



Neurological monitoring in ECMO patients: current state of practice, challenges and lessons

Hassan Aboul-Nour^{1,2} · Ammar Jumah² · Hafsa Abdulla³ · Amreeta Sharma³ · Bradley Howell² · Namita Jayaprakash⁴ · Jayna Gardner-Gray^{3,4}

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Abstract

Background Extracorporeal membrane oxygenation (ECMO) in critically ill patients serves as a management option for end-stage cardiorespiratory failure in medical and surgical conditions. Patients on ECMO are at a high risk of neurologic adverse events including intracranial hemorrhage (ICH), acute ischemic stroke (AIS), seizures, diffuse cerebral edema, and hypoxic brain injury. Standard approaches to neurological monitoring for patients receiving ECMO support can be challenging for multiple reasons, including the severity of critical illness, deep sedation, and/or paralysis. This narrative literature review provides an overview of the current landscape for neurological monitoring in this population.

Methods A literature search using PubMed was used to aid the understanding of the landscape of published literature in the area of neurological monitoring in ECMO patients.

Results Review articles, cohort studies, case series, and individual reports were identified. A total of 73 varied manuscripts were summarized and included in this review which presents the challenges and strategies for performing neurological monitoring in this population.

Conclusion Neurological monitoring in ECMO is an area of interest to many clinicians, however, the literature is limited, heterogenous, and lacks consensus on the best monitoring practices. The evidence for optimal neurological monitoring that could impact clinical decisions and functional outcomes is lacking. Additional studies are needed to identify effective measures of neurological monitoring while on ECMO.

Keywords ECMO · ECLS · Neurologic Monitoring · Neuromonitoring · Cerebrovascular accidents · Ischemic stroke · Hemorrhagic stroke

Abbreviations

ECMO Extracorporeal membrane oxygenation
ECLS Extracorporeal life support
ICH Intracerebral hemorrhage

MRI Magnetic resonance imaging
NCCT Non-contrast computed tomography
CTA CT angiography
CTP CT perfusion
CBF Cerebral blood flow
CCA Conventional cerebral angiogram
CMB Chronic microbleed
MES Microembolic signals
TCD Transcranial doppler
MFV Mean flow velocity
EEG Electroencephalography
SSEP Somatosensory evoked potential

Hassan Aboul-Nour and Ammar Jumah contributed as co-first authors.

✉ Hassan Aboul-Nour
aboulnourh@gmail.com

- ¹ Department of Neurology, Emory University, Atlanta, GA, USA
- ² Department of Neurology, Henry Ford Hospital, Detroit, MI, USA
- ³ Division of Pulmonary and Critical Care Medicine, Henry Ford Hospital, Detroit, MI, USA
- ⁴ Department of Emergency Medicine, Critical Care Medicine, Henry Ford Hospital, Detroit, MI, USA

Background

Extracorporeal membrane oxygenation (ECMO), a type of extracorporeal circulatory life support (ECLS), is a form of mechanical cardiopulmonary support utilized for end-stage cardiorespiratory failure that is refractory to maximal medical therapy. Since its introduction by Gibbon in 1953, major advances have been made to its technique and application, allowing for prolonged survival of some of the most fatal medical and surgical conditions [1]. Standard approaches for evaluating the neurological status of these patients are challenging during ECMO support. In this narrative literature review, we provide an overview of these challenges and available strategies for performing a neurological assessment in this patient population.

Methods

We performed a search in July 2021 using PubMed. The terms “ECMO”, “ECLS”, “Neurologic Monitoring”, “EEG”, “Neuroimaging”, “Transcranial Doppler”, “Somatosensory Evoked Potential”, “COVID-19” and “Neuromonitoring” were used either individually or in combination. The results of the search highlighted 73 relevant articles which were summarized by two critical care fellows and two neurology residents with oversight from a neuro-intensivist and two emergency medicine and critical care physicians who have expertise in ECMO.

