Organ Support

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Combined Extracorporeal Lung and Kidney Support in Fluid Overload

During artificial organ support, kidney injury is multifactorial and related to the high severity of patients treated with extracorporeal membrane oxygenation (ECMO). The successful delivery of continuous renal replacement therapy (CRRT) during ECMO requires a clear prescription of the target solute clearance and fluid removal rate based on the cumulative fluid balance and physiological variables. The role of CRRT and the optimal time, modality, and dose still need clarification.

Introduction

Extracorporeal membrane oxygenation (ECMO) is a widely recognised lifesaving support strategy for the management of patients with severe heart or/and lung failure of various aetiologies. ECMO finds its place when other conventional therapeutic strategies fail (Eckman et al. 2019). Providing support of the lung and/or the heart function, ECMO is a heart and/or lung bridge therapy for resting or replacing organ functioning.

According to the Extracorporeal Life Support Organisation (ELSO) Registry, ECMO patients are at high risk of Acute Kidney injury (AKI); the incidence ranges from 20% to as high as 85% in specific populations (i.e., neonates with congenital diaphragmatic hernia or congenital heart disease). This high variation in reported incidences is based on differences in patients' characteristics, clinical settings and the use of diverse methods to outline AKI (Ostermann and Lumlertgul 2021).

During artificial organ support, the kidney injury is multifactorial and particularly related to the high severity of patients treated with ECMO and the lung-kidney (Gu et al. 2021). Indeed, additional circuit-related risk factors for AKI during ECMO system are represented by non-pulsatile blood flow, blood exposure to the artificial surfaces of ECMO circuit, red cell stress, haemolysis, bleeding, coagulopathy, limb ischaemia, and infection. Even more, patients requiring ECMO with high blood flows are particularly prone to develop fluid overload (FO) that is associated with prolonged use of ECMO and AKI (Patil and Salunke 2020).

Fluid balance (FB) is a fundamental aspect of critical care practice and the association between FO and worse outcome is widely recognised in intensive care (Samoni et al. 2016). For this reason, the assessment of the hydration status, for a tailored FB, represents a central and critical aspect of patients' management (Kalantari et al. 2013). Although volume resuscitation strategy is indispensable for the intravascular volume preservation and organ perfusion, salt and water intake excess can lead to tissue oedema, increasing venous pressure with consequent altered renal blood flow, contributing to ongoing organ dysfunction (Ostermann et al. 2014). Nevertheless, FO plays a well-known negative impact on lung function and recovery. A tight FB evaluation may allow the administration of adequate nutrition and blood produc-

tion avoiding further fluid accumulation with less diuretic intake. Consequently, conservative fluid administration and strategy to prevent or treat FO are essential in critically ill patients, likewise, in ECMO patients (Silversides et al. 2017).

Major indications for renal replacement therapy (RRT) during ECMO are represented by prevention of FO (16%), treatment of FO (43%), AKI (35%) and electrolyte imbalance (4%) (Fleming et al. 2012). RRT during ECMO is usually provided as a continuous modality (CRRT) because of the haemodynamic instability characteristic of such patients. CRRT allows a more constant and reliable fluid elimination and electrolyte adjustment over a longer period of time. ECMO and CRRT can be combined in two main modalities; parallel approach vs integrated application (Martins-Costa et al. 2022). The choice of the modalities is influenced, generally, by local experience and technical availability. Both techniques present advantages and disadvantages and it is vital to know the drawback and the potential of such technologies before CRRT initiation (Ostermann et al. 2018).

Central aspect of effective delivery of CRRT during ECMO is represented by a clear prescription of the target solute clearance and fluid removal rate with regular reassessment and re-adjustment of the prescription based on the changing needs of the patient (Tandukar and Palesvsky

2019). Finally, while the deleterious impact of AKI and FO on outcomes for ECMO patients is clear, critical questions that warrant further study remain regarding the device, the modality, and the optimal timing of initiation.

Fluid Balance in Critical Care

In ECMO patients, fluid management is critical to prevent complications such as fluid overload, which can lead to oedema, hypoxaemia, and increased mortality. Particularly, positive fluid balance is associated with increased mortality, especially in patients with underlying cardiorespiratory and renal disease (Malbrain et al. 2014; Neyra et al. 2016). Several factors are responsible for fluid overload and the consequences are multisystemic. Therefore, the restoration of euvolaemia is an essential goal in intensive care settings (Kim et al. 2022). FO is also proven to increase the length of mechanical ventilation, the incidence of AKI, the need of CRRT, and the risk of infection and of intra-abdominal hypertension (Salahuddin et al. 2017). AKI, oligo-anuria, positive pressure mechanical ventilation, stress response retention of sodium and water, abdominal compartment syndrome, and iatrogenic simultaneous fluid loading are potential risk factors of FO (Wang et al. 2015). Concurrently, an inadequate fluid balance evaluation and an insufficient fluid unloading strategy may even worse fluid retention.

