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REVIEW

# Brain monitoring in adult and pediatric ECMO patients: the importance of early and late assessments

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## ABSTRACT

Monitoring brain integrity and neurocognitive function is a new and important target for the management of a patient treated with extracorporeal membrane oxygenation (ECMO), in particular because of the increasing awareness of cerebral abnormalities that may potentially occur in this setting. Continuous regular monitoring, as well as repeated assessment for cerebral complications has become an essential element of the ECMO patient management. Besides well-known complications, like bleeding, ischemic stroke, seizures, and brain hypoperfusion, other less defined yet relevant injury and clinical manifestations are increasingly reported and impacting on ECMO patient prognosis at short term. Furthermore, it is becoming more evident that neurologic complication may not occur only in the early phase. Indeed, other potential adverse events related to the long-term neurocognitive function have been also recently documented either in children or adult ECMO patients. Despite increasing awareness of these aspects, generally accepted protocols and clinical management strategies in this respect are still lacking. Current means to monitor brain perfusion or detecting ongoing cerebral tissue injury are rather limited, and most techniques provide indirect or post-insult recognition of irreversible tissue injury. Continuous monitoring of brain perfusion, serial assessment of brain-derived serum biomarkers, timely neuro-imaging,

and post-discharge counselling for neurocognitive dysfunction, particularly in pediatric patients, are novel pathways focusing on neurologic assessment with important implications in daily practice to assess brain function and integrity not only during the ECMO-related hospitalization, but also at long-term to re-evaluate the neuropsychological integrity, although well designed studies will be necessary to elucidate the cost-effectiveness of these management strategies.

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Adverse events during extracorporeal membrane oxygenation (ECMO) are unfortunately common and some have a substantial impact on the ultimate patient outcome.[1-3] Neurologic injury, undoubtedly, represents one the most feared complications on ECMO, and its occurrence is due to its complex and invasive nature and therefore multifactorial.[3-6] Hypoperfusion, hypoxemia, intracranial hemorrhage, thrombo-emboli, edema, severe impairment of cerebral autoregulation, and many other mechanisms potentially involved may act individually or synergistically, jeopardizing brain integrity.[2, 6-10] Hence, continual vigilance for the any predisposing conditions or the early signs of impending brain damage is of paramount importance for either prevention or limitation, and for initiating an adequate response to counteract ongoing threats that may lead to permanent cerebral injury. Furthermore, timely recognition of a potentially high-risk event may lead to institution of neuroprotective measures and interventions that favor recovery or mitigation of the cerebral insult. ECMO is an invasive and unnatural physiological state, which may also lead to subtle and not necessarily overt cerebral impairment, which usually become clinically evident later after ECMO weaning at clinical discharge or even beyond. Furthermore, neuromonitoring might be helpful and critical in guiding ECMO management, *e.g.* in cardiac arrest setting in which ECMO use is increasing and brain injury is a relevant issue,[11] hopefully improving the neurological outcome.

The combination of well-recognized neuropsychological impairment linked to prolonged ICU stay along with a multitude of cerebral insults potentially mediated by ECMO will likely influence the long-term neuropsychological and cognitive status, affecting the social and professional outcome and quality of life of the ECMO survivors. The importance of all these "early" and "late" neurological and neuropsychological aspects are now increasingly becoming a focus of more in-depth clinical analyses, thus making brain monitoring a key intervention with a dual advantage, not only addressing ECMO-related hospitalization but also equally focusing on the post-discharge patient course and related assessment and appropriate interventions.

Adult- and pediatric-based approaches to brain monitoring will also be addressed in order to provide a comprehensive overview for different populations, also giving some insights about new perspectives and future directions in this setting.

## Neuro-monitoring on ECMO

Despite the ever-increasing use of ECMO for refractory cardiorespiratory failure in children and adults,[6, 12-14] there is still a lack of consensus about the most appropriate way to achieve effective and reliable brain monitoring in patients supported on ECMO. Several investigators have reported single-centre experiences and protocols, which are small studies reflecting local practices, and not powered to provide evidence that can be generalized for universal use. There are currently some recommended procedures and assessments, either at an early or later stage after ECMO, but general consensus is still missing for some of the proposed means.

