, the occurrence of seizures seems to be associated with neurodevelopmental disorders in neonates as well as an increased risk of death and worse functional outcomes [43]. Continuous EEG monitoring can help with early identification of ictal patterns and guidance of pharmacologic treatment.

While more studies are still required, the presence of EEG background abnormalities and certain electrographic patterns can aid in the prediction of neurologic outcome after ECMO support. In one study, the presence of an unexplained burst suppression pattern was associated with an increased risk of death or severe disability [44], while low voltage or isoelectric EEG patterns are usually correlated with poor outcomes after global cerebral ischemia [45].

6. Laboratory studies as predictors of neuronal injury and clinical outcome

6.1. Biomarkers as predictors of neuronal injury and clinical outcome

Given that neuromonitoring modalities during ECMO vary widely among institutions and their reported use is limited to small studies, the introduction of plasma biomarkers has emerged as a monitoring tool to aid in outcome prediction for patients on ECMO. An ideal biomarker would have high sensitivity for detection of both ischemic and hemorrhagic injury, provide real-time information, and allow detection of injury at the cellular level that precedes cellular death. While such an ideal marker is not available yet, a number of plasma proteins have been studied to date.

In general, these biomarkers can be divided into three groups, those that reflect glial injury (glial fibrillary acidic protein [GFAP] and S100b), those indicative of neuronal injury (neuron-specific enolase [NSE], intercellular adhesion molecule-5 [ICAM-5], and brain-derived neurotrophic factor [BDNF]), and those suggestive of increased neuroinflammation (ICAM-5 and monocyte chemoattractant protein 1/chemokine (C-C motif) ligand 2 [MCP-1/CCL-2]) [43]. For instance, elevated plasma levels of GFAP in patients with ECMO were associated with a higher risk of brain injury and death (odds ratio of 11.5 and 13.6, respectively) [44]. Similarly, S100B may serve as an early indicator of cerebral complications, in particular intracerebral hemorrhage [46].

In a more recent investigation, a combination of six different biomarkers measured daily for the duration of ECMO demonstrated that GFAP, MCP-1/CCL-2, NSE, and S100b were all significantly higher in patients with unfavorable outcomes and that peak concentrations of GFAP, NSE, S100b, and MCP-1/CCL-2 were higher in non-survivors [47]. Even after adjusting for potentially confounding variables, GFAP and NSE remained significantly associated with unfavorable outcome and NSE associated with increased mortality. Lastly, elevated concentrations of GFAP and ICAM-5 predicted abnormal neuroimaging in this cohort. Taken together, while validation in larger studies is still required, these results suggest that the biomarkers mentioned above could serve as indicators for obtaining further investigations (i.e. neuroimaging) and for initiation of neuroprotective therapies.

7. Brain death examination

The America Academy of Neurology (AAN) has outlined criteria for the determination of brain death [48]. Given the high reported mortality rates—and in particular, brain death—in patients treated with ECMO, a thorough understanding of the definition and determinations of brain death is critical. Despite the importance of the assessment of brain death, objective protocols for patients on ECMO are clearly lacking.

A key component to the determination of brain death in the ECMO patient is the bedside clinical exam—ideally performed by a neurologist or clinician specifically skilled, or credentialed, in the assessment of brain function in ICU patients. The first step is to evaluate for coma. Coma is defined by the lack of all responsiveness, including eye opening or movement (spontaneous or provoked) and motor function in response to painful stimuli (not including spinal reflects). The potentially reversible causes of coma must be excluded (**Table 1**):

Acid-base abnormalities
Electrolyte abnormalities
Endocrine complications
Presence of central nervous system depressants (neuromuscular blockade, suppressive drugs/medications
Hypothermia
Hypotension
Hypovolemia

Table 1. Potentially reversible causes of coma.

Other components to the clinical exam must include assessment of brainstem reflects and cranial nerve testing. Any evidence of brainstem function, or an incomplete assessment, is, by definition, inconsistent with a diagnosis of brain death (**Table 2**).

