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Evaluation, Treatment, and Impact of Neurologic Injury in Adult Patients on Extracorporeal Membrane Oxygenation: a Review

Benjamin Illum, MD[1]
Mazen Odish, MD[2,*]
Anushirvan Minokadeh, MD[1,3]
Cassia Yi, APRN, MSN, CNS[4]
Robert L. Owens, MD[2]
Travis Pollema, DO[5]
Jamie Nicole LaBuzetta, MD[1]

Address
[1]Department of Neurosciences, Division of Neurocritical Care, La Jolla, USA
[*,2]Department of Medicine, Division of Pulmonary, Critical Care, and Sleep Medicine, 9300 Campus Point Drive Mail Code #7381, La Jolla, CA, 92037-7381, USA
Email: modish@health.ucsd.edu
[3]Department of Anesthesiology, Division of Critical Care, La Jolla, USA
[4]Department of Nursing, Clinical Mechanical Circulatory Program Coordinator, La Jolla, USA
[5]Department of Surgery, Division of Cardiovascular and Thoracic Surgery, La Jolla, USA

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Abstract

Purpose Extracorporeal membrane oxygen (ECMO) is increasingly used as an advanced form of life support for cardiac and respiratory failure. Unfortunately, in infrequent instances, circulatory and/or respiratory recovery is overshadowed by neurologic injury that can occur in patients who require ECMO. As such, knowledge of ECMO and its implications on diagnosis and treatment of neurologic injuries is indispensable for intensivists and neurospecialists.

Recent findings The most common neurologic injuries include intracerebral hemorrhage, ischemic stroke, seizure, cerebral edema, intracranial hypertension, global cerebral hypoxia/anoxia, and brain death. These result from events prior to initiation of ECMO, failure of ECMO to provide adequate oxygen delivery, and/or complications that occur during ECMO. ECMO survivors also experience neurological and psychological sequelae similar to other survivors of critical illness.
Summary Since many of the risk factors for neurologic injury cannot be easily mitigated, early diagnosis and intervention are crucial to limit morbidity and mortality from neurologic injury during ECMO.

Introduction to extracorporeal membrane oxygenation

Extracorporeal membrane oxygenation (ECMO) is the most advanced level of life support used in the setting of cardiac and/or respiratory failure refractory to conventional medical therapies [1, 2]. By temporarily performing the work of the heart and/or lungs, ECMO preserves and promotes recovery of vital organ function and allows time for possible recovery of the cardiovascular and/or respiratory systems. Although definitive mortality data are lacking for many conditions in which ECMO is employed, there is growing interest in its use, and the clinical indications for which ECMO is initiated have expanded in recent years.

The utilization of ECMO in adult patients in the USA increased substantially in the last decade from 1830 cases in 2007 to 8673 in 2019 [3, 4] (see Fig. 1). Its use has further increased in 2020 due to severe acute respiratory distress syndrome (ARDS) associated with the SARS-CoV-2 pandemic [5, 6]. Many patients who might otherwise have died are able to return to a meaningful quality of life as a result of this revolutionary technology. However, neurologic injuries can occur while on ECMO and can be devastating. The reported incidence of such injuries ranges widely from 1 to 78% with a median of 13% [7–10]. As utilization of ECMO becomes more mainstream, the overall prevalence of associated neurologic injuries is also expected to increase.

There are two types of ECMO therapy: veno-venous ECMO (VV ECMO) and veno-arterial (VA ECMO). VV ECMO removes blood from the venous system and returns it to the venous system. It is used in severe respiratory failure and provides only respiratory support (adding oxygen to and removing carbon dioxide from the blood). Therefore, the use of VV ECMO requires sufficient intrinsic cardiac output to perfuse vital organs [4]. In contrast, VA ECMO removes blood from the venous system and returns it to the arterial system [5]. VA ECMO is used in patients with impaired cardiac function. In addition to providing organ perfusion when the heart is unable to do so, it also provides respiratory support.

The ECMO circuit consists of a drainage (inflow or venous) cannula, a mechanical pump, a membrane oxygenator, and a return (outflow or arterial) cannula. Venous blood enters the circuit via the inflow cannula and is driven forward by the mechanical pump. Oxygen (O_2) and sweep gas (air) flow into the membrane oxygenator where oxygen is added and carbon dioxide (CO_2) is removed from the blood. Gas bubbles, thrombi, and other particulate matter are also filtered out in the membrane oxygenator. Blood is then reinfused into a large vein (e.g., superior vena cava) or large artery (e.g., abdominal aorta) via the outflow cannula (see Fig. 2). Blood O_2 and CO_2 levels are modulated by adjusting the fraction of delivered O_2 and the sweep gas flow rate (typically 1–15 l/min), respectively. CO_2 removal is proportional to the sweep gas flow rate.