## Adults supported on ECMO (early assessment)

### *Near-infrared spectroscopy*

Since a few years now, the most common tool for brain monitoring, particularly dur-

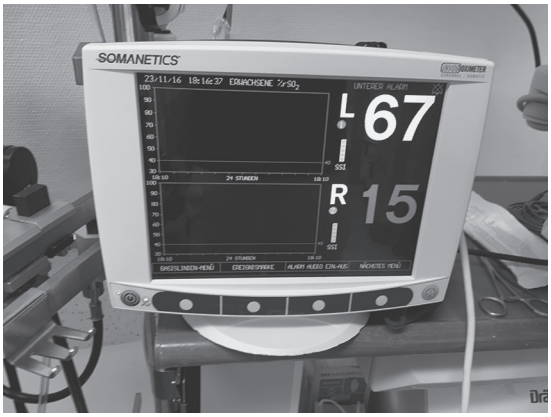


Figure 1.—Example of near infra-red spectroscopy performed in an ECMO patients showing abnormal value during support (lower value).

ing the early days of the ECMO run, is forehead near-infra-red spectroscopy (NIRS).[10, 15] NIRS uses an infrared light source to measure regional oxyhaemoglobin saturation ($rSO_2$) or tissue oxygenation index (TOI) continuously and non-invasively within 2.5 cm from the skull into the cerebral tissue, and has been around for nearly two decades now (Figure 1).[16] The actual value of such a method is still a matter of debate. The most accepted theory relies on following the trend of NIRS values rather than the absolute numbers. No agreement exists regarding the minimal threshold that is considered as to identify brain ischemia. Wong and associates have described about the use and actions in patient management based on the NIRS assessment and values.[17] Among 20 adult patients showing reduced NIRS values, 16 reacted positively to increased ECMO flow, whereas four patients had no change in NIRS values. All patients of the latter group had a neurologic complication, whereas the "responder' group had no brain-related adverse event.[17] This limited case-series apparently strengthens the sensitivity and specificity of NIRS in terms of perfusion-related acute neurological events. Cerebral and peripheral oximetry have been reported to provide a non-invasive assessment of hemodynamic variables.[18] However, an important limitation of NIRS is that the signal depends on the depth of resolution into the tissue. Indeed, in case of atrophy of the brain tissue as seen in elderly patients, the clinician should take into account that the depth of the spectrophotometry, usually between 1.7 and 2.5 cm, might be insufficient to reach the brain, and, therefore, limited or inadequate information may be generated in these circumstances.[19, 20] The majority of NIRS devices available on the market obtains the NIRS values with an algorithm that uses proportions of ~70% for the venous and 30% for the arterial blood as average of tissue hemoglobin saturation.[21] Nevertheless, biological inter-patient variations in cerebral venous/arterial blood ratio can produce not negligible differences between reported and actual $rSO_2$ values.[22] Moreover, a confounding element is the significant individual variation in hemoglobin concentration, especially as a consequence of hemodilution which could produce meaningful changes in cerebral $rSO_2$ levels.[23]

*Neuroimaging*

The use of neuro-imaging has been deferred by clinicians due to the difficulty of transporting ECMO patients to a radiology suite, though the utility of performing computed tomography (CT) scans has been described,[24, 25] while MRI is not feasible in ECMO patients due to hardware incompatibility. In many centers, an early neuroimaging analysis of ECMO candidates or receivers has been incorporated into the initial work-up routine. This approach has often allowed the recognition of pre-existing brain lesion incompatible with ECMO runs, thereby prompting the attending physicians to stop futile procedures, whereas in others it served as precious comparison for subsequent scanning. The availability of portable CT equipment, still not common in daily practice, will certainly enhance timely and accuracy of brain evaluation, particularly in patients with hemodynamic instability, with serial assessments if indicated by clinical suspicion.

