Extracorporeal Life Support Organization Guidelines for Fluid Overload, Acute Kidney Injury, and Electrolyte Management

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Disclaimer: This guideline for extracorporeal membrane oxygenation (ECMO) fluid and electrolyte management for all patient populations is intended for educational use to build the knowledge of physicians and other health professionals in assessing the conditions and managing the treatment of patients undergoing extracorporeal life support (ECLS)/ECMO and describe what are believed to be useful and safe practice for ECLS/ECMO, but these are not necessarily consensus recommendations. The aim of clinical guidelines is to help clinicians to make informed decisions about their patients. However, adherence to a guideline does not guarantee a successful outcome. Ultimately, healthcare professionals must make their own treatment decisions about care on a case-by-case basis, after consultation with their patients, using their clinical judgment, knowledge, and expertise. These guidelines do not take the place of physicians' and other health professionals' judgment in diagnosing and treatment of particular patients. These guidelines are not intended to and should not be interpreted as setting a standard of care or be deemed inclusive of all proper methods of care nor exclusive of other methods of care reasonably directed to obtaining the same results. The ultimate judgment must be made by the physician and other health professionals and the patient in light of all the circumstances presented by the individual patient, and the known variability and biologic behavior of the clinical condition. These guidelines reflect the data at the time the guidelines were prepared; the results of subsequent studies or other information may cause revisions to the recommendations in these guidelines to be prudent to reflect new data, but Extracorporeal Life Support Organization (ELSO) is under no obligation to provide updates. In no event will ELSO be liable for any decision made or action taken in reliance upon the information provided through these guidelines.

Key Words: acute kidney injury, neonatal, pediatric, adult, extracorporeal membrane oxygenation, fluid overload, diuretics, renal replacement therapy

The Extracorporeal Life Support Organization (ELSO) Guidelines for Fluid and Electrolyte Management have been written to present a consensus for the clinical care of neonatal, pediatric, and adult patients supported with extracorporeal membrane oxygenation (ECMO). These guidelines are written to complement the recommendations for ECMO support outlined in the 5th Edition of the ELSO Red Book. Our panel represents an international group of ECMO clinicians, and our goal is to provide an evidence-based approach to acute kidney injury (AKI), fluid overload (FO), and interventions including the use of diuretics and renal replacement therapy (RRT).

Neonatal and Pediatric Extracorporeal Membrane Oxygenation Fluid and Electrolyte Management

Fluid Overload

FO is a frequent complication of ECMO.[1–3] Defined globally as a positive fluid balance, a strict threshold to define FO in neonatal and pediatric populations is lacking. The American College of Critical Care Medicine defines >10% volume overload as a key threshold at which to act in neonatal and pediatric septic shock.[4] This same threshold of >10% FO is independently associated with multiple adverse outcomes including both increased duration of ECMO and increased mortality in neonatal and pediatric patients.[1–3] In patients supported with ECMO, FO has been associated with impaired oxygenation, increased duration of ECMO, and mortality.[2] Importantly, once established, correction of FO to ≤10% has not been associated with improved survival, underlining the importance of prevention and early, aggressive fluid management strategies.[2] Traditionally, fluid balance methods, whereby FO is assessed by measuring fluid input and output volumes, have been used to calculate %FO. However, accurate fluid intake and output can be difficult to quantify, particularly in neonatal and pediatric patients with mixed diaper output. To better quantify accurate outputs, urinary catheters can be utilized. However, the risk of urinary tract infection with long-term catheter placement must

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be considered. Daily body weight has been used as a surrogate for FO, and weight-based determinations of FO are highly correlated with fluid balance methods with similar predictive abilities in pediatric intensive care unit patients.[5] However, the most common method used to determine FO in critically ill children was established by Goldstein *et al*.[6] as follows:

$$\%FO = \frac{\text{Fluid in (L)} - \text{Fluid out (L)}}{\text{ICU Admission Weight (Kg)}} \times 100.$$

Again, because correction of FO to ≤10% has not been associated with improved survival, prevention of FO > 10% is critical. Management strategies to minimize FO for patients supported with ECMO are listed in **Table 1**.

