Chapter 14
Sedation Considerations for ECMO

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Overview

Extracorporeal life support (ECLS) or extracorporeal membrane oxygenation (ECMO) is a form of mechanical support that can provide life sustaining respiratory and/or circulatory support when conventional measures are unsuccessful. Historically patients have been deeply sedated and paralyzed due to concern for accidental dislodgement of cannulas, interruption of flow, or self-removal of tubes or lines, and there are still populations of patients where deep sedation and neuromuscular blockade is necessary in order to sustain adequate flow, keep patients safe, and promote lung rest. Long-term utilization of ECMO while waiting for patient recovery or transplant has become common and has required clinicians to rethink sedation and neuromuscular blockade strategies due to detrimental side effects associated with long-term utilization, such as bone demineralization, muscle and strength loss, withdrawal, and delirium, among others. This has led to the trend of lightened sedation and even awake extubated patients being supported with ECMO.

Though awake ECMO may be the goal, some degree of sedation will likely still be necessary for initial cannula placement, for procedures on ECMO, or for the entire run in selected patients. Sedation strategy is highly dependent on the patient physiology-machine interactions. ECMO use poses its own set of challenges in addition to that seen in critically ill patients including: an increased volume of distribution from the increased circuit volume; drug adsorption/sequestration in the

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circuit and components; and changes in drug pharmacokinetics based on charge, protein binding, and lipophilic properties. These properties all have the potential for influencing drug selection and dosing regimens.

Effect of ECMO Circuit

ECMO circuits are each unique. Circuits are assembled from constituent parts based on institutional experience and preference of components. Basic key components of the circuit include cannulas, tubing, a pump device, an oxygen exchanger (referred to as membrane oxygenator), and a heat exchanger [1]. Additional optional components include a bridge (to connect the patient side and the blood flow return side), infusion ports (useful in patients with limited venous access), a bladder (serving as a reservoir for fluctuations in circuit pressure to ensure pump function), and an arterial filter (serves as additional point to trap entrained air) [1]. Patients may also have tandem in-line plasma exchange or hemofiltration devices based on institutional practice/patient condition [2, 3].

Circuits can be primed with either blood or crystalloid solution. However, smaller pediatric/neonatal patient circuits are generally blood primed due to smaller patient blood volume relative to the volume required to maintain the circuit even in the advent of smaller ¼ inch tubing [1]. Specific priming criteria and constituents are variable based on institution, and in addition to a base of blood, they often include bicarbonate, calcium (to counter citrate from the blood), and heparin added and titrated to ensure optimal pH, calcium levels, hematocrit, as well as prevent circuit thrombosis prior to cannulation. Additionally, circuits may be pre-primed with albumin to "coat" or occupy potential binding sites from circuit-protein interactions. Circuits used for ECPR may differ in priming constituents due to time constraints. The additional circuit volume and dilutional effect lead to an increased volume of distribution [4]. There have been reports of increased need for sedation immediately following cannulation as well as throughout the entire ECMO run; conversely, some reports have demonstrated similar sedation requirements in ICU patients irrespective of ECMO utilization [5]. These reports are somewhat difficult to interpret in the light of shifting tolerance of lighter sedation and with the advent of nurse-driven sedation protocols. It is also worth mentioning that sedation may vary in different ECMO populations (i.e., an ARDS patient in the acute phase of illness with multiorgan dysfunction vs a patient with single organ dysfunction awaiting transplant) as critical illness itself leads to altered pharmacokinetics with leaky capillaries, altered renal or hepatic blood flow/clearance, and altered cardiac output [6].