*Brain injury-related biomarkers*

A panel of proteins that potentially reflect glial injury (glial fibrillary acidic protein

[GFAP] and S100b), neuronal injury (neuron-specific enolase [NSE], intercellular adhesion molecule-5 [ICAM-5], and brain-derived neurotrophic factor [BDNF]), and neuroinflammation (ICAM-5 and monocyte chemoattractant protein 1/chemokine [C-C motif] ligand 2 [MCP-1/CCL-2]) have been used and described in ECMO patients.[26-29] Floerchinger *et al.* have addressed the importance of blood biomarkers in elucidating severe cerebral damage. In their study, seven patients showed a high blood levels of NSE (mean 218±155 μg/L) and six of them (86%) developed severe neurologic complications. Although four of these patients could be weaned from ECMO, in-hospital mortality was 86%.[28] In adults, there is no report about the use of additional cerebral-based biomarkers, whereas these factors have been studied in children.[27, 30] It should be mentioned, however, that NSE is elevated also in case of hemolysis, a condition rather frequently encountered in ECMO patients. Another critical issue is represented by the timing of blood markers assessment. Currently, limited evidences and incomplete agreement exist in terms of cut-off values for neuronal injury, and, therefore, the serial assessment of the biomarkers might provide much more relevant clinical information than single absolute values.

Until new evidence becomes available, it seems advisable to monitor brain-related biomarkers, particularly in patients at high-risk of pre-existing or ongoing cerebral damage, *e.g.* post-cardiopulmonary resuscitation (CPR), along with expeditious high-quality neuroimaging in case of high serum levels. At the same time, additional investigations are certainly mandatory to provide more robust data and conclusive association between brain-related biomarkers and presence as well as extent of brain injury.

### *Transcranial Doppler – somato-sensory evoked potentials*

The application of transcranial Doppler (TCD) or somato-sensory evoked potentials (SSEP) has also been advocated as a valid diagnostic tool in the ECMO setting. Moreover, the application of TCD has been shown to be useful in detecting microemboli arising from the ECMO system in real time.[7, 31] Interestingly, microembolic signals were only observed in patients with full ECMO flow and were related to air embolism.[7] The feasibility and applicability of TCD in ECMO patients is still limited, but may represent a future option based on the ongoing technological advancements and refinements (miniaturization, user-friendly, continuous assessment), however, if identification of microemboli will affect clinical outcome remains to be determined.

### *Other neuromonitoring techniques*

The optic nerve sheath diameter (ONSD) measurement, a very simple, readily learned and reproducible technique, is actually used at the bedside to detect increased intracranial pressure (ICP) in adult patients after a traumatic brain injury.[32] The cut-off threshold of 5.2 mm of ONSD is sensitive and specific in detecting raised ICP. However, its role in ECMO patients, where increased ICP might be secondary to intra-cranial bleeding, to large ischemic insult, or in the presence of extensive post-cardiac arrest brain tissue derangement, remains to be determined.

The use of SSEP, the cortical potentials generated by sensory stimuli and which monitor the integrity of the somato-sensory pathway and in particular the somato-sensory cortex, in conjunction with clinical neurological assessment of consciousness and brain stem reflexes (like pupillary reflex), may provide useful insights in detection and the prognostication of cerebral insults, particularly in the difficult situation of postcardiac arrest patients. As shown by Zanatta *et al.*, middle- and short-latency SSEP were positive predictors of consciousness recovery, whereas middle-latency SSEP was a positive predictor of 6-month outcome. The prognostic capability of 50 mA middle-latency-SSEP was demonstrated to occur earlier than that of electro-encephalograpy (EEG) reactivity.[32]

*Neurologic assessment after ECMO weaning and hospital discharge*

In addition to the neurological morbidity from in-hospital events and abnormalities involving the neurologic profile, recent investigations highlight the importance of medium and long-term follow-up post ECMO status.[33-35] Follow-up assessment of ECMO survivors has revealed significant abnormalities either on physical examination or at neuro-imaging. Long-term longitudinal follow-up in children has shown that a proportion of survivors develop neurodevelopmental and neuropsychological deficits that affect motor and cognitive function leading to learning disabilities at school,[36, 37] some of which become apparent with increasing age.[38] Several studies have addressed this issue also in the adult patients with interesting and relevant findings.[34, 39] Risnes *et al.* were the first investigators who clearly pointed out the actual relevance of ECMO for post-discharge outcome and its impact on neurologic integrity in the long term.[39] Indeed, in 28 adult ECMO patients, they showed that, at five years from ECMO-related hospitalization, 43% were without clinical findings, whereas 41% had impaired neuropsychological performance. Regarding the neuro-imaging standpoint, 52% of the ECMO subjects had abnormal neuroimaging findings, and 41% had a pathologic EEG.[39] Neuroimaging abnormalities were correlated with cognitive impairment, and this condition was more frequent in veno-arterial (VA) than veno-venous (VV) ECMO.[39] Thorough neuropsychological tests showed new psychiatric disorders as compared to pre-hospitalization state, namely organic mental, obsessive-compulsive, and post-traumatic stress disorders.[40] Besides these findings, they also found high levels of distress, physical aggression, anger, and alexithymic traits.[40] Interestingly, 50% of the patients resumed normal working capacity.[39] In this context, it is certainly difficult to differentiate long intensive care (ICU) stay-related neuropsychological disorders from specific ECMO-related abnormalities. Moreover, it should be also mentioned that 54% of the Swedish ECMO patients had lifetime psychiatric disorders prior to ECMO and this new trauma might have exacerbated pre-existing abnormalities.[41] It is however noteworthy that psychiatric counseling and periodical examinations appear highly advisable, particularly in young patients. Obviously, more follow-up information and feedback are still needed to confirm these findings and provide appropriate solution to improve long-term quality of life and professional as well as social recovery of ECMO patients.