Acute Kidney Injury

Etiology. AKI is another common complication experienced by many neonatal and pediatric patients supported with ECMO.[7,8] The cause of AKI during ECMO is multifactorial. AKI may be related to several conditions derived from or associated with extracorporeal therapy. Before ECMO initiation, these patients are often subjected to sepsis, ischemia, cardiac and/or respiratory failure, hemodynamic instability, vasoactive agents, and nephrotoxic medications. All these factors place patients at high risk for AKI.[9] Further contributing factors include the inflammatory cascade activated by interaction with the ECMO circuit, and also factors directly related to ECMO such as red cell stress and hemolysis. Concomitant occurrence of other organ failures and complications including neurologic events, thrombosis, infection, bleeding, and coagulopathy can also contribute to renal injury. ECMO initiation with subsequent adjustments in vasoactive agents can cause rapid hemodynamic fluctuations that alter renal blood flow leading to reperfusion injury associated AKI. FO before and during ECMO contributes to and worsens AKI.[3]

Table 1. Prevention of Fluid Overload in Patients Supported with ECMO

Variable	Clinical Management
Fluid balance	Strict inputs and outputs with clinician evaluation at least every 12 hours Determine and evaluate net fluid balance goals every 12 hours, aiming to achieve even or negative fluid balance Daily weights
Fluid Intake	Minimizing unnecessary intravenous fluids, medications, and blood products Concentration of intravenous medication infusions
Urine output	Goal urinary output of >0.5–1 ml/kg/hour for patients not on renal replacement therapy* Consider urinary catheter placement
Nutrition	Utilizing enteral nutrition over parenteral nutrition whenever possible
Hypoalbuminemia	Consider replacement of albumin for level < 2.5 g/dl

*Depending on clinical situation and fluid balance goals, urine output goals may need to be adjusted to meet fluid balance goals.
ECMO, extracorporeal membrane oxygenation.

Definition. With the lack of a standardized definition for AKI, there is a wide variation in the reported incidence of AKI on ECMO, anywhere between 30% and 85%.[10–12] In a publication by the KIDMO research group, 60% of neonatal and pediatric patients supported by ECMO developed AKI using a definition of an increase in baseline creatinine and 74% developed AKI using a definition of an increase in baseline creatinine and/or the need for renal support therapy.[8] AKI during ECMO is independently associated with both increased duration of ECMO as well as mortality in neonatal and pediatric patients.[7,8] Multiple AKI definitions and staging systems have appeared in the literature over the last 20 years, including RIFLE (risk, injury, failure, loss, end-stage renal disease), AKIN (Acute Kidney Injury Network), and more recently, KDIGO (Kidney Disease: Improving Global Outcomes).[13–15] KDIGO is the most contemporary, expert-endorsed staging system available for the diagnosis and reporting of neonatal and pediatric AKI. In the ELSO Registry International Summary, renal complications are categorized as serum creatinine 1.5–3.0 mg/dl (0.13–0.27 mmol/L), creatinine > 3.0 mg/dl (>0.27 mmol/L), and the requirement for renal replacement therapy. The percentage of ECMO runs with renal complications reported are listed by age category and indication in **Tables 2 and 3**.[16]

Evaluation. Once diagnosed, a detailed history and physical examination should be conducted to determine the underlying cause of AKI, and a multidisciplinary team is advisable. ECMO itself is a recognized risk factor for neonatal and pediatric AKI, as is hypoperfusion secondary to disease processes such as sepsis and cardiac disease. An initial evaluation with urinalysis and renal ultrasound with renal vessel Doppler study to rule out congenital renal anomalies, obstructive uropathy, and renal vein thrombosis should be considered. Providers should assess and ensure adequate mean arterial blood pressure is maintained to perfuse the kidneys. Renal near-infrared spectroscopy (NIRS) may be a useful, noninvasive means of monitoring neonatal and pediatric patients supported with ECMO. Careful and ongoing assessment of volume status including body weight, vital signs, as well as fluid intake and output is necessary as FO is very common and associated with increased mortality in these patients. A thorough review of the medication list to identify and potentially eliminate nephrotoxic agents is also needed and non-nephrotoxic medications should be considered as appropriate. Serial electrolyte monitoring is necessary for the duration of AKI, and electrolyte abnormalities including hyperkalemia and hyponatremia are common in critically ill children.