REVIEW

ECMO: review of the types of support and indications for use

The two major configurations for ECMO support are veno-venous (V-V) and veno-arterial (V-A) ECMO [2]. V-A ECMO provides respiratory and circulatory support, most often for cases of cardiac arrest, refractory cardiogenic shock, right ventricular failure, as a bridge to cardiac transplantation and in the post-cardiotomy syndrome following cardiac bypass surgery. V-V –ECMO provides respiratory support and is used most often in cases of acute respiratory distress syndrome (ARDS) and severe hypercapnic respiratory failure.

Early data on its use involved small observational studies as well as uncontrolled trials that reported increased survival rates up to 50–71% compared to patients who did not receive ECMO [3–6]. During the 2009 H1N1 influenza A pandemic, the use of V-V ECMO provided a successful organ support for patients with ARDS, failing

conventional ventilation, with survival rates of up to 68% [7]. Additionally, the “Conventional ventilatory support versus extracorporeal membrane oxygenation for severe acute respiratory failure (CESAR trial)” was conducted in 2009. It randomized 180 patients with severe ARDS to either referral to an ECMO center or continued conventional management. This trial found a difference in the 6-month survival rate between the patients referred to the ECMO center and control subjects (63 vs. 47%) and was terminated early due to its futility with findings favoring the use of ECMO support [8]. A major criticism of this trial was the heterogeneous ventilation strategies within the control subjects.

The ECMO to rescue lung injury in severe ARDS (EOLIA trial), published in 2018 examined 249 patients with severe ARDS. It randomized patients to receive early V-V ECMO support or conventional lung-protective ventilation with the use of low tidal volumes and low-pressure ventilation, with the possibility of crossover to ECMO for patients with refractory hypoxemia. They found a significant improvement in oxygenation and days free of renal failure (46 vs. 21%) with lower rates of ischemic stroke (IS) (0 vs 5%) in patients in the ECMO compared to the conventional therapy arm. This trial was also terminated early for futility with findings favoring the use of ECMO. Final analysis showed an 11% improvement in absolute mortality rates with ECMO compared to the control group. Many believe that the EOLIA trial supports early ECMO use in severe ARDS not responding to optimum management strategies involving lung protective ventilation, pulmonary vasodilators, prone ventilation and the use of neuromuscular blockers [9].

Thiagarajan et al. examined data from the extracorporeal life support registry organization (ELSO) from 1989 to 2016, analyzing the use of extracorporeal life support (ECLS) and survival rates. They reported survival to discharge rate of 58% in 78,397 patients who received ECLS [10]. A systematic review of practices and outcomes following V-A ECMO resuscitation for refractory out-of-hospital cardiac arrest in adult patients identified a 22% survival rate amongst the 822 patients who received eCPR. Of the survivors, 13% had good neurological outcomes [11]. More recently in the ARREST (Advanced reperfusion strategies for patients with out-of-hospital cardiac arrest and refractory ventricular fibrillation) trial, 30 patients with out-of-hospital cardiac arrest were randomized to eCPR versus standard advanced cardiac life support. The study was terminated early because the superiority of the ECMO arm exceeded the preplanned endpoint with 43% survival to hospital discharge in the ECMO group versus 7% in the control group [12].

These shifts propelled the utilization of ECMO for organ support and the number of centers providing ECMO have grown exponentially [13].

Neuromonitoring and challenges in ECMO patients

Neurological disturbances impacting patients receiving ECMO may occur during the initiation of ECMO support and as a complication of ongoing ECMO support. Thus, the neurological assessment of the patient is paramount yet presents challenges.

CO₂ reactivity during ECMO

Carbon Dioxide (CO₂) and pH play a significant role and are quite critical in the regulation of cerebral blood flow [14]. Having that said, the abrupt reduction in CO₂ blood levels during the initiation of ECMO Support can facilitate complications including intracranial hemorrhage [15]. The pathophysiological mechanism attributed to this is blood vessels vasoconstriction resulting from hypocapnia. This in turn results in an ischemic infarct and hence, hemorrhagic conversion. This is also precipitated by the systemic anticoagulation frequently used while on ECMO support [16].