## Children supported on ECMO

Increasing number of children with refractory cardiorespiratory failure are being supported on ECMO with an improved survival ranging from 45% (cardiac) to 58% (pediatric respiratory) to 75% (neonatal respiratory) of ECMO cases.[12] Despite all the advances in the management of patients on ECMO, neurological complications such as seizures, intracranial haemorrhage and infarct remain a major cause of death and long-term neurological morbidity in survivors.[41, 42] The incidence of neurological complications on ECMO in neonates and children has been reported to be between 10% and 20%.[36, 38, 42-47] Several risk factors such as prematurity, lower body weight, carotid artery cannulation, congenital heart disease, cardiac failure, pre ECMO cardiac arrest and coagulopathy, use of bicarbonate and surfactant, hypotension and hypocarbia before and during ECMO, severe physiological instability during ECMO, non-pulsatile flow on VA-ECMO, mechanical complications and cannulation/manipulation of great vessels itself have been reported to increase the odds of neurologic complications.[43, 44, 46-53] Following acute neurologic injury on ECMO, 36-38% of children survive to hospital discharge,[42, 46] while 9% to 26% experience more minor motor difficulties or cognitive delays identified on serial, longitudinal follow-up.[45, 54-58] However, as more problems occur when children get older, it seems that neonatal ECMO survivors grow into their deficits and experience more motor disabilities and problems with academ-

ic achievement at older age.[59-62] Hence there is an important need to monitor neurological function on ECMO in addition to regular bedside clinical examination, the importance of which cannot be emphasized enough.

*Neuroimaging with cranial ultrasonography and computed tomography scan*

Current neurological monitoring modalities are insufficient to predict which children receiving ECMO therapy will suffer neurological injury. Even after a clinical suspicion of neurological injury on ECMO has been raised, diagnosis can be difficult, as transport of patients on ECMO for CT scan to radiology is logistically challenging, and in itself can put the patient at risk of clinical deterioration. The reported frequency of abnormal neuroimaging has ranged from 17% to 52%, depending on neuroimaging techniques and methods of classification.[63, 64] Cranial ultrasonography (cUS) is the preferred modality to image the brain of infants with an open fontanelle.[65, 66] The advantages of cUS are numerous: it can be performed at the bedside, it is relatively safe, and can be repeated when needed, enabling the evaluation of any evolution of lesions. However, cUS also has several limitations: quality of imaging depends on the skills and experience of the ultrasonographer, some areas of the brain are difficult to visualize, and several abnormalities remain beyond its scope.[66] Sensitivity of cUS for detecting extra-axial lesions, intraparenchymal hemorrhage and/or cerebral ischemia is limited as compared to MRI, which is not possible for patients on ECMO.[67, 68] Khan *et al.* found that daily sonograms are found to be cost effective only during the first 3-5 days on ECMO unless there is a change in neurological status or multi-organ failure.[69] Cerebellar hemorrhages can be difficult to identify by cUS via the anterior fontanelle, and a transmastoid view or imaging via the posterior fontanelle may improve the sensitivity of identifying these hemorrhages.[26] Parenchymal hemorrhage is the most common finding (67%) in infants on ECMO, with 27% incidence of cerebellar hemorrhage.[52] Early cUS screening has been used to identify infants with severe oedema on pre-ECMO sonograms, which progressed to subsequent major intracranial complications in 63% of cases.[70] CT brain contributed additional information in 73% of neonates with intracranial abnormalities,[52] whilst 6.8% of normal cUS were reported with abnormalities.[70] cUS with the TCD modality allows, through trans-temporal and anterior transfontanellar acoustic windows, the assessment of cerebral blood flow alterations during ECMO. In pediatric patients it is a key issue to verify the correct establishment of intracranial pathways of compensation after changes in the anterior and posterior cerebral circulations due to cannulation.[71] Left-to-right blood flow through the anterior communicating artery and retrograde flow in the proximal segment of the right anterior cerebral artery is the usual compensation for carotid obstruction.[72] In addition to the direction of flow, its speed provides important information by TCD. Children who develop cerebral hemorrhage had higher than normal cerebral flow velocity in the day prior to the recognition of bleeding.[73] On the contrary, lowest cerebral artery flow velocity has been associated to onset of ischemic lesions in the newborns undergoing ECMO.[74]