Initiation and maintenance of ECMO alter normal blood flow, O_2 delivery, CO_2 clearance, and hemostasis. These changes affect cardiovascular and cerebral physiology, as well as coagulation in ways that increase risk for neurologic injury. Additionally, there are intrinsic aspects of ECMO that make it

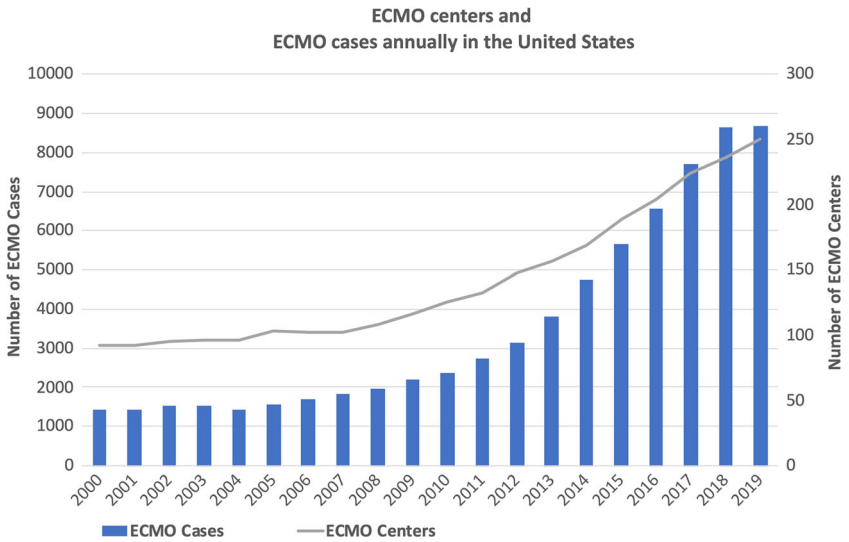

Fig. 1. Annual numbers of ECMO centers and ECMO cases in the USA reported to Extracorporeal Life Support Organization. The number of ECMO cases in 2019 is under-reported at the time of this review.

more difficult to diagnose and treat these injuries if they do arise. Therefore, an understanding of ECMO and its implications on diagnosis and management of associated neurologic conditions is essential for intensivists and neurological specialists.