Management of Fluid Overload and Acute Kidney Injury

Unfortunately, specific therapeutic agents for AKI are limited and care is primarily supportive. Treatment options for FO and AKI during neonatal and pediatric ECMO include

Table 2. October 2021 ELSO Registry Renal Complications 2016 to 2020, Respiratory Indication

	Neonatal Respiratory	Pediatric Respiratory	Adult Respiratory
Cr 1.5–3.0	3.4%	5.3%	11.1%
Cr > 3.0	0.3%	1.6%	5.2%
Renal replacement therapy	24.9%	29.6%	26.8%

ELSO, Extracorporeal Life Support Organization.

Table 3. October 2021 ELSO Registry Renal Complications 2016 to 2020, Cardiac Indication

	Neonatal Cardiac	Pediatric Cardiac	Adult Cardiac
Cr 1.5–3.0	3.8%	6.3%	14.1%
Cr > 3.0	0.6%	1.9%	7.5%
Renal replacement therapy	30.3%	29.6%	27.5%

ELSO, Extracorporeal Life Support Organization.

fluid restriction, diuretics, and continuous renal replacement therapy (CRRT). Intermittent furosemide dosing is a common practice in many institutions as is continuous infusions of diuretics such as furosemide and bumetanide, but little data exist to guide practice. Recently, investigators have developed a "furosemide challenge test" using a single dose of furosemide to challenge and assess renal tubular integrity, with low urine output following a single dose of furosemide predictive of progressive AKI.[17] In such an instance, fluid restriction, rather than continued diuretic challenge, should be strongly considered and early CRRT may be a necessary.

CRRT is frequently utilized during ECMO. In a survey publication by the KIDMO study group, 23% of respondents reported using no CRRT during ECMO. However, the majority of centers used CRRT during ECMO for indications including FO, AKI, and electrolyte abnormalities.[18] The timing of CRRT initiation remains controversial. As the need for CRRT during neonatal and pediatric ECMO is independently associated with increased mortality, providers may be inclined to only utilize CRRT in the face of overwhelming FO or anuria.[7] However, early initiation of CRRT may have a role, as optimizing the timing and delivery of CRRT could positively impact survival through improved fluid balance management.[2,3,19] With this goal in mind, some centers use early CRRT with most of their ECMO patients. In a recent multicenter report, early CRRT utilization, defined as CRRT beginning on ECMO day 0 or 1, was not associated with ECMO mortality or hospital mortality.[20]

Indications for Renal Replacement Therapy on Extracorporeal Membrane Oxygenation

Center-specific expertise and experience with RRT on ECMO currently drive decisions to initiate therapy. The International ELSO guidelines recommend to "return the extracellular fluid volume to normal (dry weight) and maintain it there."[21] There are multiple studies that suggest early RRT to prevent FO may improve outcomes and warrant further investigation. Several studies highlight cumulative FO and its association with increased mortality, length of stay, and duration of mechanical ventilation.[1,22–24] Cumulative FO and failure to return to dry weight are associated with higher mortality and prolonged ECMO duration.[5,25] A decrease in fluid balance is associated with improved lung function and time to weaning of ECMO support.[26]

Technical Considerations for Renal Replacement Therapy on Extracorporeal Membrane Oxygenation

RRT options during ECMO include peritoneal dialysis, intermittent hemodialysis, and CRRT. CRRT is commonly used in ICUs to provide an efficient method of renal replacement and fluid management while ensuring hemodynamic stability. CRRT consists of a broad range of techniques. Several modalities exist based on membrane permeability, method of molecular clearance, and the duration of treatment and equipment used. Previous studies show wide variation in practice regarding RRT during ECMO.[18] Since there are no comparison studies of these techniques, practice is often based on local experience. There are three major methods for performing CRRT during ECMO: 1) independent CRRT access, 2) introduction of an in-line hemofilter into the ECMO circuit, and 3) introduction of a CRRT device into the ECMO circuit.