The consequence of excessive fluid administration and retention leads to an expansion of interstitial space and increased venous congestion. The resulting elevated mean circulatory filling pressure, and the altered transmural pressure of the circulatory system leads to tissue oedema, severe hypoalbuminaemia, inflammatory capillary leakage and impaired lymphatic drainage that in turn may impair intra-abdominal pressure, cardiac function and pulmonary gas exchange, and also reduce lung compliance, increases the work of breathing, potentially leading to a multiorgan failure (Monnet and Teboul 2018). Additionally, venous congestion and increased intraabdominal pressure are well recognised risk factors of AKI

development, with a huge impact of fluid removal. Increased venous pressure alters renal blood flow with consequent inadequate glomerular filtration rate (Doty et al. 1999).

In order to tailor fluid balance to the needs of patients, it is also crucial to set specific treatment strategies in different clinical situations (e.g., resuscitative vs. post-resuscitative phase) to prevent or treat FO (Ramesh et al. 2019). In an intensive care setting, specific patient demands can vary quickly, and sometimes conflicting requirements may coexist (Malbrain et al. 2018). Indeed, in the acute "resuscitative" phase, fluid administration is mandatory to reach haemodynamic goals. Even more, large amounts of fluid are often required in order to meet nutrition demand or drug dosage targets. In all these situations, CRRT may represent an important aid, allowing the continuous manipulation of net fluid removal. Even if there is not a solid conclusion about the optimal timing of initiation and CRRT modality, CRRT may allow clinicians to meet the dynamic changes in a patient's fluid requirement (Prowle and Mehta 2021). Clinicians have to evaluate at fixed intervals, the total volume of fluid that is essential to be removed, in the light of fluid administration required to meet specific needs, and of haemodynamic and volume status (Neyra et al. 2022). In order to provide precise fluid management therapy, CRRT can regulate, not only the total volume of fluid removal, but also the rate of fluid removal (Murugan et al. 2016). This is particularly important in haemodynamic unstable critical care patients, also to maintain a physiological plasma refilling rate.

Finally, another important aspect to consider is the fact that fluid administration is important for the maintenance of the patency of the CRRT circuit itself. Fluids administered before the filter (pre-dilution) can maintain circuit integrity and prevent clotting formation. Fluid balance can be achieved modifying the ultrafiltration rate and the replacement fluid, keeping in mind that the variation of the effluent volume will affect solute clearance (dose) (Claure-Del Granado and Clark 2021).

Continuous monitoring of circuit integrity is essential for optimal delivery of CRRT and patient safety.

Fluid Status Assessment in ECMO Patients

Fluid status assessment is an essential part of the management of patients undergoing ECMO therapy (Freitag et al. 2010). Although the clinical examination includes a physical examination of the patient for signs of fluid overload, precise fluid assessment and recording is extremely challenging in a critically ill setting. Daily weights could be an essential tool for fluid status assessment in patients with extracorporeal multiorgan support, but it is necessary to record the "dry body weight" (i.e., weight before fluid resuscitation) with a goal to return from the extracellular volume to normal (dry weight).

There are several formulas that can be used to assess fluid status in ECMO patients. Fluid balance can be calculated by subtracting total fluid output (urine output, insensible losses, drainage) from total fluid input (oral, intravenous, enteral). Net fluid balance could be calculated by subtracting the amount of fluid removed by ultrafiltration or haemofiltration from total fluid input. This formula can help assess the effectiveness of fluid removal therapy. In addition, cumulative fluid balance could be assessed as the sum of daily fluid balance over a defined period, such as 24 hours or 48 hours. This formula can help assess trends in fluid status over time. Extracellular fluid volume (ECFV) could be also determined by body weight×(1−haematocrit)×0.9. This formula assumes that the haematocrit is a good estimate of the intravascular volume. It is important to note that these formulas should be used in conjunction with clinical examination and other monitoring methods to assess fluid status accurately in ECMO patients. However, haemodynamic monitoring can help determine fluid status and guide fluid management.

Indeed, predicting fluid responsiveness is important in avoiding unnecessary fluid administration, reducing the risk of renal failure, and improving outcomes for criti-

cally ill patients. Although pulse pressure variations and stroke volume variations accurately predict fluid responsiveness during mechanical ventilation, unfortunately there is scarce evidence on fluid responsiveness assessments in patients with ECMO (Yang and Du 2014; Jozwiak et al. 2018). Luo et al. (2021) found that changes in left ventricular outflow tract velocity-time integral (ΔVTI) induced by the Trendelenburg manoeuvres could effectively predict fluid responsiveness in VA-ECMO patients.