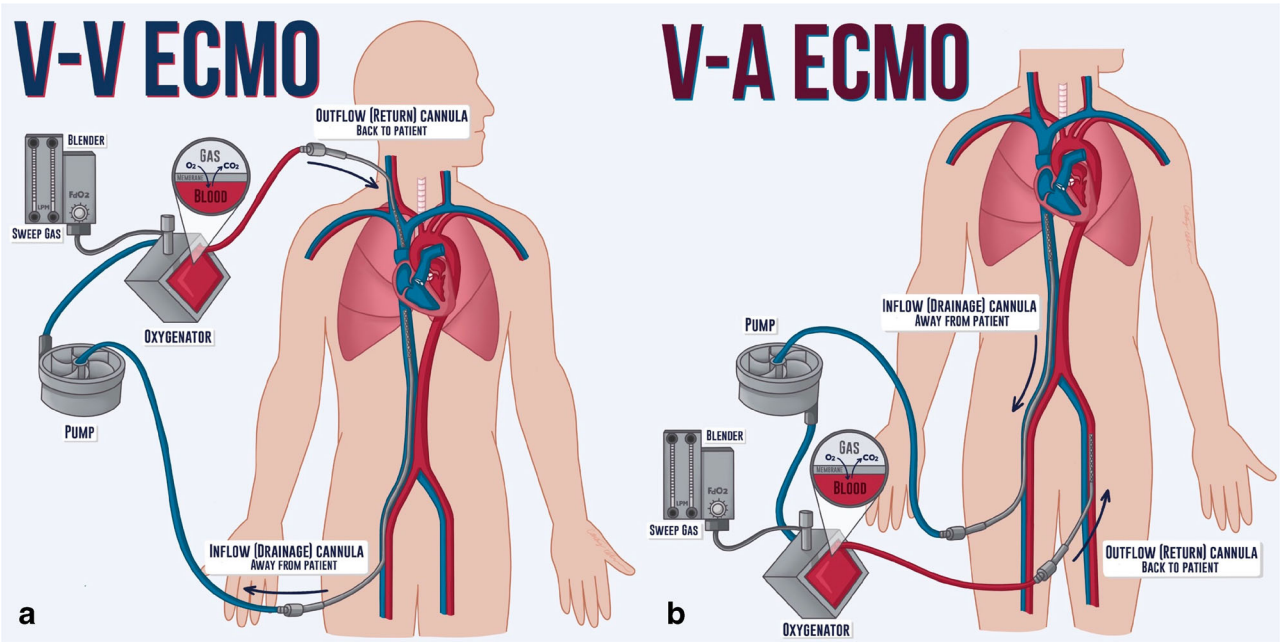

Fig. 2. (**a**) Veno-venous (V-V) ECMO with a duel site cannulation. Drainage cannula inserted into the right femoral vein and return cannula in the right internal jugular vein. (**b**) Veno-arterial (V-A) ECMO, with a duel site cannulation, with the drainage cannula inserted into the right femoral vein, and the return cannula to the left femoral artery. Credit: Catherine Cichon, MD, MPH.

Implications of ECMO on diagnosis and treatment of neurologic injuries

As mentioned above, there are aspects of ECMO that make it more difficult to diagnose and treat acute neurologic injury.

Sedation

Frequent neurologic examination of an awake, interactive patient is the optimal monitor for acute neurologic injury. Unfortunately, the ability to perform and accurately interpret the neurologic examination is limited in many ECMO patients due to deep levels of sedation and, in some cases, by the administration of neuromuscular blockade (NMB). Deep sedation and NMB may be required in some patients prior to consideration for ECMO. However, it is often possible to discontinue NMB and dramatically reduce the depth of sedation once ECMO is initiated. The goal of sedation is to keep the patient calm and comfortable while preserving the neurologic exam. In this context, most of the cranial nerve reflexes and limited motor and sensory function can be tested even while on low-to-moderate levels of sedation. These examinations should be performed at regular intervals to verify the integrity of the central nervous system. Therefore, in addition to the benefits of minimizing sedation in all ICU patients [11], maintaining the neurologic exam allows for early diagnosis of neurologic injuries in ECMO patients.

There is now momentum among many ECMO centers toward discontinuing NMB, reducing sedation, and even keeping patients completely awake when feasible. However, there is a paucity of data to guide sedation and NMB in ECMO patients, and the limited guidelines that currently exist are based largely on expert opinion (see Fig. 3). Sedation strategies must take into account changes in plasma concentrations of opioid, anxiolytic, and sedative-hypnotic agents caused by hemodilution due to addition of priming solution, sequestration due to nonspecific binding to circuit components, and impaired metabolism and clearance due to hepatic and renal dysfunction. The volume of distribution of commonly used sedation agents such as fentanyl, propofol, and midazolam is increased, and much higher than normal doses are often required to achieve sedation goals [12]. Furthermore, after continuous infusions of such agents are discontinued, sequestered drug is released back into the plasma, which prolongs sedation in an unpredictable manner [13]. Importantly, changes to the circuit, such as replacing a clogged filter or oxygenator, can reset this process in unpredictable ways. Given these complexities, a more practical approach is to preserve the neurologic exam and use it as a guide to depth of sedation when feasible.

Challenges to obtaining neuroimaging

Neuroimaging modalities such as magnetic resonance imaging (MRI), computed tomography (CT), CT angiography, and CT perfusion scans are standard diagnostic tools used to assess acute neurologic injuries. However, obtaining these studies in ECMO patients must take into account a number of considerations, including incompatibility of ECMO circuit components with MRI,