Continuous electroencephalographic (EEG) testing can be helpful when positive, but external electromagnetic energy sources, including the pump and ECMO circuitry, can make conclusive interpretation of results difficult. Cerebral angiography or nuclear scanning may document the absence of cerebral blow flow, but such testing in patients on ECMO can be difficult

as transporting the patient and all of the mechanical equipment (ventilator, ECMO system, etc.) to remote areas of the hospital for testing can be dangerous and sometimes logistically impossible (i.e. will all of the equipment, the patient, and necessary clinical staff fit in a transport elevator?).

Prerequisites
Exclude the presence of central nervous system depressant drugs, neuromuscular blocking agents.
Rule out severe electrolyte, acid-base, or endocrine disturbance
Achieve normal core temperature
Achieve normal blood pressure (systolic blood pressure >100 mmHg)
Clinical evaluation of a coma
Absence of eye opening or movement to noxious stimuli
Absence of motor response other than spinally mediated reflexes to noxious stimuli
Absence of brainstem reflexes
Absence of pupillary response to a bright light in both eyes
Absence of ocular movement using oculocephalic and oculovestibular testing
Absence of corneal testing
Absence of facial muscle movement to noxious stimuli
Absence of pharyngeal and tracheal reflexes
Apnea test absence of breathing drive to carbon dioxide challenge
Ancillary tests
Electroencephalography, cerebral angiography, nuclear scan, transcranial Doppler, cerebral tomography angiography, and magnetic resonance imaging/angiogram

Table 2. Brain death criteria.

Formal apnea testing is the key procedure used in the establishment of brain death. The principle behind the test is that the absence of an appropriate respiratory drive, as manifested by an increased in PaCO₂ following a CO₂ challenge, is indicative of a potentially irreversible brain-stem injury and, therefore, when positive, supportive of the diagnosis of brain death. Specific criteria must be met prior to attempting an apnea test. In the absence of a history of comorbidities that might predispose to abnormalities in, or blunted responses to, CO₂ retention (e.g. COPD, sleep apnea, and/or morbid obesity), such testing can be diagnostic. Proper conduct of the test involves insuring an adequate blood pressure, preoxygenation with 100% oxygen for at least 10 min with a goal PaO₂ > 200 mmHg, normo-capnia with a ventilatory rate of 10 breaths/min, and a reduction of positive end-expiratory pressure to ~ 5 mmHg. If the patient remains hemodynamically stable and blood saturation remains >95%, then a baseline, pretest, arterial blood gas is obtained. The patient is then disconnected from the ventilator, but given a source of oxygen. A continuous source of oxygen, such as a T-piece or cannula placed directly into the trachea, is mandatory to prevent acute hypoxemia and therefore in validating the test. Continuous monitoring of the patient, looking for any evidence of respiratory function, gasping, or chest rise is required. Any signs of initiating a breath during the test should prompt discontinuation of the test and rule out a diagnosis of “brain death”. Hypotension or desatu-

ration mandate test termination. After 8 min of observation, a repeat blood gas is obtained. If the PCO_2 level is >60 mmHg or 20 mmHg above the baseline, then the test is considered positive and diagnostic of brain death. Longer periods of apnea (10–15 min), provided the patient remains hemodynamically stable, can be used when the initial blood gas results or clinical findings are inconclusive. Unfortunately, patients who require ECMO support often have physiologic conditions that might further challenge apnea testing. For patients being supported on veno-arterial ECMO, pulsatile flow and blood pressures might be too low as mandated by the AAN prior to attempting an apnea test. As discussed above, a systolic blood pressure >100 mmHg is a prerequisite for apnea testing – a threshold that might be very difficult to accomplish in patients on VA-ECMO with non-pulsatile flow in the absence of significant doses of vasoactive agents. In such circumstances, some experts have advocated using mean arterial pressure of 75–80 mmHg as an appropriate surrogate [49].