Bedside ultrasound can be used to evaluate fluid status in ECMO patients. Non-invasive ultrasonographic assessment of skin tissue thickness seems to give further information to identify fluid shifts to the extravascular space and to guide fluid management (Sarvazyan et al. 2005; Wagner and Cotter 2021). The evaluation of the interstitial thickness measuring the distance between superficial dermis surface and the bone tissue interface in the calcaneus area with a linear array transducer is one of the proposed methods to determine hydration status. The measurement of subcutaneous tissue depth between the skin surface to the adipose-muscle boundary in four different body areas (i.e., upper anterior chest, lateral chest, lateral abdomen and anterior tight) could be another tool to estimate FB. These methods, even if particularly interesting, still require further evaluation.

Obviously, point of care ultrasound (POCUS) to assess volume status have gained a huge role in fluid management for intensive care specialists in the last years (Argaiz et al. 2021). However, despite the assessment of inferior vena cava collapsibility and the presence of pleural effusions that can help identify fluid overload, the use of VV-ECMO and VA-ECMO always entails presence of semi-rigid central venous cannula(s) occupying the inferior vena cava (IVC) to a variable extent, thereby limiting its collapsibility (Via et al. 2016).

In addition, the negative venous pressure that can interfere with the IVC size and respiratory dynamics, the masses compressing/occupying the vessel, vena cava filters or IVC thrombosis can equally affect physiological IVC patency and size. However, a deep description of the role of LUS and ultrasonographic haemodynamic evaluation (i.e., inferior vena cava collapsibility index – IVC CI) for fluid management is beyond the scope of this paper.

Bioelectrical impedance vector analysis (BIVA) may represent a viable promising tool that involves the measurement of electrical resistance to assess body composition, including extracellular fluid volume (Samoni et al. 2016; Basso et al. 2013). Although BIVA can reflect the fluid overload state earlier and bypass errors due to fluid balance accounting, it is not well investigated in both ECMO and integrated systems settings (Wang et al. 2021).

Fluid Overload in ECMO Patients

Due to the severity of the underlying disease and to the intrinsic characteristic of the circuit, patients on ECMO may receive a large volume of crystalloids and blood products (Chiu et al. 2021). In order to maintain a sufficient rate of vascular blood drainage for ECMO flow, clinicians often administered large volumes of fluid especially during the initial phases of ECMO. Even more, due to the several complications that may arise during the treatment (e.g., bleeding, anaemia, coagulopathies), patients also receive an important amount of blood products. Fluid administration is important for the maintenance of the patency of the ECMO circuit and to prevent premature circuit changes. This liberal approach of fluid infusion during ECMO exacerbated the underlying disease, often characterised by systemic hypovolaemic status. Even more, blood exposure to the artificial surfaces of ECMO circuit, can worsen systemic capillary leakage, with consequent increase in interstitial and tissue oedema. To make things worse, the high concomitant prevalence of AKI in ECMO patients, reducing fluid output, aggravates fluid overload (Cheng et al. 2014).

Fluid overload can exacerbate the underlying cardiopulmonary disease and prolong cardiorespiratory recovery and time to ECMO weaning. FO during ECMO has been associated with prolonged ECMO duration and mortality (Selewski et al. 2017). Another important aspect that emerges from the existing literature is that a percentage of ECMO patients (up to 50%) present FO before ECMO cannulation and that higher level of FO at CRRT beginning is associated with increased mortality and ECMO duration. Consequently, pre-ECMO fluid balance represents an important target intervention. Even more, He et al. (2018) found that fluid balance on the third day of ECMO initiation and lactate level at CRRT beginning both represent prognosis independent risk factors for patients undergoing CRRT while on ECMO. Therefore,
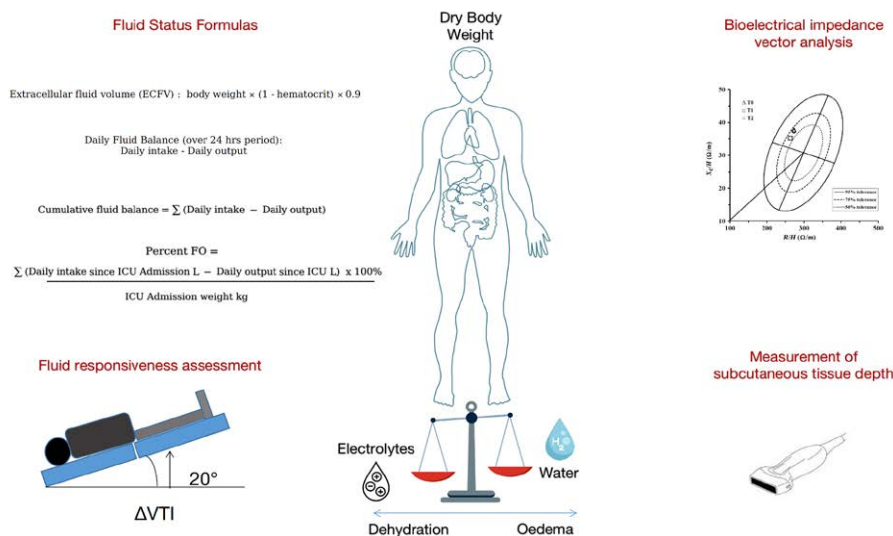
Figure 1. Methods to evaluate the determination of fluid balance and fluid overload