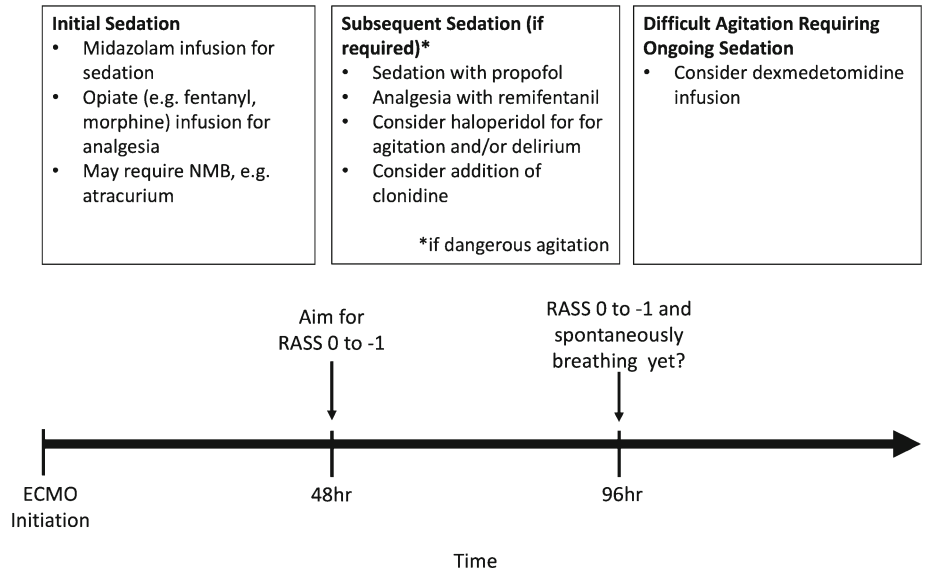

Fig. 3. Sedation guidelines, adapted from Extracorporeal Life Support Organization recommendations with modifications. NMB, neuromuscular blockade.

logistics of transport, timing of contrast administration, and interpretation of contrast-enhanced CT imaging in the setting of altered blood flow patterns.

The ECMO circuit has necessary components that are not compatible with MRI. Therefore, this valuable imaging modality is unobtainable until after decannulation and removal of the ECMO pump. Confirmation of a clinical diagnosis of cerebral ischemia, hypoxic/ischemic encephalopathy, or subtle intracranial hemorrhage is limited, and clinicians must rely on non-MRI modalities such as CT head to evaluate acute brain injury.

While portable CT scanners exist, they are not widely available. As such, patients must be transported to a stationary CT scanner in many cases. Similar to other critically ill patients, this requires substantial staffing resources and time to achieve [14]. The skillsets of multiple providers are required including bedside nurses, respiratory therapists, perfusionists/ECMO specialists, and sometimes physicians. Additional personnel are usually needed to assist in the movement of the bed, ventilator, ECMO circuit, and pumps for intravenous infusions. Care must be taken to not dislodge vital life support devices during movement through the halls, elevators, and onto and off of the imaging table. Our center performs annual ECMO transfer training and simulation with our nursing ECMO specialists.

Contrast-enhanced head CT is useful for evaluation of acute ischemic stroke and other enhancing abnormalities such as abscess. Under normal physiological conditions, contrast is injected into a peripheral vein, passes through the right heart, pulmonary vascular system, and left heart before reaching the cerebral vasculature; the timing of contrast enhancement of cerebral arteries and veins depends on intrinsic cardiac output, and a bolus tracking system is used to identify the arterial and venous phases of contrast enhancement.

In ECMO patients, intravenously injected contrast is directed into the inflow cannula, transits the ECMO circuit, and returns to patient circulation via the outflow cannula. In VV ECMO, the contrast returns to the central veins. Since

cardiac output is relatively preserved, bolus tracking is performed in the usual manner [15]. However, imaging technicians who protocol these studies should be made aware that there is a delay of contrast enhancement due to ECMO circuit transit time [16]. Reducing ECMO flows briefly, if tolerated, during the contrast injection mitigates this effect.

In VA ECMO, intravenous contrast diverted to the ECMO circuit is returned to the aorta, and contrast enhancement of cerebral vessels depends on retrograde flow into the aortic arch. Retrograde filling is proportional to ECMO pump flow rate and is opposed by residual left ventricular (LV) function [16]. If there is little-to-no intrinsic LV function, enhancement of cerebral vessels is more rapid and symmetric. Conversely, if LV function is relatively preserved, un-opacified cardiac output will preferentially fill the right-sided cerebral circulation, while the opacified ECMO flow preferentially fills the left-sided cerebral circulation. This results in asymmetric enhancement of the left and right head and neck vessels [15]. As with VV-ECMO, this can be partially mitigated by briefly decreasing the ECMO flow rate if hemodynamically tolerated [15].

Lastly, air bubbles generated during contrast administration pose a unique challenge in VA ECMO. An air bubble detector senses the presence of air in the circuit and turns off the pump to avoid introducing arterial air emboli. Patients that are highly reliant on ECMO flow for mechanical circulatory support will not tolerate this transient loss of flow. However, if this function is turned off during contrast injection, air bubbles might enter the arterial circulation and embolize to the brain.

Anticoagulation strategies on ECMO

Despite advances in biocompatibility and reduced size of ECMO circuits, interaction between the blood and circuit still results in a prothrombotic state. As a result, anticoagulation is needed to maintain the circuit's integrity and minimize clot formation in the membrane oxygenator. There are multiple anticoagulation strategies employed when initiating ECMO therapy, and these vary by center. In general, therapeutic anticoagulation is necessary in VA ECMO to prevent arterial thromboembolism. Anticoagulation is also used for VV ECMO; however, it can be held for prolonged periods of time or sometimes not started at all. The Extracorporeal Life Support Organization (ELSO) publishes general guidelines on anticoagulation during the initiation and maintenance of ECMO [17–20].