In older children and adolescents, head CT imaging is a central component of the initial assessment and management of patients with acute brain insult. Portable head CT imaging can be carried out on the pediatric intensive care unit (PICU) in critically ill children with acceptable radiation exposure.[75]

*NIRS*

NIRS has been applied to evaluate effects of vessel ligation and induction of ECMO on cerebral oxygenation in children.[9, 51, 76] NIRS studies on ECMO patients have focussed on relative and absolute changes in NIRS parameters during vessel ligation and alterations in the ECMO flows.[77] Preliminary results using a multichannel NIRS system (12 channels) indicate regional variation in cerebral oxygen-

ation responses during ECMO flow changes.[78] Wavelet cross-correlation (WCC) was introduced as the cross-correlation between continuous wavelet (CWT) coefficients of mean arterial blood pressure and oxyhemoglobin as obtained by NIRS.[8, 79] Multichannel NIRS in conjunction with WCC analysis can be used to form a non-invasive neuromonitoring system, which has the potential to assess regional variations in cerebral oxygenation and autoregulation.[8] A multicenter, multinational survey of NIRS use in pediatric cardiac ICUs showed that there was marked variability in the use of NIRS with very few centres having any protocol to guide intervention.[80] Despite this, NIRS however is being increasingly used in children on mechanical circulatory support where it is believed to reflect the mixed venous oxygen saturation and help reduce morbidity.[22, 81, 82]

*EEG*

A study of the United States Extracorporeal Life Support Organization (ELSO) Registry of 26,529 children that excluded children with cardiopulmonary arrest reported clinical seizures in 8.4% and electrographic seizures in 2.1% of patients. Seizures occurred in 9% of neonates with respiratory conditions, 8.1% of neonates with cardiac conditions and 6% of pediatric patients with respiratory conditions.[42] Seizures may be a risk factor for neurodevelopmental disorders, death or severe outcome.[42, 83, 84] Continuous EEG is not routinely employed for monitoring on ECMO patients. Intermittent conventional multichannel EEG is commonly used and classified as mildly, moderately, or markedly abnormal.[85] Fifty one to eighty percent of ECMO patients have abnormal EEG [85] with the proportion of electrographic seizures at 8-20%.[85, 86] Continuous EEG (CEEG) refers to the simultaneous recording of EEG and clinical behavior (video) over extended time periods (hours to weeks) in critically ill patients at risk for secondary brain injury and neurologic deterioration and is being recommended in critically ill children including those supported on ECMO.[87, 88]

Amplitude integrated EEG (aEEG) using biparietal electrodes has been reported as a continuous neuromonitoring method during neonatal ECMO.[89] In a study, aEEG recordings were used continuously for the first five days on ECMO showing that 62% were normal, whereas 38% were moderately or severely abnormal.[90] Severe abnormalities on aEEG before and/or during ECMO predicted death or moderate-to-severe intracranial neuropathology.[89, 91]