Physical examination

The 2017 ELSO guidelines recommend sedation for at least the first 12–24 h of ECMO initiation to prevent air embolism from spontaneous respirations as well as for patient comfort [17]. Thus, the sensitivity of the neurologic exam in patients on ECMO is often compromised due to the use of sedatives, analgesics and sometimes paralytics [18, 19]. The combined central nervous system (CNS) depression due to sedatives and analgesics reduces the level of consciousness and precludes the assessment of higher cortical function. Additionally, deeper levels of pharmacologic CNS depression impair brainstem reflexes. One study reports 24% of patients suffering from neurologic complications while on ECMO had no clinical neurological signs prior to neuroimaging [18].

Neuroimaging

Obtaining neuroimaging to investigate suspected neurological disturbances in ECMO patients poses a challenge. From a technical perspective, contrast-based imaging modalities can be particularly misleading due to ECMO [19, 20]. Logistically, the severity of the critical illness and the degree of mechanical support in patients supported by ECMO poses a challenge for safe transport to radiological testing areas [18]. The instability of the underlying cardiorespiratory illness often requires the availability of multiple team members including respiratory therapists and perfusionists for safe transport to an imaging suite.

Non-contrast computed tomography

Non-contrast computed tomography (NCCT) is a comparably feasible, relatively safe and cost-effective method of neurologic assessment in ECMO patients [18, 21]. Lidegran et al. reviewed 123 consecutive cases of adult and pediatric ECMO patients over a ten-year period. They identified neurologic complications confirmed by NCCT-influenced treatment, ranging from adjusting anticoagulation to weaning ECMO for withdrawal of care in cases of catastrophic insults (ex. diffuse cerebral edema) [18]. In patients sustaining a survivable insult such as focal hemorrhagic or AIS adjustments were made in systemic anticoagulation intensity to facilitate continued ECMO support [18]. No specific lateralization of neurological injury on NCCT was noted in relation to the side of cannulation [18]. LaRovere et al. showed that 41% of patients treated with ECMO had bilateral infarctions, however, the unilateral injuries showed no relation to the side of cannulation [22].

CT angiography, CT perfusion and conventional cerebral angiograms

Limited studies identify challenges facing contrast-based neuroimaging in ECMO patients including computed tomography angiography (CTA) of the head and neck, CT perfusion (CTP) and conventional cerebral angiograms (CCA) [19, 20]. This can become an issue with distinct sites of V-AECMO cannulation including outflow cannulas placed in the common iliac or axillary arteries. In our experience cannulation through the axillary artery presents an issue of high-pressure non-opacified blood flow competing with the systemic contrast-opacified blood causing unilateral non-opacification of the extracranial and intracranial vessels. The CTA and CTP resulted in false positives mimicking LVO with irreversibly infarcted tissue, respectively [19]. CCA can demonstrate the reversal of flow in the brachiocephalic and subclavian arteries in patients with right axillary cannulation [19]. Another group has shown similar disturbances of hemodynamics from V-A ECMO where the outflow cannula is in the common iliac artery. Acharya et al. described a case where a draining cannula was placed near the right atrium and the return cannula was placed in the common iliac artery. As the contrast is injected intravenously, the draining (venous cannula) will siphon the opacified blood through the ECMO circuitry. The contrast-opacified blood will flow retrogradely in the descending aorta (V-A ECMO) and hence, will compete with the un-opacified blood flowing antegrade from the left ventricle into the aortic arch. The opacified blood will preferentially flow into the left subclavian and left common carotid arteries while the non-opacified blood will preferentially flow into the right brachiocephalic and

common carotid arteries giving rise to asymmetric contrast opacification of extracranial and intracranial vasculature on CTA [20].