Neurologic injuries in ECMO patients

The same major neurological injuries occur with both VV and VA ECMO, but at different rates. According to a retrospective review of patient data collected in the ELSO registry for VV ECMO (includes 4988 adults treated from 1992 to 2015), the most commonly reported neurologic injuries were intracranial hemorrhage (3.6%), brain death (2%), ischemic stroke (1.7%), and seizure (1.2%) [21••]. Contrast this with ELSO registry data for VA ECMO (includes 4522 adults treated between 1992 and 2013), where the most commonly reported neurologic injuries were brain death (7.9%), ischemic stroke (3.6%), seizure (1.8%), and intracerebral hemorrhage (1.8%) [22]. Despite significant

improvements in ECMO technology and understanding of its application, more recent observational studies in adult patients treated at an advanced ECMO center indicate that both intracranial hemorrhage and ischemic injury are still common: the reported incidences of intracranial hemorrhage and ischemic stroke in VV ECMO (135 patients) are 7.5% and 2%, respectively, and 2.8% and 5.3% in VA ECMO (878 patients), respectively [23, 24••].

Intracranial hemorrhage

Intracranial hemorrhage (ICH) includes non-traumatic, spontaneous intraparenchymal hemorrhage, subarachnoid hemorrhage, and subdural hemorrhage. Interestingly, it is reported that 85% of ICH are present on the head CT performed shortly after cannulation [25]. However, the percentage of ICH that is present prior to cannulation and anticoagulation is unknown. For this reason, some institutions now include a head CT in their screening protocol prior to cannulation (as safety permits). If a patient is too unstable or was placed on mobile ECMO at an outside institution, then many centers will obtain a head CT after ECMO cannulation.

The exact mechanisms by which ICH occurs are unknown. Cavayas et al. propose a two-step process wherein there is first some injury to the blood-brain barrier followed by propagation of hemorrhage due to impaired hemostasis [26]. This is certainly true in hemorrhagic conversion of ischemic strokes which occur on ECMO and is also consistent with many—but not all—of the risk factors which have been identified in retrospective analyses. Some risk factors are unfortunately intrinsic to ECMO itself, such as the use of systemic anticoagulation, duration of ECMO, hematologic derangements due to hemolysis and platelet consumption, and rapid correction of arterial CO_2 (P_aCO_2) levels after initiation of ECMO (which may result in an ischemic area that is more susceptible to hemorrhagic conversion). Other identified risk factors are intrinsic to the patient or related to the nature and severity of the underlying disease process. These include younger age, female gender, use of anticoagulation or antiplatelet medications prior to ECMO, pre-ECMO cardiac arrest, sepsis, influenza, renal failure, and renal replacement therapy [21••, 22, 23, 24••, 26–31].

Treatment for ICH should generally follow standard guidelines, including stopping anticoagulation and strict blood pressure control. There is little data regarding reversal of anticoagulation on ECMO as part of the treatment of ICH. Generally, our institutional practice is to avoid reversal of anticoagulation; however, this is a decision that must be made with caution, weighing the relative risks of hematoma expansion against the risk of thrombosing the ECMO circuit which may cause an abrupt and likely life-threatening pause in both VV and VA ECMO. Conversely, cessation of anticoagulation with gradual correction of coagulopathy is generally tolerated for periods of time. However, there is increased risk of arterial thromboembolic events with prolonged cessation of anticoagulation on VA ECMO [32–35]. The optimal time period for reinstitution of anticoagulation has not been well-studied. Visual inspection of the ECMO circuit for clot formation and monitoring circuit pressure to identify impending oxygenator failure may provide guidance for ongoing discussions regarding the risk/benefit ratio of resuming anticoagulation.

Ischemic stroke

Ischemic stroke occurs more commonly in VA ECMO [21••, 22, 23, 24••] and often results from either disruption of arterial atheromas during cannulation of large arteries or from embolic thrombi that originate within the circuit or at the tip of the outflow cannula. In patients with atrial fibrillation or VA ECMO patients with poor cardiac function, thrombi may be cardioembolic in origin. Ischemia can also result from microthrombi or more rarely from arterial air emboli.