The circuit plays a role affecting not just volume of distribution, but also drug adsorption and sequestration within the circuit itself. When broken down into components, each part of the circuit has potential for drug adsorption, with the worst offenders in one study being the heat exchanger and the oxygenator [7]. Other studies have found a main contributor to be the polyvinylchloride (PVC) tubing. Drugs with lipophilic properties have shown a greater tendency to sequestration, with

fentanyl, dexmedetomidine, and propofol being more lipophilic than benzodiazepines and other narcotic agents. Morphine showed the lowest amount of adsorption to the circuit in several studies. Protein bound drugs may also be at risk for sequestration [8–15]. Though these studies demonstrate likely interactions between sedation agents and the ECMO circuit, the results are hard to extrapolate to a pediatric population. Studies have varied in the utilization of different circuit priming solutions and methodologies that may determine the circuits potential for protein binding and alter binding capacity based on the pH of the solution. Most studies utilized a new circuit and single bolus administration of a sedative agent with subsequent serial samples to determine drug concentration. Samples were taken at predefined time points with most studies ceasing after 24 hours. Continuous administration/bolus titration in an experimental study to determine effect on drug concentration is logistically difficult to pursue. One would also imagine that a certain binding or sequestration threshold exists and that in the setting of patient-directed sedation protocol that threshold would exceed any binding capacity of the circuit [16–18].

Propofol use in ECMO has found increasing use in adult ECMO but has demonstrated the potential for theoretical decreased membrane oxygenator lifespan due to its high lipophilicity [19–22]. Though propofol is used more cautiously in pediatric populations due to the concern of propofol-related infusion syndrome, it is a mainstay in adult sedation and has desirable properties that would lend itself to intermittent use in pediatric patients on ECMO including: fast onset of action, short duration of action, and the ability to achieve adequate sedation while maintaining spontaneous respirations [23]. It has shown to be useful in adults in bolus dosing during episodes of agitation leading to interruption of pump flow, as a benzodiazepine sparing agent in the setting of delirium, and as an opiate sparing agent [24]. Clinicians should remain thoughtful to recall potential downfalls with propofol as well due to physiologic effects including the risk of hypotension from decreased systemic vascular resistance [23]. A more recent study found no decreased length of membrane oxygenator life span and potentially an increased lifespan of oxygenators [25, 26]. Another recent, larger retrospective study supported no adverse effects on oxygenator lifespan compared to midazolam [27].

Renal replacement therapy (RRT) use has become a more common addition to the ECMO circuit with many patients having acute kidney injury or organ failure at time of cannulation, and also an increased recognition of the risk of fluid overload and its association with poor outcomes in ECMO patients [28]. A hemofilter or continuous venovenous hemofiltration device can be placed in-line with the ECMO circuit using pump pressures as a driving force for hemofiltration using an in-line hemofilter or a commercial device that has been connected to the ECMO circuit [2]. If the patient has sufficient vascular access, a third potential option is to run RRT through that access point without ever needing to connect the RRT device to the ECMO circuit. Drug clearance from in-line RRT would be expected to be similar to RRT in isolation, though most studies looking at circuit effect of drug concentration are without RRT [3, 29]. Drugs with a large volume of distribution large molecular weight, and high degree of protein binding will not have good clearance with RRT due to the membrane properties of the hemofilter. However, small, hydrophilic

molecules with little protein binding will be easily filtered and circulating levels would be expected to decrease. Morphine, hydromorphone, fentanyl, midazolam, lorazepam, dexmedetomidine, and propofol all have a large volume of distribution though there is variability reported in the lower ranges seen in lorazepam and dexmedetomidine in infants and children younger than 2 years old [30, 31]. Morphine is hydrophilic with little protein binding, though has a large volume of distribution so clearance of the primary molecule would still be relatively small. Morphine does have a large number of metabolites that have been known to cause toxicity in renal insufficiency [30, 31]. Similar to the ECMO circuit, there is an expected degree of adsorption to the RRT circuit itself that may account for some degree of large molecule clearance and is partially dependent on RRT membrane selection, size of pores, and surface area [32]. Much of RRT drug dosing is extrapolated from adult data and from those with chronic renal failure; therefore, it may be difficult to apply to a pediatric population with acute kidney injury. Indication for RRT (fluid overload vs acute kidney injury) should also be taken into consideration with dose adjustments, and consultation with a pharmacist is recommended [18, 33].