Magnetic resonance imaging

MRI remains an excellent way of identifying neurologic complications such as cerebral microbleeds (CMBs) after ECMO decannulation. CMBs have a distinct distribution in adults managed with either V-A or V-V ECMO, being mostly limited to the subcortical U fibers and deep white matter compared to the more lobar distribution in cerebral amyloid angiopathy and deep grey matter in small vessel arteriopathy [23, 24]. The authors, however, did not mention whether baseline MRIs were available for comparison with MRIs after ECMO. Interestingly, a different pattern was noted in pediatric patients treated with V-A ECMO where CMBs were identified in the watershed areas in the internal carotid artery ipsilateral to the cannulation side. This may be from hypoperfusion secondary to the ECMO cannula being placed in the ipsilateral ICA or from small embolic particles such as air emboli. However, CMBs in both populations were asymptomatic [25]. Cho et al. in the (SAFE-MRI ECMO) study, found that low-field portable MRI is a safe and logistically feasible option in ECMO patients. It also offers a diagnostic advantage over NCCT [26]. However, this remains hindered by the limited availability of portable MRI at most institutions currently. A further challenge to MRI accessibility is that the ECMO machinery itself can be incompatible with the MRI magnet [27].

Other ancillary testing

The physical examination and standard neuroimaging modalities have challenges and limitations in ECMO patients. Ancillary neuromonitoring modalities are available with greater accessibility at the bedside.

Transcranial Dopplers–TCD–Supplemental Table 1

Transcranial Dopplers (TCDs) are a useful non-invasive bedside modality for cerebral hemodynamic monitoring [28]. The data behind the use of TCDs in patients with cerebrovascular disease is vast and well-established, dating back to the 1990s. Measurements obtained with TCDs provide helpful information for evaluating cerebral autoregulation through the patterns of mean flow velocities (MFV) and pulsatility indices (PI). However, not all institutions have access to TCDs, and implementation of a TCD program requires an

experienced technician and vascular neurologist for acquisition and interpretation, respectively.

Applications of TCD in pediatric ECMO population

A retrospective review of 27 pediatric patients on ECMO investigated the association between cerebral blood flow velocities and neurological injury, using TCDs. Although Rilinger et al. found that mean, systolic and diastolic blood flow velocity increased after ECMO decannulation, there was no association found between cerebral blood flow velocities and the presence of neurological abnormalities. An interesting finding from this study, however, was neonates on ECMO were found to have higher velocities than expected when compared to age-matched controls [29].

A 2019 study of 52 V-A ECMO patients showed that in the 13 patients that suffered a neurologic injury (electrographic seizures, AIS or ICH), the middle cerebral artery (MCA) PI was significantly higher compared to those not suffering from neurologic injury. However, there was no side-to-side difference in blood flow velocities. Patients not suffering from neurologic injury have lower than predicted systolic and MFV as well as PIs in the first few days following cannulation. This in part could be secondary to heavier sedation in the first few days following cannulation. There was no difference in diastolic flow velocities of their entire cohort compared with the predicted normal. The lack of pulsatility attributed to V-A ECMO support, adds some uncertainty to the interpretation of PIs. Although there was a greater than 30% side-to-side difference in systolic flow velocities in peripherally cannulated patients, none of them suffered neurologic injury. However, the authors suggested that a persistent side to side difference should trigger sedation cessation for a better neurologic exam [30].

In a 2013 study of TCDs in ECMO patients, four out of eighteen patients suffered from ICH across the V-A and V-V ECMO groups, the velocities including systolic, diastolic, and mean exceeded predicted values by 23, 30 and 27%, respectively. The elevated velocities were noted between 2 and 6 days before the clinical event. Additionally, in those four patients, the Lindergardt ratio was lower than 3 suggesting the presence of hyperemia at the time of the TCD and the underlying etiology of ICH [31].