There are no formal guidelines on the best practice for treatment of ischemic stroke in ECMO patients. In many cases, it is impossible to determine a last known well time due to sedation, NMB, or lack of detailed neurologic examinations. Furthermore, thrombolytic therapy is usually contraindicated in patients with active anticoagulation. While experience is limited, there are case reports of improved outcomes with mechanical thrombectomy in VA ECMO patients [36]. Therefore, in cases where CT angiography reveals a large vessel occlusion, mechanical thrombectomy should be considered.

Seizure

Abnormal electroencephalography (EEG) is noted in 50–80% of ECMO patients with electrographic seizures reported in 8–20% of patients [37]. While it may be necessary to monitor continuous EEG for 24–48 h to capture electrographic seizures, many centers do not have the resources to do so. A common practice is to perform intermittent EEG monitoring for 30 min to several hours. While it may be difficult to obtain, continuous EEG should be considered in patients with focal and global neurologic deficits which are not completely explained by brain imaging.

Seizure activity can be secondary to ICH, embolic infarcts, or global cerebral hypoxia/anoxia. When detected it should be aggressively treated with antiepileptic medications (AEDs) and by increasing sedative hypnotic agents (e.g., propofol). Severe cases of status epilepticus may require prolonged burst suppression and multiple AEDs to adequately treat. Other epileptiform activity such as triphasic waves, polyspikes, and generalized and lateralized epileptiform discharges suggests focal or global cerebral injury and may warrant treatment depending on the clinical scenario. As with sedative medications, AEDs have altered pharmacokinetics in ECMO patients [12], and plasma drug levels should be monitored if clinically available.

Cerebral edema and intracranial hypertension

Large hematomas and ischemic strokes may result in cerebral edema which puts the patient at risk for cerebral herniation syndromes. Additionally, cerebral artery dysautoregulation is associated with non-pulsatile arterial flow during short runs of cardiopulmonary bypass [38, 39]. This phenomenon may be even more pronounced during long periods of VA ECMO and could predispose to abrupt changes in cerebral blood flow, thereby contributing to cerebral edema and intracranial hypertension. Intracranial pressure monitoring may be indicated, and elevated pressures should be aggressively managed when necessary. Protocols exist for the treatment of malignant edema and intracranial hypertension [40, 41]. In severe, refractory cases, craniectomy may be helpful to decompress the affected intracranial compartments [36]. While systemic

anticoagulation does increase the risk of severe bleeding complications associated with neurosurgical intervention, it is not an absolute contraindication. Furthermore, in most cases, anticoagulation can be stopped temporarily to reduce this risk.

Hypoxic ischemic encephalopathy

Inadequate oxygen delivery to the brain results in hypoxic ischemic encephalopathy (HIE). HIE may be due to conditions that occur before ECMO is initiated (e.g., severe respiratory failure) or to failure of ECMO to provide adequate oxygen delivery to the brain [42]. In normal circumstances, the primary determinants of cerebral oxygen delivery are arterial oxygenation and cerebral blood flow (CBF).

Arterial oxygen content can be reduced in patients on VV ECMO by high cardiac output states (which will overwhelm the ability of ECMO to provide oxygenated blood) and by severe lung disease (in which there is increased intrapulmonary shunting). Reduced cerebral arterial oxygen content can also be seen in VA ECMO, especially when there is preserved or improving intrinsic LV function and persistent respiratory failure. This results in a condition known as Harlequin syndrome, wherein the native LV output perfuses the brain with poorly oxygenated blood (returning to the heart from the diseased lungs), while ECMO-driven flow of oxygenated blood is directed to the abdominal organs and lower extremities. For this reason, arterial blood is usually sampled away from the return cannula (e.g., right radial artery for a femoral return cannula) to determine gas exchange abnormalities experienced by the brain. Cerebral hypoxia may be a factor in developing cerebral injury, and patients with cerebral desaturations have worse outcomes [43].

Cerebral blood flow results from a dynamic balance of mean arterial pressure (MAP), intracranial pressure, cerebral venous outflow, P_aCO_2, and vasoreactivity. Insufficient CBF results in cerebral ischemia, while excess CBF causes cerebral hyperemia. It is generally accepted that cerebral autoregulation maintains steady CBF over a wide range of MAPs through cerebral blood vessel vasoreactivity. Insufficient CBF occurs when the MAP falls below the lower limit of autoregulation (unique to each person). Importantly, the cerebral autoregulation curve may be right shifted in patients with chronic hypertension, such that a higher MAP is required to maintain CBF and avoid ischemia. Impaired autoregulation presents an additional challenge. Up to 24% of patients on cardiac bypass have signs of impaired autoregulation [39], and this may be applicable in ECMO as well because of non-pulsatile blood flow (VA ECMO), increased cerebral vascular resistance from rapid correction of arterial CO_2 (VV ECMO), or other unknown causes [7, 18]. In these patients with impaired autoregulation, CBF is reliant on systemic blood pressure, and the range of safe pressures (resulting in sufficient perfusion without hyperemia) is much narrower.

