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Extracorporeal Membrane Oxygenation and Continuous Renal Replacement Therapy

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Abstract

Extracorporeal membrane oxygenation (ECMO) is a supportive therapy, which provides cardiopulmonary and end-organ support in critically ill patients when other measures fail. These patients receive large amounts of fluid for volume resuscitation, blood products and caloric intake, which results in fluid overload and which in turn is associated with impairment of oxygen transport and increased incidence of multiple organ failure especially heart, lungs and brain. It is common to see a decrease in urine output during ECMO that may be associated with acute renal failure. The acute renal failure is a manifestation of multiple organ system failure due to acute decompensated heart failure, sepsis, hemolysis, use of vasopressors/inotropes, nephrotoxic medications, and activation of complement system during ECMO support. It is associated with poor prognosis and higher mortality in ECMO patients. Continuous renal replacement therapy (CRRT) in patients on ECMO provides an efficient and potentially beneficial method of fluid overload and acute kidney injury management. In addition, recent data suggest that the use of CRRT may remove inflammatory cytokine released as a result of circulation of blood across synthetic surfaces during ECMO. The two most common methods to provide CRRT are through the use of an inline hemofilter or through a traditional CRRT device connected to the extracorporeal circuit. The primary objective of this chapter is to discuss current state and role of renal replacement therapy in patients on ECMO and address the controversies and challenges about its application.

Keywords: CRRT, ECMO, mortality, technical consideration, complications

1. Introduction

Extracorporeal membrane oxygenation (ECMO) is a modality of treatment used in the intensive care unit (ICU) to improve gas exchange in patients with life-threatening respiratory failure and when conventional therapeutic methods fail to sustain sufficient oxygenation and/or the removal of carbon dioxide. Renal replacement therapy (RRT) is added to the ECMO for the treatment of acid-base as well as electrolyte imbalance and fluid overload. This chapter is trying to discuss the current state and role of renal replacement therapy in patients on ECMO and address the controversies and challenges about its application.

2. Continuous renal replacement therapy

Continuous renal replacement therapy (CRRT) is the mode of therapy adopted in patients with hemodynamic instability in whom intermittent hemodialysis cannot control volume or metabolic derangements. The concept of CRRT was introduced in 1980 and was used mainly for management of critically ill patients with acute kidney injury (AKI). The better hemodynamic tolerance seen in CRRT is due to slower solute clearance and removal of fluid per unit of time. CRRT works on the principle of convection and diffusion. In regular hemodialysis, diffusion is the modality of solute movement and ultrafiltration is added to the process for the purpose of fluid removal. One of the major disadvantages of conventional hemodialysis is that it is done only for limited amount of time, and hence it is difficult to achieve adequate fluid removal in patients who have hemodynamic instability. Moreover, critically ill patients receive large amounts of fluid and in the presence of reduced renal function keeping the fluid balance is a challenge. Hence, CRRT treatment is appropriate for patients with hemodynamic instability, fluid overload, catabolism, or sepsis with acute kidney injury (AKI) [1].

The usual CRRT circuit involves a double lumen catheter, tubing to carry blood from patient's body through the catheter to the CRRT machine, CRRT machine and return tubing which sends the blood back to the patient's body. There are three different modes of doing CRRT: continuous venovenous hemofiltration (CVVH), continuous venovenous hemodialysis (CVVHD), and continuous venovenous hemodiafiltration (CVVHDF). CVVHD works on the principle of diffusion and hence it is inefficient in terms of removal of large molecular weight substances. On the other hand, CVVH works on the principle of convection, which is the movement of water along with electrolytes, and CVVHDF employs both diffusion and convection. Convection is dependent on the pressure and pore size of the membrane. Perfusion pressure generated by a peristaltic pump drives the ultrafiltration of plasma across a biosynthetic hemofiltration membrane. In this process, a high ultrafiltration rate is required to achieve convective clearance and hence replacement fluid must be added to the extracorporeal circuit to restore fluid volume and electrolytes [1].