Applications of TCD in adult ECMO population

In 2010, Zanatta and colleagues studied 6 patients undergoing V-A ECMO using TCDs for micro embolic signal (MES) detection. There were 4 patients treated with

100% blood flow support on V-A ECMO and all had MES detected by TCD. However, the other 2 patients were treated with blood flow support of 50% of normal flow requirements and had no MES [32]. In a similar study on MES detection, Marinoni et al. divided MES detection into mild, moderate and severe groups depending on the number of signals counted during a 60-min continuous TCD as 1–20, 21–99, and ≥ 100 MESs, respectively. In the V-V ECMO group 26.2% had no MESs, and none saw ≥ 100 . MESs were detected in 81.8% of their V-A group, 45.4% of which had ≥ 100 . Consistent with this pattern, was the higher number of MESs detected in patients with lower left ventricular ejection fraction. There was no difference shown in the laterality of the MES. Also no correlation was seen between MESs and coagulation values, raises the likelihood that air emboli comprise the majority of MESs [33]. On a similar note, Min Cho et al. showed that no V-V ECMO patients suffered from MESs. However, MES was detected in 47% of the V-A group and 77.7% of the embolic events occurred in this group. Interestingly, MES was noted across therapeutic and non-therapeutic aPTT levels (29.4 and 18%, respectively) [34].

V-A ECMO patients with severely decreased cardiac function also have the added feature of reduced or lost pulsatility of blood flow [28, 35]. One study found that PIs directly correlate with the severity of myocardial suppression with loss of pulsatility in patients with EF < 10% and should not be confused for cerebral vasodilation. Another study showed that pulsatility was lost with EF as low as 20%, and rising PI coincided with an improvement in myocardial function. PIs typically normalized following ECMO decannulation [28, 36].

In a systematic review of neuromonitoring in adult and pediatric ECMO patients, PIs were inversely associated with ECMO flow rates. An increased CBF with a low PI at high ECMO flow rates may suggest a hyper-perfusion injury mechanism contributing to the development of ICH [37].

Yang et al. evaluated the effect of IABP on CBF, as measured at bilateral MCAs, by TCDs during V-A ECMO support. The addition of IABP in post-cardiac surgery patients showed either increased CBF in those without stunned myocardium (pulsatile pressure > 10 mmHg) or reduced CBF in those with it (pulsatile pressure < 10 mmHg). This adds more value to the importance of CBF monitoring during ECMO by TCDs [38].

Despite conflicting statements in the Salna et al. comment that in V-A ECMO patients cannulated through either axillary or femoral arteries there was no difference in MFV and PI at the MCA between axillary and femoral groups. There was a statistically significant trend of bilaterally increased MFV in the axillary group that they attributed to higher flow rates. The study was limited by its sample size and the lack of a control group [39].

Electroencephalography–EEG– Supplemental Table 2

Critically ill patients admitted to ICUs are at an elevated risk of developing seizures [18, 27, 40–44]. Non-convulsive seizures (NCS) in comatose patients can only be diagnosed by EEG. Strikingly, NCS rates can range from 7 to 18% in critically ill patients, with an even higher incidence of epileptiform discharges in up to 22% [45–47].

The American Clinical Neurophysiology Society recommended, in a 2015 consensus statement, continuous EEG monitoring for ECMO patients requiring paralysis and who are at risk of seizures. EEG has predictive value using background reactivity for outcomes in comatose patients. Lack of reactivity has been reported as a poor prognostic sign in patients with depressed levels of consciousness [48]. Epileptiform activity in critically ill patients has been associated with poor outcomes [49].

Applications of EEG in pediatric ECMO population

In 1992, Strelets et al. showed that EEG features did not significantly correlate with ECMO cannulation sites. Most abnormal EEG findings were generalized or bilateral and improved following discontinuation of ECMO. EEG changes did not correlate with structural abnormalities on head ultrasound. Seizures were associated with poor outcomes, defined as either death or delay in further development [50].