Brain death

Despite the best therapeutic interventions, patients with acute brain injury may progress to irreversible coma and brainstem areflexia consistent with brain death. However, the diagnosis of brain death while on ECMO poses some challenges. First, VA ECMO patients with severely reduced intrinsic cardiac

function do not have a measurable systolic blood pressure (SBP); MAP is used in these patients to monitor perfusion. However, current AAN guidelines for brain death stipulate a minimum SBP measurement with no mention of MAP criteria [44, 45]. Secondly, the apnea test may not be technically feasible in patients on ECMO because it is either impossible to achieve a sufficient baseline PaO2 in patients with severe respiratory failure or it is challenging to achieve the required rise in PaCO2 without turning the sweep gas flow rate significantly down or off. However, traditional oxygenators require a minimal sweep flow, and oxygenation will not occur when sweep flow rate equals 0 L/min. Although some authors have suggested methods for successful apnea testing on ECMO [46], these strategies are not often employed. In accordance with AAN guidelines, if an apnea test is aborted, inconclusive, or cannot be completed, ancillary testing is required. However, the routinely used ancillary tests are also complicated by ECMO and have not been specifically validated in this population [46]. Current brain death guidelines do not account for use of supportive therapies such as ECMO, and additional research is required to devise a national standardized protocol.

Neuromonitoring adjuncts in the setting of ECMO

In addition to the neurologic exam, technologies that provide continuous or intermittent neurologic monitoring include serial computed tomography (CT) scans, transcranial Doppler (TCD), near-infrared spectroscopy (NIRS), and EEG (quantitative or otherwise). Alone or in combination, these provide useful information regarding neurologic function. Given the increased risk posed by undetected brain injury in patients on ECMO, the use of such neuromonitoring adjuncts should be considered. Although a full review of neuromonitoring techniques is outside the scope of this manuscript, it has been explored in detail in other literature [47•]. Table 1 notes some modalities that may serve as surrogates for the neurologic exam. However, none of these has yet to be widely adopted nor has any shown a significant impact on outcomes measures.

CT and MR imaging—as well as the limitations of these modalities—have been discussed elsewhere is this review. TCD and NIRS monitor surrogate measures of cerebral flow and autoregulation [48–50]. While TCD measures flow velocity, NIRS measures regional oxygen saturation by determining the relative concentrations of oxygenated and deoxygenated hemoglobin in the cerebral circulation [51–53]. While definitive data is lacking, TCDs and NIRS might be utilized in ECMO patients to guide optimization of cerebral arterial oxygenation and CBF. TCD can also detect microemboli arising from the ECMO circuit in real time.

EEG monitoring can be used intermittently or continuously to evaluate for changes in either generalized or focal background. Modules that quantitatively process EEG waveforms may reduce the time needed to review hours of recordings and can alert providers to early problems such as seizures and cerebral dysfunction (due to ischemia and other causes). For example, a reduction of the ratio between alpha (8–13 Hz) and delta (<4 Hz) frequencies along with an increase in slower frequencies can identify cerebral ischemia before neurologic deficits or changes in head CT become evident [54, 55]. However, any findings identified by a non-epileptologist will need to be confirmed by those credentialed to read EEG.

Table 1. Monitoring strategies for patients undergoing ECMO therapy, including advantages and limitations

	Utility and regions monitored	Advantages	Limitations
Neurologic exam	Cranial nerves, language comprehension, motor, sensory, rarely gait	Clinically accurate reflection of neurologic function, can trend over time to detect neurologic deterioration	Often limited by sedation or other pharmacological therapy
Computed tomography (CT) and CT angiography	Brain parenchyma, ventricular system, and brain vasculature	Portable CT if available, rapid acquisition	Transport, IV contrast timing must be coordinated based on VA or VV cannulation, does not rule out acute ischemia, no information on dynamic cerebral hemodynamics
Magnetic resonance (MR) imaging and magnetic resonance angiography	Brain parenchyma, ventricular system, and brain vasculature	Characterizes edema, masses, and early ischemia with higher sensitivity than CT and may be useful for evaluation of neurologic injury post-ECMO	MR modalities incompatible with ECMO circuit. Long duration, no information on dynamic cerebral hemodynamics
Transcranial Doppler ultrasound	Blood flow in cerebral vasculature: internal, middle cerebral, posterior cerebral, and basilar arteries	Provides blood flow velocity. Real-time microemboli detection, non-invasive, portable	Only rarely offers continuous monitoring. Can be operator dependent
NIRS	Frontal lobe, measures regional cerebral oxygenation	Continuous, non-invasive scalp electrode	Uses regional oxygenation to estimate global function
EEG	Superficial cortical areas	Seizure detection, minimally invasive	Limited resource, artifact from ECMO circuitry