Independent Renal Replacement Therapy Access

RRT can be provided by obtaining venous access independent of the ECMO circuit. However, this requires line placement done before ECMO or attempting vascular access on an anticoagulated ECMO patient. In neonatal and pediatric patients that require ECMO, establishing adequate vascular access is often challenging. Once a patient is established on ECMO support, the extracorporeal circuit can be used as a platform in which other forms of organ support can be connected without exposing the critically ill patient to the risks of placing additional vascular access.

Introduction of a Hemofilter into the Extracorporeal Membrane Oxygenation Circuit (In-Line Hemofilter)

The introduction of a hemofilter into the ECMO circuit is a technique used to provide CRRT[18] and has the advantage of being relatively simple and inexpensive. The hemofilter is typically placed after the pump to provide forward blood flow and before the oxygenator to trap any air or clots introduced into the circuit. With the hemofilter and the creation of a circuit shunt, there is a discrepancy between the measured flow and the flow being delivered to the patient (which indicates the hemofilter blood flow rate). An ultrasonic flow probe should be placed on the return limb of the ECMO circuit to determine the actual flow delivered to the patient.

Some centers use this technique to provide only slow continuous ultrafiltration, and other centers use an in-line hemofilter in conjunction with renal replacement fluids or dialysis fluids (**Figure 1**). Since these hemofilters are designed for use with high pressure systems, the fiber characteristics make diffusive clearance less effective than conventional membranes. The hemofilter has the potential to generate large amounts of ultrafiltrate, and this is typically regulated using a standard intravenous infusion pump device connected to the effluent port of the hemofilter. These intravenous fluid pumps often have a maximal flow of approximately 1 L/hour. The use of an in-line hemofilter and intravenous fluid pump has been shown to provide less accurate fluid management during ECMO than the use of a CRRT device connected to the ECMO circuit.[27] There are several methods to determine the amount of fluid being removed. Measuring the actual volume of the ultrafiltrate removed by weight or using a volumetric measuring device is common.

Introduction of a Continuous Renal Replacement Therapy Device into the Extracorporeal Membrane Oxygenation Circuit

The CRRT device can be connected to the venous limb of the ECMO circuit before the pump when a roller head pump is used (**Figure 2**). If a centrifugal pump is used, it is preferable to connect the CRRT device after the pump because of the risk