In 1993, Hahn et al. reported ECMO patients had more repetitive or periodic discharges from the right hemisphere (36 vs 23% in the control group). This was proposed to relate to the right common carotid artery ligation during ECMO cannulation [51]. There were also more right-sided IS in their ECMO group (13.8 vs 0%, $p < 0.05$). That study did not show any difference in lateralization of electrographic seizures between the ECMO and control groups. Within the ECMO group, the presence of electrographic seizures, status epilepticus and burst suppression patterns were associated with unfavorable outcomes compared to patients with favorable outcomes [51].

In another study evaluating the relation between EEG abnormalities and post-ECMO neuroimaging, 3 of 10 patients suffered from neurologic complications. One patient on V-A ECMO showed a markedly asymmetric EEG background with right hemispheric low amplitude and slow activity correlating with right hemispheric IS seen on neuroimaging post-ECMO. This patient survived with left-sided impairments that were nearly resolved on

follow-up. Of note, the patient was treated with antiepileptics and osmotic agents after the abnormal EEG. Another patient suffered a global hypoxic injury and the EEG showed slow diffuse activity. The third patient had bilateral venous infarctions and the EEG showed slow activity in the bilateral posterior head regions with subclinical seizures originating in the right. The latter 2 patients were also treated with antiepileptic drugs and osmotic agents after the EEG abnormalities were detected but suffered severe neurological outcomes on follow-up [52].

Lin et al. studied 99 patients undergoing V-A or V-V ECMO support. None of the V-V ECMO patients experienced electrographic seizures. However, 21% of V-A ECMO patients experienced electrographic seizures. The only statistically significant risk factor that was associated with seizures was low cardiac output. Additionally, although statistically insignificant, seizures did not occur in patients when their initial EEG background was normal or attenuated-featureless [53].

In a study by Sansevere et al. out of 75 patients managed with V-A ECMO, 20 had a bilateral injury; 26 had left hemispheric lesions; and 29 had isolated right hemispheric lesions. It was shown that right-sided lesions were more associated with right common carotid (peripheral) cannulation and left-sided lesions were associated with ascending aortic (central) cannulation ($p=0.03$). In this study, electrographic seizures and epileptiform discharges did correlate with the side of injury ($p=0.005$). They also found that using antiseizure medications as clinically indicated for a convulsive seizure prior to EEG start shortened the burden of electrographic seizures from 75.3 to 19.3 min ($p=0.04$). The higher burden of electrographic seizures in the initial 24 h of EEG monitoring was associated with death and severe background abnormalities (including attenuated/featureless or burst suppression in pediatrics and burst suppression or electrographic inactivity in neonates) and had 96% specificity as a prognosticator for death [54].

Applications of EEG in adult ECMO population

Sinnah et al. showed the presence of a discontinuous or unreactive background on 30-min EEG and lack of sleep architecture on continuous EEG. These were associated with poor outcomes (composite acute brain injury or death at 14 days). There were no differences in the sedation dosing between patients with or without background abnormalities or absence and presence of sleep transients [55]. Cho et al. showed that poor EEG reactivity and poor background variability were associated with poor outcomes (defined as Cerebral Performance Category 3–5). The EEG backgrounds had a fair mix of theta delta or delta frequencies

not typically associated with poor outcomes. Most of the 13 patients included did not have a neurological exam indicative of a catastrophic injury to the brain or brainstem and only 2 had neuroimaging findings that can explain being comatose (anoxic injury in one and right thalamic and occipital infarcts with midline shift in the other) [56].