IV intravenous, *VA* veno-arterial, *VV* veno-venous, *NIRS* near-infrared spectroscopy, *EEG* electroencephalogram

Neurocognitive outcomes following ECMO

Depending on the underlying reason for initiation of ECMO, published survival rates are variable and dependent on multiple factors [56–61]; however, recovery after ECMO means more to many patients than just surviving their critical illness. Adverse events such as the ones described within this review impact outcomes greatly, and any of these events may individually or synergistically jeopardize brain integrity [47•]. For the purposes of this section, we will focus on long-term neuropsychological outcomes in ECMO survivors with or without cerebral injury.

Long-term neurological outcomes that are associated with critical illness are also seen in ECMO patients. These include impaired memory, psychiatric disturbance, chronic pain, motor disability, neuropathy and sensory deficits, hearing loss, and visual deficits [61–63]. All of these can potentially impact health-related quality of life and social recovery. That said, in the CESAR trial [64], no difference was demonstrated in health-related quality of life measures between surviving patients with severe respiratory failure randomized to ECMO versus the control group. However, only 50% of survivors in both groups had follow-up information available for analysis. In another study evaluating multi-modality outcomes in 28 adult patients at 5-year (on average) follow-up, 43% of patients had impaired neuropsychological performance (especially in the domains of attention and verbal memory), 52% had abnormal neuroimaging (seen more frequently following VA ECMO than VV ECMO), and 43% had pathological electrophysiological studies, even though EEG findings did not correlate with neuropsychological performance or neuroradiographic abnormalities [62]. Neuroradiographic complications were associated with poorer cognitive performance, though radiographic abnormalities are not always associated with overt clinical syndromes.

Post-intensive care syndrome is a described phenomenon in critically ill patients [65], and the neuropsychological impact of critical illness is also seen in ECMO patients with or without overt neurologic injury. Although their 36-Item Short Form Survey psychological domain is comparable to the general population [66], studies have identified that patients surviving to 6-month follow-up or longer have persistent emotional and mental health difficulties [61, 66–68, 69•, 70]: depression (20–42%), anxiety (20–55%), and post-traumatic stress (PTS) symptoms (5–47%). The rates of psychological sequelae are unrelated to the duration of ECMO or length of follow-up [61, 67]. Return to work is only seen in 50–65% of patients receiving ECMO for ARDS [61–63]. Moreover, informal caregivers (often family members) suffer from increased rates of depression, anxiety, and PTS disorders as well [65], with significant correlation between mental health sequelae in patients and their informal caregivers following VV ECMO for ARDS [69•]. These rates of neuropsychological sequelae may not differ substantially when compared with survivors of severe ARDS without ECMO [70], but they do highlight the need for intense follow-up that includes physiological and psychological evaluation and support for patients and their loved ones [71]. Such follow-up can be performed in an ICU recovery clinic [72, 73], which is the standard of practice at our institution.

Conclusions

ECMO is a lifesaving technology that is increasingly utilized for mechanical circulatory and respiratory support. While it has many benefits, uncommon devastating neurologic injuries contribute to significant morbidity and mortality. Overall, the incidence and severity of these injuries are likely underestimated due to lack of continuous monitoring of neurologic function, inability to obtain frequent, reliable neurologic examinations, and limitations of diagnostic imaging in ECMO patients. Moreover, some neurologic injuries may never be identified due to withdrawal of ECMO without any attempt at neurologic evaluation in patients who fail to recover cardiac or pulmonary function.

Clinicians should be vigilant in minimizing sedation, performing frequent neurologic assessments, and utilizing available monitoring technologies. Suspected and confirmed neurologic injuries should be proactively monitored and managed to minimize further injury. The role of highly trained neurologists—and, where available, neurointensivists—in evaluating and guiding management of neurologic injuries associated with ECMO cannot be overemphasized. Further research is necessary to determine optimal sedation and anticoagulation strategies, validate neuromonitoring adjuncts, identify interventions to improve long-term outcomes in survivors, and develop a standardized protocol for diagnosis and declaration of brain death.

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Compliance with Ethical Standards

Conflict of interest

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Papers of particular interest, published recently, have been highlighted as:

- • Of importance
- •• Of major importance

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