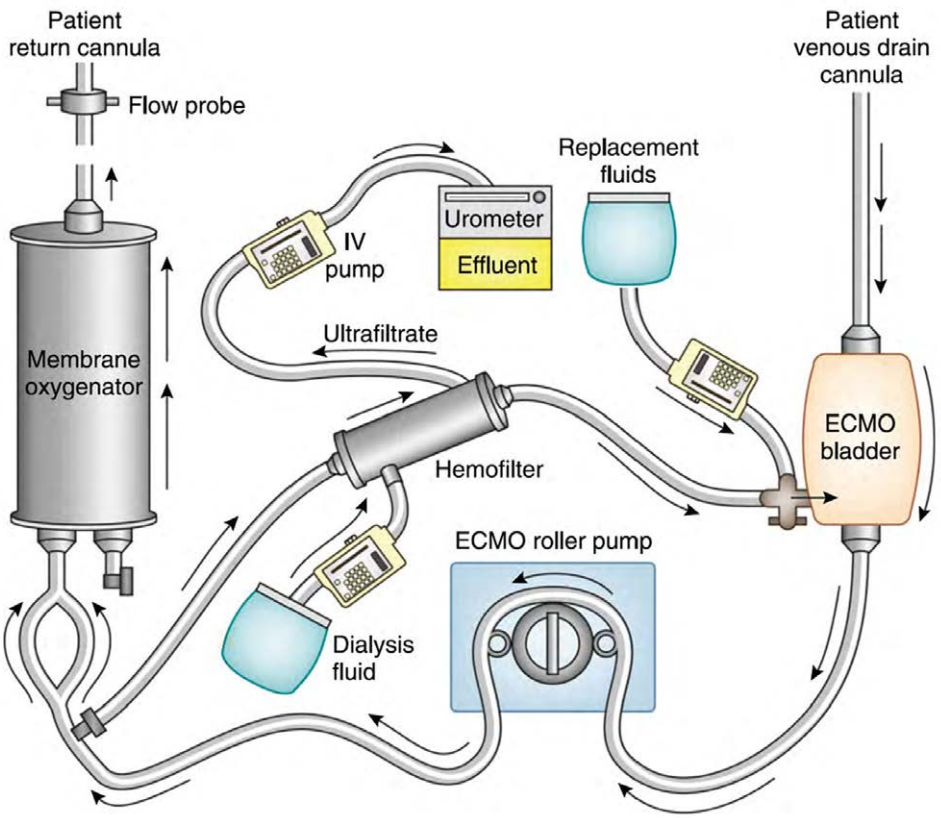

Figure 1. Blood is shunted through a hemofilter that is in-line with the ECMO circuit. Ultrafiltrate production is regulated with an intravenous fluid pump. Renal replacement fluids or dialysis fluids can be used in conjunction with the hemofilter to provide additional solute clearance. Figure originally published in Askenazi *et al.* CJASN 2012;7:1328–1336. Reproduced with permission. ECMO, extracorporeal membrane oxygenation.

of drawing air into the ECMO circuit (**Figure 3**). Regardless of the type of pump used, it is advisable to return blood from the CRRT device to the pre-oxygenator side of the ECMO circuit to ensure that any air or thrombus is sent to the oxygenator instead of being returned to the patient. Longer filter life was achieved with this method than when CRRT was performed through an independent venous access.[28] Software is available for some CRRT devices to allow for positive pressure access or to adjust access alarm limits into the positive range to facilitate the use of CRRT in-line with an ECMO circuit.

Long-Term Implications of Continuous Renal Replacement Therapy During Extracorporeal Membrane Oxygenation

Sparse data are available examining the long-term renal impact of the use of CRRT during ECMO support in children. However, a large single-center study demonstrated that in the absence of primary renal disease, chronic kidney disease did not occur following CRRT utilization during ECMO in neonatal and pediatric patients.[29]

Adult Extracorporeal Membrane Oxygenation Fluid and Electrolyte Management

Fluid Overload

Fluid administration and removal for adult patients supported on ECMO is a common practice. The reasons for FO in adult critically ill patients sustained on ECMO are multifactorial. Although the underlying disease process contributing to severe cardiopulmonary failure may require large volumes of intravenous fluid administration during the initial resuscitation, blood transfusion and fluid loading may be required to maintain adequate ECMO blood flow. Fluids used for drug administration can also contribute greatly to daily inputs and positive fluid balance. It is established that patients requiring ECMO support who develop AKI and FO have higher mortality. Euvolemia can be achieved using diuretics for fluid removal, and CRRT can be used for those refractory to diuretics or with overt renal failure.

The management of vasopressors and fluid therapy is usually driven by clinical endpoints such as maintaining a mean arterial pressure of more than 60–65 mm Hg. Intravascular hypovolemia, chattering of the ECMO circuit, and hyperlactatemia typically invoke volume resuscitation. It is important that ECMO drainage pressures are regularly monitored, keeping in mind that higher negative pressures predispose to a greater degree of hemolysis and should be avoided. Observational studies have shown that a positive fluid balance on day 3 has been associated with poor survival in patients on ECMO.[30–32] Both negative cumulative daily fluid balance and more negative mean daily fluid balance are strongly associated with an improvement in pulmonary compliance in adult patients on VV-ECMO and CRRT.[33]

Acute Kidney Injury and Renal Replacement Therapy

There is wide variability in the reported incidence of AKI during ECMO, given the dissimilarities in clinical settings, patient subgroups, ECMO modes, and the use of diagnostic