In 2020, Peluso and colleagues reported no difference in EEG findings between their V-V and V-A ECMO groups. Moreover, they found that a severely suppressed background (defined by the absence of any EEG activity at $<10 \mu\text{V}$ during the entire epoch) and nonreactivity were independently associated with worse outcomes (as measured by GOS at 3 month). However, the presence of seizures (8%) or periodic discharges (7%) did not associate with worse outcomes. Additionally, they showed that a change in the symmetry of the background can be an indicator of underlying neurological insult. In one patient a diffuse low voltage activity was noted on day 5 and developed left hemispheric attenuation secondary to IS on neuroimaging. In addition, in one patient there was the detection of nonconvulsive status epilepticus on EEG which influenced treatment and resulted in a good outcome [57].

On a similar note, Magalhaes and colleagues, in 2020, showed that combining unreactive background with a background slowing to equal or less than 4 Hz had a 0% false positive rate for predicting worse outcomes at 28 (defined by death) and 90 (defined by death or an mRS of 4–6) days, in their V-A ECMO population. However, after adjusting for covariates, a low background frequency was the only independent association with the primary unfavorable outcome at 28 days. This study was limited by the short 30-min EEG monitoring and that only one patient experienced status epilepticus [58].

Recently, Touchard et al. have shown that even a simplified 4 lead frontal EEG can allow the intensivist to pick up common EEG patterns associated with poor outcomes (Death at 28 days or 90-day mRS of 4–6). They used Synek scores (Ranging between 1 as benign and 5 as malignant) as the predictor of poor outcomes based on the score's correlation with EEG background discontinuity and rhythm [59].

Somatosensory evoked potential—SSEP

SSEP has been used for several years as a prognostic tool for patients with hypoxic-ischemic encephalopathy and an absence of response has been associated with poor neurological outcomes. [60, 61] Cho et al. in 2019, studied 13 ECMO patients who underwent SSEP. The entire cohort had normal or delayed responses in at least one hemisphere. In the 6 patients with a delayed response, only one patient had a bilateral hemisphere delay pattern and NCCT showed a non-correlating right cerebellar infarct. However, in 1 patient an

absent left median response correlated with a right thalamic infarct. Twelve patients of these 13 patients suffered a poor neurologic outcome [56]. In 2020 Cho et al. studied a cohort of 20 ECMO patients in which 7 patients had SSEPs with intact N20 responses despite having poor outcomes [34]. This reinforces the need for more data to determine the value of SSEP in neurological monitoring in ECMO patients.

Near-infrared spectroscopy—NIRS

NIRS has been evaluated in ECMO patients for its potential to detect brain injury. A prospective observational study by Hunt et al. assessed the balance between cerebral oxygen delivery and consumption through regional oxygenation tissue saturation (rSO₂), to detect acute brain injury in V-A ECMO. A drop in rSO₂ of > 25% below baseline indicated an acute brain injury with a sensitivity of 86% [62]. A retrospective analysis by Pozzebon et al. showed that cerebral desaturation indicating an acute brain injury was detected by NIRS in 74% of patients undergoing V-A ECMO [63].

Neurologic adverse events in ECMO patients

Patients on ECMO are at substantial risk of neurologic adverse events with an incidence ranging from 10.9 to 50%. These include ICH, acute ischemic stroke (AIS), seizures, diffuse cerebral edema, hypoxic brain injury, global and focal hypoperfusion or hyperperfusion injury and brain death [18, 19, 27, 40–44]. Lorusso et al. reviewed the ELSO registry of 4522 patients and identified 15.1% developed neurological complications: brain death (7.9%), AIS (3.6%), and equal incidence of seizures and ICH (1.8%). More than one complication in the same patient occurred in 1.5%. A catastrophic rate of in-hospital mortality reached 100% in patients with 3 or more neurological insults [43]. The reported frequencies of ICH range between 3.6 and 15%; AIS between 4.1 and 9%; and cerebral edema, 13%. Seizures are reported in 4.1% and up to 18% in one study in pediatrics, of which 83% were purely electrographic [18, 41, 53]. Additionally, AIS increases the risk of seizures in ECMO patients [22]. ECMO patients are also at risk of developing cerebral microbleeds [23]. Cerebral hemorrhages in this patient population are also reported to be at a higher risk with a positive family history of intracranial bleeding [64]. Complications during V-A ECMO with intra-aortic balloon pump (IABP) include spinal cord infarctions and peripheral neuropathy, form either a direct injury to the nerve, vascular compromise or compressive injury from a hematoma [65].