*Brain injury-related biomarkers*

The potential of using a simple plasma test for neuromonitoring in the PICU is highly appealing, not only for the ECMO population but also for other critically ill children at high risk for neurologic injury, such as those who suffer cardiac arrest or undergo cardiopulmonary bypass for repair of congenital heart defects.[27, 92] Recently, Bembea *et al.* have published on biomarkers for brain injury on ECMO in pediatric population.[26, 28] The peak plasma levels of four bio-markers (GFAP, NSE, S100b, MCP-1/CCL-2) were significantly associated with unfavourable outcome and mortality, while NSE was significantly associated with the primary outcome. Significant increase in plasma S100b and glial fibrillary acidic protein (GFAP) was found 1-3 days prior to any signs of neurologic injury.[30] S100b, neuron-specific enolase, and GFAP have been reported to be elevated in pediatric and adult ECMO patients with a neuroradiologically confirmed diagnosis.[27, 29, 93] As mentioned for the adult patients, additional evidences are still required to conclusively consider this assessment as a valuable as well as reliable assessment of ongoing brain damage.

*SSEP*

SSEP may be used in children supported on ECMO to evaluate brain injury.[94] The limited ability to determine to what degree a patient may recover consciousness and brain function impairs appropriate decision-making.[95] Several studies have shown that mismatch negativity (MMN) is an auditory evoked potentials (AEP) waveform with a high specificity to predict the

return of consciousness in patients with coma from different etiologies.[96] Although the detection of MMN may indicate the likelihood for awakening, it currently is unknown which characteristics of the MMN (*i.e.*, latency, amplitude) would be associated with a complete functional recovery. Recording of MMN early in the course of coma can predict awakening and the extended absence of waves III and V in the brainstem AEPs suggested poor prognosis.[96] Evidence for usage of MMN and AEP in ECMO patients is only based on several case reports.[97]

### *Combinations of monitoring modalities*

Multimodal neuromonitoring could definitely offer a better chance of identifying neurological abnormalities. However, there are few studies that have explored this combination of EEG and cUS was highly correlated with brain CT or MRI findings post-ECMO decannulation.[45] Plasma S100b and middle cerebral artery PI were significantly higher in patients with neurological injury, and they were increased 1-3 days prior to any neurological event. An additive effect of the two monitoring modalities was not evaluated.[93]

### *Neurological assessment of children after ECMO weaning and hospital discharge*

Early neuroimaging has been shown to help categorize the risk for development of neurodevelopmental sequelae, though not predict the neurodevelopmental outcome. Goodman *et al.* showed in a small series of testable survivors of neonatal ECMO that EEG record-

TABLE I.—*Modalities for Neuromonitoring in ECMO patients.*

| Method | Quality of information Grading of evidence | Studies in adults (references) | Studies in pediatrics (references) |
|---|---|---|---|
| NIRS | Partial – Grade III | Yes [12, 16, 17, 20, 21] | Yes [10, 11, 48, 74, 76] |
| EEG – Intermittent Continuous aEEG | Partial – Grade III | Yes [32] | Yes [77, 78, 81, 84-86, 95, 96] |
| SSEP, visual and auditory EP | Partial – Grade III | Yes [32] | Yes [89] |
| Transcranial Doppler | Partial – Grade III | Yes [9, 33] | Yes [67] |
| CT Scan | Partial – Grade III | Yes [23] | Yes [23, 49, 61] |
| Cranial Ultrasound (in children) and Carotid Doppler (in adults) | Partial – Grade III | Yes<br>Carotid Doppler [26] | Yes<br>Cranial Ultrasound [49, 62, 64, 66, 78, 98] |
| Brain injury blood biomarkers | Partial – Grade III (NSE, S-100, GFAP, ICAM-5, MCP-1/CCL-2, BDNT) | Yes [27, 29] | Yes [28, 30, 31, 88] |
| Neuro-developmental and neuropsychological follow-up | Partial – Grade III | Yes [25, 34, 35, 39] | Yes [36, 38, 57] |

aEEG: augmented electro-encephalography; ANE: acute neurological event; CT: computed tomography; ECMO: extracorporeal membrane oxygenation; ECPR: extracorporeal cardiopulmonary resuscitation; EEG: electro-encephalography; GFAP: glial fibrillary acidic protein; ICAM-5: intercellular adhesion molecule-5; ICU: intensive care unit; NA: not applicable; NIRS: near-infrared spectroscopy; NSE: Neuron Specific Enolase; MCP-1/CCL-2: monocyte chemoattractant protein 1/chemokine ligand 2; BDNT: brain-derived neurotrophic factor; SSEP: Somato-sensory evoked potentials; TCD: transcranial Doppler.