Fluid Status Formulas

Extracellular fluid volume (ECFV) : body weight × (1 - hematocrit) × 0.9

Daily Fluid Balance (over 24 hrs period): Daily intake - Daily output

Cumulative fluid balance = Σ (Daily intake − Daily output)

Percent FO = $\frac{\Sigma \text{ (Daily intake since ICU Admission L} - \text{ Daily output since ICU L)}}{\text{ICU Admission weight kg}} \times 100\%$

Fluid responsiveness assessment

20°

ΔVTI

Dry Body Weight

Electrolytes   Water

Dehydration   Oedema

Bioelectrical impedance vector analysis

Measurement of subcutaneous tissue depth

even if volume resuscitating strategy is fundamental especially during initiation of ECMO treatment, excessive volume overload impacts survival and outcome (Schmidt et al. 2014). However, to find a specific threshold is still challenging. From this perspective, the possible correlation between specific threshold of fluid balance (mL/kg) and mortality warrants further studies (Kim et al. 2018). Even more, it will be interesting to evaluate if the threshold diverges according to the indication for ECMO treatment (i.e., cardiovascular versus respiratory disease).

The prevention or the treatment of FO in these kinds of patients can require aggressive use of diuretics with potential collateral effects or fluid restriction with consequent reducing ideal caloric intake.

Consequently, the addition of CRRT during ECMO can diminish the administration of diuretics and allow a precise nutritional target. However, also in this group of patients, open questions still exist on the optimal timing, dose prescription target, and ideal modality technique (Paek et al. 2018).

However, FO is a common complication in paediatric patients receiving ECMO therapy, and it can have serious consequences such as pulmonary oedema, decreased oxygen delivery, and increased mortality. Over 75% of patients had a positive fluid balance while on ECMO, suggesting that FO and the ability to achieve a negative fluid balance are potentially important therapeutic targets (Selewski et al. 2017; Sakurai and Singhal 2022). The ability to

achieve a negative fluid balance on ECMO is associated with improved survival. CRRT provides flexibility and control in fluid management and has been shown to enhance the ability to achieve dry weight and negative fluid balance during ECMO (Rajapreyar et al. 2021).

Taken together with the epidemiology of FO and its independent association with adverse outcomes in this study, these results suggest that a trial utilising CRRT to manage fluids in children on ECMO may be warranted and probably as a need for earlier intervention. While these studies provide some evidence for the use of ECMO-CRRT integrated systems in managing fluid overload in the paediatric population, larger, randomised controlled trials are needed to establish the safety and