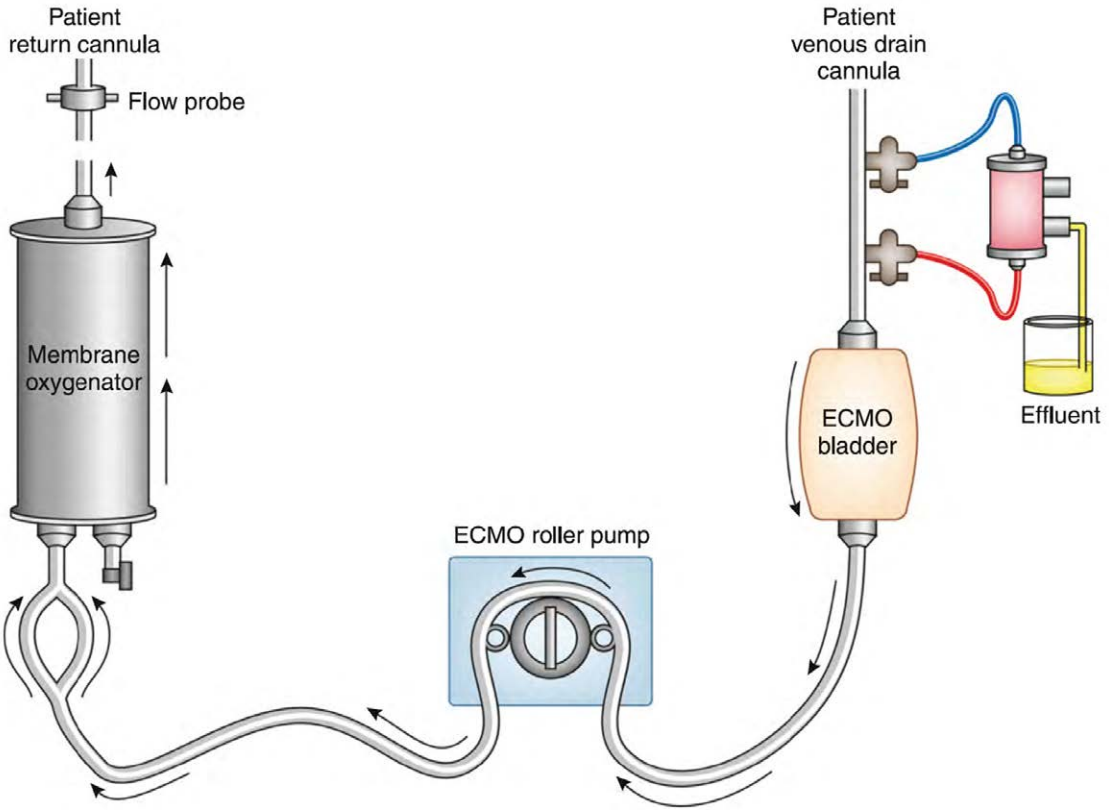

Figure 2. A commercially available CRRT device is connected to an ECMO circuit with a roller-head pump. Figure originally published in Askenazi *et al.* CJASN 2012;7:1328–1336. Reproduced with permission. CRRT, continuous renal replacement therapy; ECMO, extracorporeal membrane oxygenation.

criteria to define AKI. Single-center studies that used the RIFLE definition have demonstrated that the incidence of AKI in adult ECMO is around 78% in patients with respiratory failure[12] and 81% of patients that are postcardiotomy.[34]

Indications and Timing of Renal Replacement Therapy on Extracorporeal Membrane Oxygenation

FO and AKI are the most common indications for RRT on ECMO. RRT has also been used to prevent FO, treat electrolyte disturbances, as well as clear toxins ingested intentionally or accidentally. While single centers have used RIFLE, AKIN, and KDIGO criteria for RRT initiation in adult patients with AKI, the use of RRT for FO is more abstract and is usually done in patients with less severe AKI who are refractory to standard diuretic therapy. Early initiation of CRRT has shown to be beneficial for outcomes in neonates supported with ECMO[35]; however, similar data in adult ECMO patients are currently lacking. It has been established that adult patients with AKI and septic shock had no significant 90-day mortality difference between those assigned to an early strategy (< 12 hours) for RRT initiation *versus* those to a delayed strategy (>48 hours).[36] As a guiding principle, RRT should be considered among adult ECMO patients with FO refractory to diuretic therapy and in situations where AKI causes metabolic derangements that impede the chances of recovery from cardiorespiratory failure.