Sedative Choice

No standard first-line recommendation or protocol exists for sedation of ECMO patients. An international survey of ECMO centers examining sedation practices of physicians managing adult ECMO patients found that morphine and fentanyl were the most commonly used opiates, and midazolam was the most frequently used benzodiazepine. Approximately one-third of responders used propofol routinely, and the most commonly used second-line agents were dexmedetomidine, ketamine, and clonidine, though one-third of responders stated they didn't use any second-line agents. Interestingly, only half routinely used sedation scores to monitor sedation in this particular patient population. It is unclear if this finding is secondary to ECMO patients being excluded from initial protocol inclusion or if they were targeting a deeper level of sedation as 40% of responders targeted a sluggish response to loud or physical stimuli or no response to loud or physical stimuli [34]. A more recent single-center retrospective study of pediatric PICU/CICU patients looked at their sedation practices and found opiate and benzodiazepine use in 99% and 91% respectively with 31% requiring a second-line agent. Patients requiring a second-line agent were of younger age and had higher opiate and benzodiazepine doing requirements during their time on ECMO. Median ECMO run duration was overall short 9.5 days, and there was a high incidence of additional procedures needed on ECMO (36%). The level of sedation the authors were targeting was unclear [35].

The RESTORE trial was a multicenter cluster randomized pediatric trial across 21 PICU's comparing nurse-driven sedation protocols to usual care. They performed a secondary analysis comparing sedation practices of patients on venoarterial and venovenous ECMO as well as potential factors affecting sedation. They noted a significant increase in benzodiazepine and opioid use in the first 3 days after ECMO

was initiated, with an overall increase in opioid use of 108% and benzodiazepine use by 192% by the time of decannulation with lighter levels of sedation compared to pre-ECMO sedation, with a significant decrease within 3 days post decannulation. It is difficult to assess the potential for tolerance to sedation prior to cannulation as it is not clear how long patients were mechanically ventilated or required sedation prior to cannulation. By day 3, 43% of patients still required use of a neuromuscular blockade (though reasoning to continue neuromuscular blockade is not discussed) and remained heavily sedated. They also noted an increased incidence of withdrawal in patients requiring ECMO compared to those with pediatric acute respiratory distress that did not require ECMO though it is unclear if there was an overall longer period of sedation utilization between these two groups. Most frequently used second-line agents included dexmedetomidine (35%), barbiturates (32%), methadone (38%), and ketamine (17%) [5].

Approaches and Adjuncts in Difficult to Sedate Patients

Opioids and benzodiazepines are the most common first-line agents in ECMO patients reported in multiple populations. ECMO patients have been reported to have increasing sedation requirements as ECMO duration becomes longer. Adjuncts to typical sedation are, therefore, a necessary tool to have in your armamentarium though the preferred second-line agents appear to vary significantly based on population and institution [34–36].

Adult studies cite a more frequent use of quetiapine and haloperidol with some instituting inclusion as part of a standard protocol in those expecting a prolonged ECMO course as a method to combat delirium, which has been noted in up to 50% of adult ECMO patients, or in patients with agitation. Little mention of utilization of these agents is made for standard practice in pediatric ECMO patients [26, 37–39].

Ketamine has a favorable effect on hemodynamics, despite having some myocardial depressant properties, with less predisposition for hypotension which may be a concern for interruption of pump flow particularly in patients with already tenuous hemodynamics [37]. An additional benefit includes maintenance of a patient's spontaneous respiratory rate. In one study of pediatric ECMO patients, it was used in up to 17% of patients—most frequently on day of decannulation [5]. In a small retrospective study looking at ketamine use in adult ECMO patients, ketamine use was associated with decreased vasopressor dosing, though based on the study design it was hard to discern whether or not there was a meaningful change in sedation scores of patients [40].

Propofol has the benefit of having a fast onset of action and short duration of action allowing for evaluation neurologic assessment. It is generally not used continuously for a long duration in pediatric patients due to the risk of propofol infusion syndrome; however, it may be useful if deeper sedation is needed for a brief procedure [23]. An additional area of utilization in adults is as a temporary sedative measure when patient agitation causes interruption of ECMO flow, intermittent boluses

can act as a physiologic "reset" or a temporizing measure until sedation adjustments can be made to address the agitation [38]. Major concerns around its utilization are related to potential interference with oxygen extraction due to its high lipid content and lipophilicity though more recent studies show no difference in oxygenator lifespan with propofol use compared to benzodiazepines [22].