Authors/Year	Study Design	Participants	Method of Fluid Overload Assessment	AKI, RRT and Modality	Integrated Systems	Findings
Hoover et al. 2008	Retrospective case-matched study (patients receiving CRRT +ECMO vs. ECMO alone)	52 paediatric patients with respiratory failure receiving ECMO with CRRT	Fluid balance was calculated as the difference between fluids (ml) in and out over total ECMO course divided by weight (kg) divided by total ECMO days (ml kg^{-1} day^{-1}). Fluid overload was not defined.	No AKI classification used. 26 (30% of respiratory failure ECMO) required RRT CVVH modality for all patients.	CRRT combined (in-line) with ECMO.	Use of CVVH in ECMO was associated with improved fluid balance and caloric intake and less diuretics than in case matched ECMO controls.
Blijdorp et al. 2009	Retrospective single centre, case-comparison study	61 new-borns (less than 28 days postpartum) on ECMO treated with RRT	Fluid balance was assessed as mean net fluid balance per ECMO day, by measuring total fluid input and output and dividing the difference by the time on ECMO. The difference between predilution and filtration flow rate was included.	No AKI classification used. Ultrafiltration was targeted to achieve a normal or negative fluid balance depending on the clinical condition of the patient while maintaining normal haemodynamic parameters.	Haemofilter placed parallel to the ECMO circuit, distal to the ECMO roller pump.	Haemofiltration during ECMO improves clinical outcome. This is expressed by a shorter duration of ECMO treatment, and of mechanical ventilation after ECMO. Moreover, the use of haemofiltration resulted in fewer blood transfusions in this group.
Schmidt et al. 2014	Retrospective single centre study	172 adult critically ill patients receiving VA -ECMO or VV-ECMO	Daily FB was calculated as the difference between fluid administered and fluid loss (dialysis effluent–dialysate from CRRT, urine output, enteral losses, drain losses) in a 24-h period. Negative daily FB was present when fluid loss was greater than fluid administered per day.	Incidence of RIFLE-defined AKI. 46 (27%) required RRT. RRT modality not specified.	CRRT combined (in-line) with ECMO.	Patients who had positive fluid balance on ECMO day 3, regardless of RRT status, were more likely to experience 90-day mortality. In their adjusted analyses, day-3 fluid balance was an independent predictor of long-term mortality. In addition, 60% (n=103) of patients received RRT in the setting of ECMO and receipt of CRRT did not guarantee negative fluid balance.
Selewski et al. 2015	Retrospective single centre study	53 paediatric critically ill patients receiving VA -ECMO or VV-ECMO	The change in FO while on CRRT was determined as follows: Change in FO = Initiation FO – Discontinuation FO FO was also examined as a categorical variable using a cut-off of 10% (<=10% versus >10%) and 20% (<=20% versus >20%).	No AKI classification used. 57 (28%) required RRT. RRT modality was CVVHD (until 2008) and CVVHDF.	Haemofilter placed parallel to the ECMO circuit (until 2008) and CRRT combined (in-line) with ECMO.	The association between FO at CRRT initiation and mortality was found. The degree of FO at CRRT discontinuation is also associated with mortality but appears to reflect the effect of fluid overload at initiation. The correction of FO to ≤ 10% was not associated with improved survival.
Selewski et al. 2017	Retrospective multicentre study	753 children < 18 years of age receiving VA -ECMO or VV-ECMO	Daily cumulative percent FO Cumulative percent FO Change in FO on ECMO = Discontinuation FO% - Initiation FO %	Incidence of KDIGO-defined AKI. 380 (50.4%) required RRT. RRT modality not specified.	Integrated system not specified.	Severe FO commonly occurs in children on ECMO and that worse FO during ECMO is associated with mortality and ECMO duration, independent of other factors, including the presence of AKI.
McCanny et al. 2019	Retrospective single centre study	24 adult patients supported by VV-ECMO and concomitant continuous renal replacement therapy.	Daily fluid balance was calculated as the difference between all fluids in and out per day, and cumulative fluid balance was the sum of daily fluid balances for all ECMO days.	Incidence of KDIGO-defined AKI. All patients were in acute kidney failure. RRT modality not specified.	CRRT combined (in-line) with ECMO.	Negative cumulative daily fluid balance was strongly associated with improved pulmonary compliance. 79% placed on CRRT day 1 of ECMO. Early CRRT with fluid removal is associated with trend to survival. Fluid removal associated with increased pulmonary compliance.
Gorga et al. 2020	Retrospective multicentre study	357 children < 18 years of age concurrently treated with ECMO and CRRT.	Daily cumulative percent FO was determined using daily intake and output for the 28 days prior to ECMO cannulation and the first 21 days following cannulation. Fluid overload was calculated at multiple time-points (CRRT initiation, CRRT discontinuation). Change in FO on CRRT = FO% at CRRT. Discontinuation - FO % at CRRT Initiation.	Incidence of KDIGO-defined AKI. All patients were in acute kidney failure. RRT modality not specified.	Haemofilter placed parallel to the ECMO circuit and CRRT combined (in-line) with ECMO.	Severe FO occurs commonly in children supported by ECMO prior to CRRT initiation and that worse FO at CRRT initiation and at discontinuation is associated with increased mortality and duration of ECMO.