ings obtained during the neonatal course of neonates treated with ECMO do not predict cognitive and academic achievement test results in survivors at early school age.[98] Thus, EEG alone is not helpful in identifying infants at risk of subsequent abnormal neurodevelopmental outcome.[98, 99] Serial EEG may improve predictive value for poor neurocognitive deficit. cUS may be a sensitive but not specific marker of structural brain injury. In a study of 183 survivors, Bulas *et al.* devised a mean neuroimaging score based on the early neuroimaging studies (CT scan and cUS) and showed that it was worse in those survivors who had abnormal neurodevelopment.[100] They found that survivors with non-hemorrhagic abnormalities had a higher risk of delayed development than those with isolated hemorrhagic abnormalities (39% *vs.* 21%). A normal EEG and cUS may predict normal CT/MRI but abnormalities may be identified in later CT/MRI not seen on earlier cUS scans. Rollins *et al.* in a study of 50 neonates with post ECMO MRI scan reported that MRI identified significantly more abnormalities compared to routine cUS, however neither MRI nor cUS correlated with neurodevelopmental outcome using Bayley Scales. They found that the best predictor of neurologic impairment was feeding ability at discharge.[101] Recently, Schiller *et al.* reported white matter alterations in the left hemisphere and lower hippocampal volumes that correlated with worse verbal memory performance in school-aged neonatal ECMO survivors.[102] Advanced neuroimaging techniques such as diffusion tensor imaging may contribute to better risk stratification and early identification of impaired neuropsychological outcome.

| In-hospital recommendations | Follow-up | Comments |
|---|---|---|
| Yes<br>ECMO initiation<br>circuit manipulations<br>continuous is discretionary | NA | – Trend more important than absolute values.<br>– Thresholds and targets, and protocols for intervention are not universally accepted. |
| Yes<br>Pre-ECMO<br>Repeated assessments (assessing evolution) | Post-ECMO if previously abnormal but not predictive | – Serial EEGs important<br>– Continuous EEG (probably better)<br>– Particularly important in high-risk patients (*i.e.*, ECPR, neonates with asphyxia) |
| Yes<br>(Comatose patients) | Post-ECMO if previously abnormal | – Good for prognostication in ECPR and ANE on ECMO |
| Yes, if expertise available | NA | – Cerebral blood flow velocity and emboli detection<br>– Currently limited by device availability and expertise<br>– Intermittent assessment, not always available at point-of-care |
| Yes<br>- ECPR<br>- ANE | Yes<br>CT or MRI (preferred) recommended | – At hospital admission (particularly in case of ECPR) and low threshold if suspicion of an ANE on ECMO. |
| Yes<br>Pre-ECMO, serial scans for assessing evolution | Post ECMO cranial scan if previously abnormal but CT/MRI better yield | – Carotid Doppler may be used to understand blood flow patterns in cannulated vessels<br>– Also useful to assess patency of reconstruction vessels if performed post decannulation |
| Yes, if available | NA | – Expensive<br>– Not easily available<br>– Only measured in the blood<br>– Battery better than a single biomarker |
| Baseline assessments in ICU and before discharge | Structured multidisciplinary approach and follow-up at regular intervals | – Highly recommended for early identification and providing support and intervention.<br>– Neurocognitive and quality of life tests<br>– Highly relevant for future comparisons |

Structured, longitudinal long-term follow-up of ECMO survivors is crucial as it is now becoming apparent that some of the ECMO survivors may have late manifestation of neurodevelopmental and neuropsychological issues late up to adolescence.[36, 38] Bilateral sensorineural hearing loss has been commonly reported in survivors [103, 104] which may be identified up until 48 months of age despite normal initial or repeat clinical auditory brainstem responses before neonatal ICU discharge.[105] Thus, there is a need for early, routine, audiological assessment for all ECMO graduates.