Barbiturates are listed as a frequent adjunct in pediatric and neonatal patients (up to 32%) of patients. A case series of six pediatric patients with respiratory failure receiving pentobarbital for sedation (of which two required ECMO) utilized bolus dosing and then continuous infusion of 1–2 mg/kg/hr up to 4 mg/kg/hr. The patients were able to be weaned from antihypertensive agents and pentobarbital allowed discontinuation of neuromuscular blockade agents in four to six patients. It is unclear whether ability to wean antihypertensive agents were associated with improved sedation level achieved in these patients or whether it was due to a direct hemodynamic effect related to pentobarbital—though no patients were reported to need vasopressors [41]. Half of patients had withdrawal and required oral taper which was recommended in patients who required more than 7–10 days of pentobarbital, though may be seen with as little as 4 days of pentobarbital administration [42]. Pentobarbital is associated with cardiorespiratory depression and may lead to hypotension particularly in those with depressed myocardial function (has a direct negative inotropic effect as well as causes peripheral vasodilation). Hypotension may be seen more with bolus dosing compared with continuous infusion. In a retrospective review of 50 PICU patients, no excessive hypotension was seen with pentobarbital administration in these patients [42].

Inhaled anesthetics are infrequently used in PICU patients for sedation outside of life-threatening status asthmaticus due to multiple factors, though may be encountered in the operating room and in some particularly difficult to sedate patients. One of its limitations is accessibility, as it is not readily available in all PICUs. Respiratory staff may have limited training and many PICU attendings have no formal training [36]. Outside of that, there is concern in pediatric populations for neurotoxicity and the lack of long-term safety data with prolonged utilization [43]. In a recent retrospective case series looking at use of inhaled anesthetics for difficult to sedate patients in PICUs in Spain, sevoflurane showed good tolerability with the main side effects being bronchospasm in 9% (one episode potentially related to improper priming); hypotension in 30%, though none severe enough to require withdrawal of sevoflurane (all episodes hypotension observed were in cardiac patients); and withdrawal in 26% after discontinuation of sevoflurane that was responsive to dexmedetomidine, clonidine, and/or morphine [44]. An adult retrospective analysis comparing propofol and isoflurane use in ECMO patients showed no difference in ECMO duration; however, if administered via inhalation, the actual delivered anesthetic dose may be limited by the tidal volume taken by the patient. Tidal volumes of patients in this trial were not included in analysis and the patients also routinely received opiates, benzodiazepine, and delirium prophylaxis with haloperidol, clonidine, or lorazepam [45]. There have been some cases of decreased sedation noted with isoflurane during cardiac bypass cases [46]; however, in vivo studies have shown deceased uptake by the oxygenator, meaning more constant drug levels, compared to other types of sedation [9]. Some small case studies in adults have

maintained sedation with isoflurane during ECMO without membrane oxygenator failure while providing adequate sedation [47].

Dexmedetomidine is a central alpha 2-adrenergic antagonist that is more potent than clonidine. It is highly lipophilic; is protein bound; and possesses several benefits such as sedation without analgesia, an opioid sparing effect, less respiratory depression, and the ability to induce sedation that mimics non-rapid eye movement sleep. The most common adverse effects are associated with the development of bradycardia, hypotension, and decreased sympathetic tone due to inhibition of the release of norepinephrine and epinephrine. It is frequently used as an adjunct for sedation in ECMO in up to 35% of patients. However, caution should be taken using this agent in patients with cardiogenic shock or those requiring pressor support [12, 37].

Neuromuscular Blockade

Concerns related to prolonged use of neuromuscular blockade (NMB) leading to myopathy have led to more conscientious use of NMB. There is little guidance for NMB use during ECMO with few papers published and large variation of utilization nationally, internationally, and institutionally within the ECMO population. Most data contributing to our knowledge of utilization comes from international and national surveys of ECMO centers as well as retrospective institutional reviews. Reported need for NMB ranges from 13% (4% in VA ECMO population) up to 64% of patients. The most common NMB agents used are cisatracurium, atracurium, vecuronium, and rocuronium, with regional and international variation appreciated [34, 48]. NMB agents are used frequently during periods of cannulation and decannulation and often accompany phases of deep sedation. In one study, when looking at the total number of days on ECMO, 54% of ECMO days were spent deeply sedated and of those 80% also included the need for NMB [48]. Data from the RESTORE trial in pediatric patients showed that 50% of patients were still using a NMB continuously 3 days prior to ECMO decannulation [5].