Mallory et al. 2020	Retrospective single centre study	424 paediatric critically ill patients receiving VA -ECMO or VV-ECMO 261 (63.9%) of those patients were neonatal, and 153 (36.1%) patients were paediatric.	Daily cumulative FO was calculated using the daily total fluid intake and total fluid output recorded from ICU admission up to 28 days before ECMO cannulation and up to 21 days after cannulation. Cumulative FO was also calculated. The change in FO between ECMO initiation and discontinuation was calculated using the cumulative FO at those times.	Incidence of KDIGO-defined AKI. All patients were in acute kidney failure. RRT modality not specified.	Renal support therapy was defined as peritoneal dialysis, continuous renal replacement therapy using a commercially available device, intermittent haemodialysis, or the use of haemofilter in line with the ECMO circuit.	Volume overload was associated with longer duration of mechanical ventilation and increased morbidity and mortality. In their cohort, 44% of patients received RRT and, as with our cohort, patients remained in positive fluid balance despite ECMO and RRT support.
Fong et al. 2020	Retrospective single centre study	123 adult critically ill patients receiving VA -ECMO or VV-ECMO.	Daily Fluid Balance (Fluid intake - Fluid output) Cumulative Fluid Balance (the sum of the fluid balance on the preceding days). Fluid overload was defined as positive fluid balance.	Incidence of RIFLE-defined AKI. 63 (51.2 %) required RRT. RRT modality not specified.	CRRT combined (in-line) with ECMO.	A more positive fluid balance was found in non-survivors; non-survivors had lower urine and fluid outputs; and fluid intake was not associated with hospital mortality. After adjusting for potential confounders, the cumulative fluid balance on day 7, but not on day 3, was independently associated with hospital mortality.
Gunning et al. 2020	Retrospective single centre study	98 adult critically ill patients receiving VA -ECMO or VV-ECMO.	Cumulative fluid balance was categorised into three groups: negative (negative cumulative fluid balance), no volume overload (positive cumulative fluid balance but not >10% of admission weight), and volume overload (defined as achieving a positive fluid balance of 10% above admission weight over the first 72 hours after ECMO cannulation.	Incidence of KDIGO-defined AKI. 48 (58%) required RRT. CVVHD modality for all patients.	CRRT combined (in-line) with ECMO.	Patients with volume overload had an increased risk of death at 90 days compared with those without volume overload. Patients with AKI requiring RRT had an increased risk of death at 90 days compared with those without. Volume overload remained an independent predictor of 90-day mortality when adjusting for RRT, APACHE score, weight, diabetes, and heart failure.
Besnier et al. 2020	Retrospective single centre study	101 Adult Critically Ill Patients receiving VA -ECMO.	The cumulative fluid balance was obtained by the addition of each daily fluid balance from the starting of VA-ECMO therapy until the day of evaluation.	Incidence of KDIGO-defined AKI. 48 (58%) required RRT. RRT modality not specified.	Integrated system not specified.	Early and positive fluid balance was associated with worse outcomes in patients treated with VA-ECMO.
Dado et al. 2020	Retrospective single centre study	92 adult critically ill patients receiving VA -ECMO.	Fluid balance but not specified if daily and cumulative were considered.	Incidence of KDIGO-defined AKI. 48 (53.3%) required RRT. CVVH modality for all patients.	CRRT combined (in-line) with ECMO.	The use of CRRT is prevalent among patients undergoing ECMO. Fluid balance appears to be an important variable associated with outcomes in this cohort. Rates of renal recovery and overall survival were higher compared to previously published reports among those requiring combined ECMO/CRRT.
Murphy et al. 2021	Retrospective multicentre study	446 neonates receiving VA -ECMO.	Percent FO (%FO) was determined using. daily fluid intakes and outputs. Cumulative %FO was calculated using the following equation: %FO = {[Sum of Daily (Fluid in – Fluid out) (L)]/[ICU Admission weight (kilograms)]} × 100. Cumulative % FO was determined at ECMO and RRT initiation and discontinuation; peak % FO during ECMO was also determined.	Incidence of KDIGO-defined AKI . 195 (44%) required RRT. PD: 3 (2%). RRT (not better specified): 24 (12%). Inline haemofilter: 165 (86%).	RRT included peritoneal or intermittent haemodialysis, continuous RRT, or slow continuous haemofiltration.	96% of neonates with cardiac disease and AKI received. VA ECMO. Physiologically distinct. ECMO diagnoses warrant individualised treatment strategies given variable incidence and effects of AKI, FO, and RRT by category on mortality.

Table 1. Studies evaluating fluid overload and integrated systems in critically ill patients in the last years.
AKI, Acute Kidney Injury; APACHE II score, The Acute Physiology and Chronic Health Evaluation; CRRT, Continuous renal replacement therapy; CVVH, Continuous Veno- venous hemofiltration; CVVHD, Continuous venovenous haemodialysis; FO, Fluid Overload; KDIGO, Kidney Disease Improving Global Outcomes; RIFLE, Risk, Injury, Failure, Loss of kidney function, and End-stage kidney disease; RRT, Renal replacement therapy; VA-ECMO, Veno-arterial extracorporeal membrane oxygenation; VV-ECMO, Veno-venous extracorporeal membrane oxygenation

efficacy of this approach. In the meantime, fluid management should be closely monitored in paediatric patients on ECMO, and a multidisciplinary team approach should be taken to optimise patient outcomes. **Table 1** shows studies evaluating fluid overload and integrated systems in critically ill patients.

Indications and Modality for Integrated Systems

Indications for ECMO-CRRT integrated systems are represented by severe acute respiratory distress syndrome (ARDS) and AKI who require both respiratory and renal support, sepsis or multi-organ failure who require simultaneous ECMO and CRRT therapy, cardiac arrest who require ECMO and CRRT for haemodynamic and metabolic stabilisation.

During ECMO, RRT can be provided by introducing a haemofilter or RRT circuit into the ECMO circuit (integrated system) or independently via a separate catheter and circuit (parallel system) (Chen et al. 2014; Kielstein et al. 2013). Parallel systems are not the objective of the present paper.

The ECMO-CRRT integrated systems are typically configured in three different ways as following:

1. In-line haemofilter (**Figure 2, Panel A**): In this modality, the CRRT circuit is connected in-line with the ECMO circuit, allowing for continuous ultrafiltration and dialysis. The filter inlet is typically connected after the oxygenator in the ECMO circuit to avoid interference with gas exchange and the outlet is reconnected to the ECMO circuit to allow the return of the blood before it enters the oxygenator. The blood from ECMO circuit is shunted through in-line haemofilter. The intravenous pump allows the control of fluid removal. The fluid replacement or dialysis fluid can allow an additional solute clearance.