## Conclusions

Neurologic injury, either clinically evident or only manifest as subtle changes of neuropsychological and cognitive functions, are frequent in ECMO patients. Therefore, clinical or technical modalities for adequate in-hospital and post-discharge assessment of cerebral function, including neurocognitive integrity, are of paramount importance in this setting (Table I). Neurologic monitoring of adequate brain perfusion, concise and effective clinical neurological assessment as daily routine, neuroimaging upon initiation, serial blood biomarkers assessment, particularly in the presence of high suspicion of impending brain damage, and pre- as well as post-discharge neuro-psychological counseling, represent a novel integrative bundle of diagnostic modalities that should improve contemporary ECMO patient management (Figure 2). However, a review of neuromonitoring modalities during ECMO currently used revealed a large variability in the timing and definition of abnormal tests and outcome measures. Most studies were conducted in pediatric patients, in single centres, and suffered from inadequate power due to small sample sizes.[106] Furthermore, the proposed tools and approaches to check neuro-psychological integrity have several inherent limitations and may provide only partial or even incorrect information about ongoing changes and insults of structures and function.

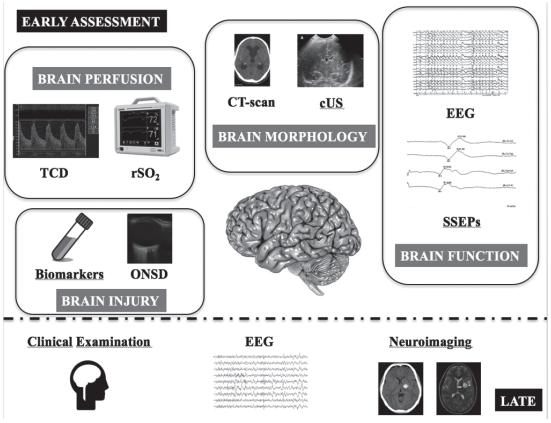


Figure 2.—Summary of early and late neurologic monitoring techniques in patients undergoing or previously submitted to extracorporeal membrane oxygenation.
TCD: transcranial Doppler; $rSO_2$: regional oxygen saturation; CT: computed tomography; cUs: cranial ultrasound; EEG: electroencephalography; SSEPs: somato-sensory evoked potentials; ONSD: optic nerve sheath diameter.

In view of the heterogeneous nature of injury during ECMO (hypoxic ischemic injury, embolic/ischemic infarction, or spontaneous intraparenchymal or extra-axial hemorrhage), it is likely that only well-defined combinations of neuromonitoring modalities are likely to be successful in the early detection of injury that would allow the institution of neuroprotective interventions and/or in guiding physician as to individually tailor the degree of extracorporeal support a specific patient requires to optimize specific variables (*e.g.*, cerebral oximetry) in order to ultimately improve outcomes.

A novel clinical management strategy of ECMO patients should focus on potential neuro-psychological sequalae and prevent or limit early or late neurocognitive derangements. In this sense, it is highly advisable to integrate multimodal neuromonitoring into clinical management and beyond to assure optimal outcome, particularly in pediatric patients. Additional relevant aspects of contemporary ECMO patient management are early awakening and mobilization, detection and relief of pain and delirium, and postdischarge psychological support, which all deserve particular attention in order to realize long-term well-being including return to work and active social life.

These outcome measures should guide optimal clinical ECMO support with special attention to minimize neurological and neurocognitive abnormalities, being increasingly recognized as important determinants of quality-of-life related outcome in ECMO survivors.

Finally, additional research to gain further mechanistic insights into this complex matter and study complementary neurologic monitoring methods, with the goals of assisting clinicians in stratifying patients into risk categories for brain injury, determining response to neuroprotective interventions, providing accurate prognostication of long-term outcomes, and establishing interventions to reintegrate individuals into a normal social life. All these aspects could potentially aid as entry criteria for future studies and randomized controlled trials. Similarly, new tools addressing adequacy of perfusion, tissue integrity and function, and *ad hoc* outpatient neurocognitive assessments, are under development or investigation, and will hopefully provide new insights.

## Key messages

— Incidence of neurologic complications during extracorporeal life support is frequent. Physiopathological mechanisms are not fully understood, however, a high level of suspicion and alertness is, therefore, mandatory in such patients.

— Although several diagnostic as well as monitoring modalities are still controversial or under investigation, a multimodal approach is highly advisable by continuous evaluation of adequacy of brain perfusion, or assessment of brain-injury markers, particularly not delaying advanced neuroimaging.

— Neurologic complications usually occur during or immediately after extracorporeal life support, but it is now evident, either in children or in adults, that long-lasting neurocognitive impairment may persist and, therefore, should represent another aspect to be evaluated during postdischarge follow-up.

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