In an international survey of ECMO centers, NMB was utilized for >24 hours in 66–100% of patients by 21% of respondents [26, 34, 49]. It is difficult to interpret from the survey data which physician and patient characteristics contribute to the need for neuromuscular blockade and during which time of the ECMO run the NMB is needed. In a survey of pediatric ECMO centers in the United States, 70% of participants did not routinely use NMB agents, but they were administered intermittently as required for agitation and problems with pump flow and for procedures while on ECMO [49]. Additionally, variation in use may in part be accounted for by center experience, physician comfort, patient population, proportion of VV vs VA ECMO, underlying patient physiology/pathophysiology, bridge to transplantation status, and concerns for circuit function.

The use of periodic NMB has been shown to be beneficial and allow for weaning of sedation, and in addition may act as a "reset" when given in conjunction with a benzodiazepine during periods of agitation or dyspnea that cause interruption of pump flow in awake ECMO patients bridging to lung transplantation [38].

Variations in Sedation Practice and Nurse-Driven Protocols

Institution of nurse-driven protocols may increase likelihood of not only patient comfort, but also lower median doses of opioids and benzodiazepines as shown in a retrospective cohort of adult patients. This particular cohort of patients included a proportion of patients who were placed on ECMO as a bridge to transplant. It has been debated whether this population has the same sedation requirements as those with acute illness and multiorgan dysfunction. Bridge to transplant patients often have single organ dysfunction and may tolerate interruption of sedation more easily than patients with acute illness and potential for multiple organ dysfunction. There may also be a bigger push to lighten sedation in bridge to transplant patients to keep their strength and improve their transplant status [26]. However, a trend of lower sedation requirements was also noted in pediatric patients who had a decrease in dosage and length of utilization of opiates in those with a nurse-driven sedation protocol compared to those with usual care, though benzodiazepine usage remained similar between the groups [5].

Sedation holidays (or the daily interruption of sedative medications) were first noted to be of use in adult critically ill patients allowing for decreased length of mechanical ventilation and length of ICU stay as well as ability to decrease total dose of sedative infused [50]. ECMO patients have been suggested to have a higher incidence of tolerance and require higher doses of sedatives and longer duration of sedative use [10]; sedation holidays may be of particular benefit in this group. However, hesitancy over patient stability, small patient size, and potential for interruption of cannula flow have been prohibitive for instituting this in neonatal and pediatric ECMO patients. A prospective observational cohort study was performed in 20 neonates that assessed the safety and efficacy of daily sedation holidays with no adverse events such as accidental cannula displacement or self-extubation. Median time before resuming sedation was 10 hours. Numerous protocol violations were also identified with morphine not being discontinued simultaneously with midazolam, being restarted prior to patient demonstration of discomfort, or being restarted concurrently with midazolam. This may have signified nursing or physician discomfort with lighter sedation levels in the setting of ECMO, fear of potential complications, or varying interpretation of pain or distress in neonatal/pediatric patients [51].

Changing Paradigm: Transition to Awake ECMO

We are pushing the boundaries of ECMO use. Patients are now using ECMO as a bridge to transplantation, a bridge to additional therapy (i.e. a ventricular assist device), or a bridge to recovery, with the longest ECMO patient staying on ECMO for 605 days with complete recovery [52]. With those changes there is an increased push to work toward optimizing patient physical and mental condition that has led to a shift toward decreased sedation, extubation, and awake ECMO with patients undergoing physical therapy, eating regular meals, and having meaningful social

interactions [24]. This has likewise added to revised strategies for sedation, physiologic considerations, and monitoring conundrums to follow respiratory status and predict need for reintubation.