Cerebral herniation from ICH or brain edema from traumatic brain injury has been considered by some an absolute contraindication to ECMO which is associated with a need

for systemic anticoagulation. There is, however, a lack of evidence for nonfatal ICH serving as a contraindication to ECMO cannulation [66]. More recent studies show that consideration of an anti-coagulation-free regimen may be a safe and feasible option with similar rates of thrombotic events and bleeding of systemic anticoagulation in certain ECMO patients [67–69].

Luyt et al. conducted an observational study and a systematic review that included 135 patients requiring V-V ECMO support. This study identified 18 patients with cerebral complications while on ECMO, including cerebral bleeding (7.5% $n = 10$), ischemic stroke (2%, $n = 2$) and diffuse microbleeds (2%, $n = 2$) [15]. Another case series by Martucci et al. demonstrated 6 cases who suffered from cerebral complications while on V-V ECMO. This included ischemic stroke due to fat embolism in 1 case, intracranial hemorrhage in 4 cases, and acute hemorrhagic encephalomyelitis in 1 case [70]. In a retrospective analysis of 878 patients undergoing V-A ECMO, 65 (7.4%) developed a cerebral insult, which included ischemic stroke (5.3%) and intracranial bleeding (2.8%) [16].

Discussion

ECMO is a lifesaving intervention in adults and pediatric patients for the support of severe cardiac and pulmonary dysfunction refractory to medical management [71]. Unfortunately, patients being treated with ECMO are at a higher risk for neurological complications that are disabling or acutely fatal [72]. The causal relationships are less clear and vary between adult and pediatric populations as well as the ECMO configuration (V-A vs. V-V). Identifying neurological disturbances and complications remain time sensitive, is challenging and may be overlooked.

This narrative literature review focused on understanding the landscape of neuromonitoring modalities as it applies to patients receiving ECMO support. We have described challenges posed by traditional evaluation methods for identifying neurological disturbances such as the physical examination or obtaining neuromonitoring modalities that can be utilized at the bedside remain under investigation for ECMO patients. Research is growing in EEG monitoring, TCDs with microemboli detection, and SSEPs in predicting complications. There remains a lack of consensus or guidance in how to interpret the results for identifying neurological insults in inpatients on ECMO. TCDs can predict neurological complications by quantifying blood flow velocity and MES detection, however, these require experienced personnel in acquisition and interpretation. EEG is a helpful bedside modality and identification of epileptiform activity may have its greatest role in neurological prognostication for patients on ECMO. SSEPs are helpful in localization,

but most recent literature suggests a limited understanding of their utility in prognosis and further studies are needed on its use. From a practical perspective, the general day-to-day management of patients on ECMO does not emphasize a need to consider neurological disturbances. Kazmi et al. describe a neuro-surveillance protocol that incorporates NCCT, TCD, EEG and NIRS in combination with goal-directed anticoagulation monitoring and a multidisciplinary team-based approach for neurological monitoring in ECMO patients [73]. Understanding the challenges and limitations of neurological assessments in ECMO patients can inform the development of local protocols that focus on neuro-surveillance in this growing patient population.

Conclusion

Neurological monitoring is an important area of focus to identify disturbances associated with the initiation of ECMO support and as a complication of continued ECMO support. The available literature is limited, heterogenous and lacks consensus on the best practices for neurological monitoring. Future studies should focus on the optimal measures of neurological monitoring modalities and utilization in the ECMO patient that can inform bedside evaluation and management.

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Data availability Data availability statement is not applicable for this study type.

Declarations

Conflict of interest Authors have nothing to disclose.

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