2. Side-by-side (**Figure 2, Panel B and C**): In this modality, the ECMO and CRRT circuits are arranged side-by-side, with a common venous access and a common arterial return, also possible via existing Luer locks on the inlet and outlet ports of the oxygenator. It requires a larger footprint and more complex tubing arrangement. There is no need for separate vascular access and anticoagulation.

This modality allows the control of pressures inside the circuit but also for higher ultrafiltration rates without the need of an external pump with better clearance of solutes (Chen et al. 2014). However, not all devices are able to recognise pressure changes leading to iterative stops and interruptions in treatment. In addition, the integration after ECMO motor pump could evoke high pressure alarms (de Tymowski et al. 2017). Therefore, since the two integrated circuits have two different pressure levels, the pressure differences can cause extremely risky situations with a shunt effect inside the ECMO circuit. The integration could be possible, and it is strongly suggested that the blood return to the ECMO circuit before the oxygenator.

The modality chosen should depend on the patient's specific needs and the available resources. The use of ECMO-CRRT integrated systems requires expertise in both ECMO and CRRT therapies and should only be performed by trained healthcare professionals.

Effects of Integrated Systems on Outcome

There is no strong recommendation on the optimal RRT modality during ECMO and the decision depends on local expertise and availability. The role of CRRT in modifying the outcome in ECMO patients is still uncertain.

Several published articles found that the mortality was high in patients receiving ECMO and CRRT in comparison with ECMO alone (Chen et al. 2014; Mitra et al. 2021; Han et al. 2015). However, it is important to stress that this data has to be interpreted with caution. First, the impact of the severity of AKI itself may contribute to the increased mortality in such fragile patients. Even more, AKI requiring RRT is associated with other life-treating complications (e.g., sepsis, immunodeficiency, hepatic failure, bleeding, neurological complications), increasing the severity of the underlying disease of ECMO patients. Nevertheless, the high heterogeneity of initiation, FO evaluation modalities and the differences in AKI definitions may have to be considered. Furthermore, there is no clear evidence that the different strategies (i.e., parallel, integrated) may impact mortality or ECMO duration. Noteworthy, the aetiology of AKI in patients on ECMO is multifactorial, consequently, even if the studies are matched for severity of illness, it is difficult to come to any solid conclusions (Martins Costa et al. 2022). Central risk factors for mortality in ECMO patients with AKI are represented and not limited to age, AKI stage, RRT duration, hypercapnia, multiorgan failure syndrome, blood loss, transfusion requirement, haemodynamic instability, liver failure, and fluid overload (Ostermann and Lumlertgul 2021).

Not only the short-term outcome but also long-term outcomes and renal recovery are other important aspects that warrant major attention. Up to now, the renal recovery, the rate of liberation from dialysis, chronic kidney disease rate and quality of life is still indeterminate and require major evaluation in future trials. What seems to emerge from the existing literature is that lower GFR at baseline, higher AKI stage prior ECMO cannulation, transfusion requirement represents risk factor for 1-year major adverse kidney events. Consequently, the risk of kidney events in ECMO survivors has to be precisely evaluated (Ostermann and Lumlertgul 2021).

Complications related to CRRT during ECMO may arise during vascular placement of the cannula (e.g., bleeding, pneumothorax, haemothorax, retroperitoneal haemorrhage, vascular injury, arterial puncture, fistula formation) and during the treatment itself (e.g., infection, thrombosis, arrhythmias, hypokalaemia, hypophosphataemia, hypothermia, nutrient losses, haemolysis, intracranial haemorrhage and gastrointestinal bleeding). Special attention has to be put on the prevention of air embolism that can arise in several procedures during the treatment (e.g., central line insertion, connecting/disconnecting CRRT or infusions and flow variations due to the interaction of pressure and flow of ECMO and CRRT system). Another vital aspect is represented by a tight control of the anticoagulation regimen (e.g., systemic, regional) in order to prevent thrombosis,
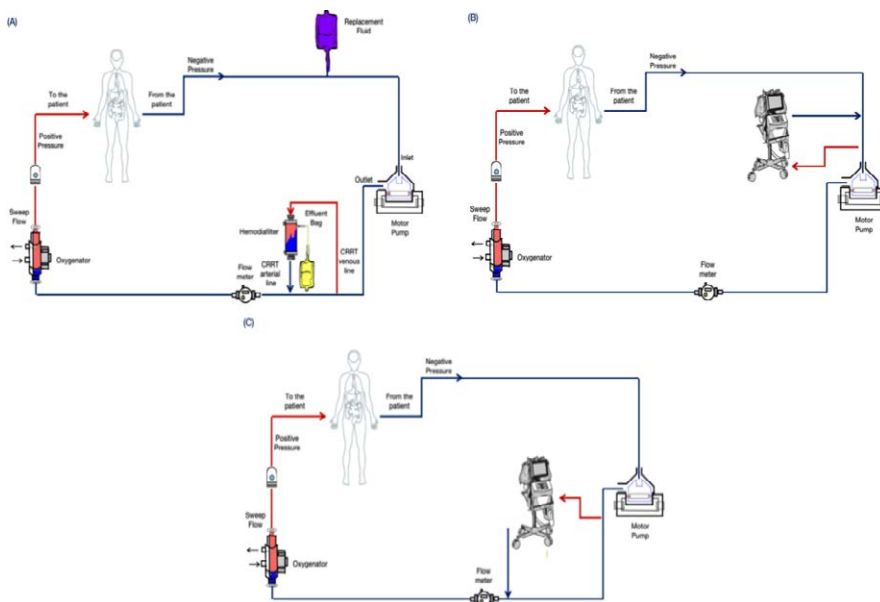