Multiple physiologic changes should be taken into account when considering awake versus sedated with or without NMB physiology and intubated versus extubated physiologic effects. Physiologic processes in favor of spontaneous breathing include more optimal displacement of diaphragm for V/Q matching, improved muscular tone leading to improved FRC, improved venous return with negative pressure ventilation, and decreased risk of lung injury from mechanical ventilation. Despite potential benefits of spontaneous breathing, there is still potential risk of lung injury from high transpulmonary pressures even in the absence of mechanical ventilation; these patients would also be at risk for increased oxygen consumption and respiratory muscle fatigue [38].

In experimental settings, physiologic breathing is controlled by PCO_2 to a greater degree than PO_2 (PO_2 has to be 40–50 mm Hg prior to triggering a ventilatory response). This physiologic regulation to change minute ventilation in response to CO_2 removal has been seen experimentally while using ECMO to regulate CO_2 exchange in healthy lungs. However, this is not well studied in sick lungs, and patients with ARDS on ECMO have been observed to have a variable response suggesting other physiologic factors are also involved in this regulation [38, 53].

Another key physiologic principle to consider is the effect of intrathoracic pressure differences on blood flow through the cannula, in addition to the role of adequate preload (venous return). During physiologic breathing in healthy lungs, minimal intrathoracic pressure changes of 4–6 mm Hg occur [54]; however, in acute lung injury, large intrathoracic pressure swings (up to 20–30 mm Hg) can be seen. This large pressure swing can cause increased venous return by pulling blood from the inferior vena cava to the superior vena cava leading to collapse of the inferior vena cava around the ECMO cannula and interruption of flow, or potentially even cavitation of the vessel. This may be less frequently observed in cannulas that obtain their blood flow from both the superior vena cava and the inferior vena cava. On the opposite spectrum, increased afterload can also cause transient interruption in ECMO flow (coughing, Valsalva or bearing down with stool passage, crying).

Many nuances to management of awake ECMO patients will not be covered in this chapter. The approach to sedation in this population is unique. Some patients on ECMO as a bridge to lung transplantation have been noted to be difficult to wean from sedation partially due to exaggerated swings in intrathoracic pressure. However, there is also suspicion for an altered physiologic perception or response leading to a sensation of dyspnea that some refer to as “drowning lung”. This sensation is reported to be unresponsive to opiates and can cause dangerous interruption of ECMO flow if associated with changes in intrathoracic pressure. One center has created a protocol for weaning sedation in these complex patients that involves the utilization of intermittent NMB preceded by benzodiazepines for their amnestic effect when this maladaptive response is present, eventually leading to the response being extinguished over time [39]. A stepwise approach to weaning opioid infusions is also used in conjunction with enteral methadone and eventual replacement of

propofol. Dexmedetomidine is utilized to inhibit an adrenergic response, and risperidone is added for all patients to help combat agitation. Periodic NMB is continued as needed in states of hemodynamic instability or uncontrollable agitation. An alternative approach to this problem taken at some centers replaces the utilization of periodic paralysis with boluses of propofol in the setting of severe agitation or ECMO flow interruption [39].

Concluding Remarks

In conclusion, no standard approach to sedation for ECMO patients exists. Fentanyl and morphine are the most common first-line agents used for analgesia in ECMO patients, and midazolam is the most common sedative agent adjunct. The ECMO circuit has an effect on the volume of distribution and drug pharmacokinetics, as does the presence of critical illness and altered renal and hepatic perfusion. Lipophilicity, protein binding, pH, and molecular weight all play a role in circuit sequestration and may play a role in sedation levels; there is likely a threshold at which all adsorptive sites are filled though this theoretical potential has not been studied. It is difficult to extrapolate data from these studies directly to patient care as all ECMO circuits are unique with varying surface area and components individualized based on institutional practice. It is also not uncommon that some of the components or the circuit itself will need to be replaced during an ECMO run which would necessitate reaching a new steady state. The need for sedative adjuncts is common, and dexmedetomidine, quetiapine, clonidine, and ketamine are all potential adjuncts. Propofol has been safely used (though more commonly in adults) with comparable membrane oxygenator lifespan to that of benzodiazepines with no noted interference in gas exchange. Lastly, our paradigms are shifting away from heavily sedated ECMO. With the push for early mobility, the benefits of having an awake patient in long-term ECMO management necessitate new approaches to sedation to maintain safe physiologic response in these subacute patients.

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