To compensate for the confounding influence of the inherent ability of the ECMO circuit to not only provide hemodynamic stability, but more importantly, to maintain adequate oxygenation and normal PCO_2 levels, some investigators have proposed modifications of ECMO flows and gas exchange during apnea testing. However, such experiences are limited to a small series of patients. For example, Reddy and colleagues from the Mayo Clinic advocating preoxygenation with 100% oxygen using the ECMO circuit. An initial blood gas is obtained and the ECMO sweep flow was then reduced to 0.5 liters/min to minimize CO_2 removal while providing some degree of continuous oxygen support. It has been advocated that at minimal sweep levels, supplemental oxygen (i.e. given directly to the trachea or airways) is not necessary. With an adequate flow (75–80% of cardiac output) and oxygen through the ECMO, significant decreases in PO_2 and hypoxemia should not occur [47]. Patients were disconnected from the ventilator and after 8 min of observation (for clinical evidence of a respiratory drive), a repeat blood gas was obtained. In two patients, a rise in PaCO_2 over 60 mmHg or greater than 20 mmHg above baseline was reported, which confirmed brain death [50]. This group of investigators also reported a series of three critically ill patients on ECMO support, each of who experienced catastrophic neurologic complications consistent clinically with brain death. However, in each of these patients, apnea testing could not be safely performed due to the absence of a defined protocol and hemodynamic instability. Nevertheless, they advocated the use of apnea testing using the protocol they described in their initial patients to assist in the timely diagnosis of brain death in appropriate patients. The benefits of a timely and definitive diagnosis include increased potential for organ donation, decreased resource utilization in futile cases, and most importantly definitive information for the family [51]. Such testing can be difficult because decreasing the sweep gas too much may theoretically result in a significant hypoxemia – and mandate cessation of the test – before a significant increase in PaCO_2 can occur to yield a definitive result [52].

Because apnea testing is dependent on intrinsic brainstem response to initiate a breath in the setting of increasing levels of carbon dioxide, it has been suggested that in patients treated with ECMO the addition of exogenous CO_2 could safely and more efficiently facilitate this test. A significant concern for apnea testing is the ability to safely provide an oxygen source during testing. Oxygen deprivation, particularly in an already compromised and potentially

brain injured patient, may worsen an anoxic injury. While ECMO is used to eliminate CO₂ (while supplementing oxygen), in theory, ECMO can be used to increase PaCO₂ levels. Pirat and colleagues describe the addition of a CO₂ source to the ECMO circuit gas blender and the flow was initiated at 0.5 liters/min and titrated to an end titer of CO₂ of 60 mmHg. The PaO₂ level was then confirmed with blood gas after a period of clinical observation. They suggested that the addition of carbon dioxide was safer by minimizing hypoxemia and hemodynamic instability that might come with the removal of ventilatory (or gas sweep/flow) support [53]. Clearly, while such an approach sounds intriguing and physiologically possible, confirmatory studies are necessary prior to wider use.

8. Conclusions

Without a doubt, ECMO has proven to be a valuable therapy for patients with severe acute respiratory and/or cardiac failure. Early initiation of the therapy, prior to the development of irreversible end-organ function, has been shown to improve outcomes in critically ill patients. Unfortunately, despite improved technologies, earlier and more aggressive therapy and a better understanding of the complex pathophysiology and human-extracorporeal circuit interface, complications are still common. Neurologic complications, either as a function of preECMO comorbidities, presenting illnesses, or as a consequence of the intricacies of either veno-veno or veno-arterial support are unfortunately not uncommon. Such complications can manifest in a variety of anoxic, embolic, hemorrhagic, metabolic, or functional ways and are often a source of significant morbidity and mortality. Early and aggressive monitoring, diagnostic testing, optimization of cerebral perfusion, and oxygenation might not prevent complications, but might limit their impact by allowing for optimization of neuroprotective interventions. In addition, earlier testing might also provide better prognostic implications of therapy and allow for optimal resource utilization, including patient selection for ECMO. As many patients experience neurologic complications, even in the absence of definitive and comprehensive testing, a more thorough understanding of the problem will allow for better management tools and therapies. Hopefully, this review not only illustrates the complex scope of this problem but provides the foundation for further explorations into how to better protect the brain while on extracorporeal membrane oxygenation support.

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