Technical Aspects of Circuit Adaptations for Renal Replacement Therapy

Intermittent dialysis, sustained low-efficiency dialysis (SLED), and all modalities of CRRT including hemofiltration, hemodialysis, hemodiafiltration, and ultrafiltration can be delivered during ECMO. RRT can be initiated by using a parallel system where a separate vascular access and circuit would ensure that the process does not interfere with ECMO flow. However, the risks of introducing a dialysis catheter in an anticoagulated patient always remain, while limiting the access sites for additional ECMO cannulas. The use of an in-line hemofilter can be cost effective, less resource intensive, and simple to set up. The placement of a commercially available CRRT device in-line with the ECMO circuit can provide excellent control of fluid balance and clearance of solutes that is superior to that provided by an in-line hemofilter. However, this arrangement requires a thorough understanding of the circuit pressures to deliver CRRT safely. ECMO circuit pressures can be highly negative before the centrifugal pump (from –40 to –100 mm Hg) and markedly positive between the pump and the oxygenator, while CRRT machines are programmed to function at low positive venous pressures of 0–20 mm Hg. This may lead to consistent alarms in both circuits and complications related to air entrapment and flow turbulence. As previously mentioned in the pediatric section, in an ECMO circuit with a centrifugal pump, it is strongly recommended that the CRRT device can be connected post