Figure 2. Methods for integrated approach of renal replacement therapy with extracorporeal membrane oxygenation. Panel A shows the in-line haemofilter configuration while Panel B and Panel C show side by side configuration. CRRT - continuous renal replacement therapy.

bleeding, premature circuit clotting and to increase circuit patency (Selewski and Wille 2021). However, in a 2014 systematic review, the authors found that the integration of ECMO and CRRT systems appear to be safe and effective with improvement in fluid removal and electrolyte disturbances (Chen et al. 2014).

Technical Issues

Each specific modality system to perform CRRT during ECMO presents specific advantages and drawbacks that need to be known before initiation of the treatment. A deep understanding of intra-circuit pressure and flow is essential to guarantee safety during the treatment (Ostermann et al. 2018; Wu et al. 2023; Na et al. 2018).

An integrated system is characterised by the introduction of an in-line haemofilter or a CRRT machine into the ECMO circuit. The introduction of a haemofilter requires a smaller priming volume compared to a parallel approach. However, ECMO circuit is characterised to work with negative pressure in the drainage part of the circuit (e.g., -20 to -100mmHg) and with positive pressure between the pump and oxygenator and between the oxygenator and the patients (Kashani and Ostermann 2019). Conversely, the CRRT machine generally works with venous pressure (from and to the patients) from about o to 30 mmHg. Furthermore, the flow within ECMO circuits is higher (3500-5000ml/min) than those working on a CRRT system (100-200mL/min). Possible complications of pressure and flows differences are represented by air entrapment, turbulences, haemolysis,

increasing shear stress and alarms out of range. Another important implication of an in-line system is represented by the difficulty of the net ultrafiltration evaluation due to the fact that part in-line system required an external infusion pump and the presence of tube ramification within the circuits (Askenazi et al. 2012). This led to an important difference between prescribed and actual ultrafiltration rate. Using a CRRT machine within the ECMO circuit can obviate of this issue (de Tymowski et al. 2017). A CRRT circuit allows to control pressure, ultrafiltration without an external pump with a more precise control of effluent volume (Santiago et al. 2009). However, also in this setting, problems with pressure alarms and connection lines may arise with consequent interruption in the treatment or complications such as air embolism and flow turbulence. Not to be underestimated, the introduction of an integrated system within the ECMO system with tube ramification is responsible of blood shunt off ECMO circuit with consequent potential alteration in oxygenation and blood flow.

Of course, such technical aspects and possible complications are not encountered in parallel systems, characterised by an independent circuit to deliver either ECMO or CRRT modalities (Martins Costa et al. 2022). In the parallel approach, no interferences are encountered between ECMO and CRRT techniques (Seczyńska et al. 2014). CRRT can be prescribed and monitored independently from ECMO and not to be underestimated, CRRT changing can be accomplished with less

risk and without the contribution of an ECMO expert. However, a separate vascular access is required, with possible consequent bleeding, infection and thrombosis risk (Subbarayan et al. 2021). Even more, the use of a vascular site for CRRT may diminish the choice of access site in case of the necessity of an additional cannula for a higher output of ECMO treatment. Furthermore, the usage of an independent circuit increases the artificial surface with increased risk of activation of coagulation cascade, systemic inflammation, shear stress and haemolysis.

In order to obviate the aforementioned issue, novel extracorporeal devices are currently under development, with particular attention on fibre arrangement, filtration mode, artificial surface characteristics and connections (Tang et al. 2022).

Conclusions

The successful delivery of CRRT during ECMO requires a clear prescription of the target solute clearance and fluid removal rate based on the cumulative fluid balance and physiological variables (haemodynamic, oxygenation). Treatment monitoring and re-adjustment are necessary and are based on patients need. While the deleterious impact of AKI and FO on outcomes for ECMO patients is clear, critical questions warranting further study remain regarding the role of CRRT in patient management, including device, modality, and optimal timing of initiation.

Conflict of interest

None. ■

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