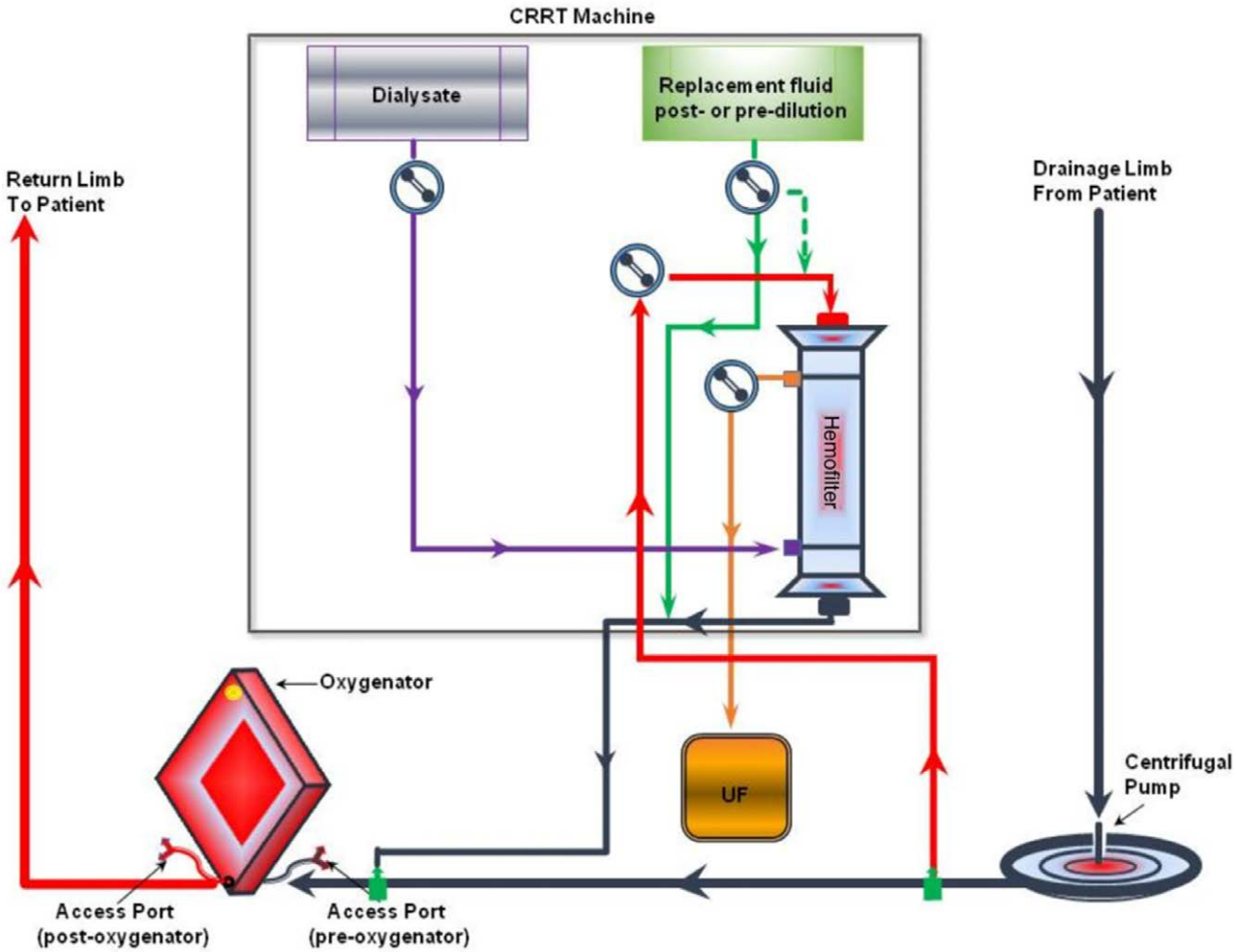

Figure 3. A commercially available CRRT device is connected to an ECMO circuit with a centrifugal pump. Figure originally published in Seczynska *et al*. Ther Apher Dial. 2014;18(6): 523–534 (reproduced with permission). CRRT, continuous renal replacement therapy; ECMO, extracorporeal membrane oxygenation.

pump to prevent air entrapment into the circuit, and that the return from the CRRT device is connected pre-oxygenator/post pump to prevent air or thrombus from being sent to the patient.

Dosing of Renal Replacement Therapy on Extracorporeal Membrane Oxygenation

The dose of RRT is based on the rate of counter current exchange or flow rate of the effluent solution that contains glucose and electrolytes in the physiologic range. However, extrapolating from the critical care literature, an effluent dose of 20–25 ml/kg/hour is generally recommended for patients on ECMO for standard solute clearance. The blood flow in the RRT circuit is typically maintained between 100 and 250 ml/minute. For intermittent dialysis, the prescription is driven by the assessment of the nephrologist or intensivist with an approach similar to other critically ill patients. For SLED, a duration of at least 6 hours is typically applied with a blood flow rate of 200 ml/minute and a dialysate rate of 300 ml/minute.

Renal Recovery After Extracorporeal Membrane Oxygenation–Renal Replacement Therapy

Patients who require ECMO and RRT are often sicker and have a higher risk of death.[37] There is a disparity between the mortality outcomes from single-center studies when compared to the ELSO registry. While single-center studies have reported mortality rates higher than 75% in adults needing concomitant RRT and ECMO,[38] the survival rates reported from the ELSO International Registry Report is 49% for adult respiratory and 32% for adult cardiac patients requiring RRT during ECMO.[16] It has also been established that CRRT during the first 3 days of ECMO initiation was an independent predictor of 90-day mortality.[31] The outcomes are worse in ECMO patients who had AKI requiring dialysis than in those with AKI not requiring dialysis.[35,39] In contrast, ICU mortality was not significantly influenced by the need for RRT when adjusted for confounders in other studies.[40] In a study of patients supported with ECMO for acute respiratory distress syndrome, the need for RRT before ECMO support was independently associated with increased mortality, but the need for RRT during ECMO support was not associated with increased mortality.[41] A recently published study of adults requiring ECMO and RRT established that patients who received RRT for ≥7 days had similar long-term survival to patients who received RRT for fewer days. However, there was a higher risk of end-stage renal disease, ventilator dependence, and readmission rates in those who received RRT for ≥7 days, implying that chronic kidney disease and long-term dialysis could be possible sequelae in those adult patients needing longer duration of RRT on ECMO.[38]

Conclusion

ECMO is being used for an increasing number of patients and for an increasing number of indications. While each ECMO center has its own set of equipment, experiences, and practices, it is imperative that the international ELSO community continues to collaborate to provide a practical and patient-centered approach to address the morbidity and mortality associated with AKI and FO.

Summary

- **FO and AKI are common in neonatal, pediatric, and adult patients supported with ECMO.**
- **FO and AKI are associated with increased morbidity and mortality in patients supported with ECMO.**
- **While some patients supported with ECMO will have FO that is adequately responsive to diuretic therapy, in those patients who are not responsive, early initiation of RRT should be considered.**
- **RRT in conjunction with ECMO allows for solute clearance, correction of electrolyte abnormalities, and the prevention and treatment of FO.**
- **The ECMO circuit provides a platform in which an in-line hemofilter or a RRT device can be connected. This eliminates the need to establish additional access for renal support therapy.**

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