The solution bags used for doing CRRT contains glucose and electrolytes (including sodium, potassium, calcium, and magnesium) in concentrations that are in the physiologic range. The dose of CRRT is decided based on effluent dose. It is defined as the flow of effluent in ml/kg/

hr. Based on clinical studies, the recommended effluent dose is 20–25 ml/kg/hr. But at the same time, solute clearance will be affected by clotting and protein deposition on the hemofilter membrane. Anticoagulants are also added to the circuit for the sake of keeping the filter patent for a longer period and usual anticoagulants used include citrate and heparin. The usual blood flow rates on CRRT circuit range 150–250 cc/min.

Although CVVHDF is preferred over CVVH in most institutions, there is no one modality, which is shown to be superior over the other. There might be a theoretical advantage for CVVH and CVVHD in terms of removing larger molecules like cytokines in septic patients. But at the same time, relevant clinical studies have not shown any benefit in terms of improvement in plasma concentration of cytokines or outcome.

3. Technical aspects of combining ECMO and CRRT

There are a number of ways CRRT can be initiated in a patient undergoing treatment with ECMO. The most common technique is using separate vascular access and circuit for CRRT and ECMO. This technique ensures that both systems do not interfere with each other's hemodynamics. One of the disadvantages with this connection is the introduction of a large cannula while the patient is on anticoagulation which increases the risk of bleeding compli-cations at the time of insertion. Additionally in some cases, multiple vascular access sites might be required for doing ECMO which will limit the number of access sites available for estab-lishing CRRT circuit.

Another method is by introducing the CRRT machine or a hemofilter into the ECMO circuit otherwise called as inline technique. Here blood for the CRRT circuit is accessed from and returned to ECMO circuit. Inlet to the CRRT circuit can be before or after the oxygenator or centrifugal pump. Similarly, venous return from CRRT circuit is connected to ECMO circuit before or after the oxygenator or centrifugal pump. In ECMO circuits, using roller pump, a similar setting can be established. Inline hemofilter is used in conditions where the goal is only to remove the fluid and not solutes. The different inline ECMO/CRRT/hemofilter connections are depicted in **Figures 1–5**. Advantages of incorporating the CRRT circuit into the ECMO circuit include (1) cost effectiveness, (2) easy to set up the circuit, (3) use of low blood volume, (4) ease of operability, (5) less resource intensive, (6) avoid additional access placement and ensuing complications especially in the background of anticoagulation use, and (7) the oxygenator in the ECMO circuit can work as an air bubble and blood clot trap for both the ECMO and CRRT circuit (provided both inlet and outlet lines are connected to the ECMO circuit before the oxygenator or to the oxygenator). One of the major disadvantages of incorporating the CRRT circuit into the ECMO line is the interference of blood flow in the CRRT as well as the ECMO circuit. If the CRRT machine's venous (outlet) line is connected to the ECMO circuit before the centrifuge pump, purified blood from the CRRT returns into the negative pressure part of the ECMO circuit. This generates low return pressure alarm in the CRRT machine which may subsequently shut down the machine. The connection of arterial line post pump can trigger too high pressure on the arterial access side of the CRRT generating alarms inside the CRRT machine. Conversely, connections with arterial line pre-pump and

venous line post-pump can trigger low-pressure arterial (access) alarms and high-pressure return (venous) alarms in the CRRT circuit, respectively. These can interfere with pressure monitoring within the CRRT filter reducing the lifespan of the filter. Moreover, the drastic difference in flow and pressure will increase shear stress, activate the clotting cascade and release noxious cytokines. This, in turn, can predispose to the potential life-threatening hemolysis, disseminated intravascular coagulation and enhanced systemic inflammation. The hemolysis through the medium of hemoglobinuria can precipitate renal injury [2, 3].
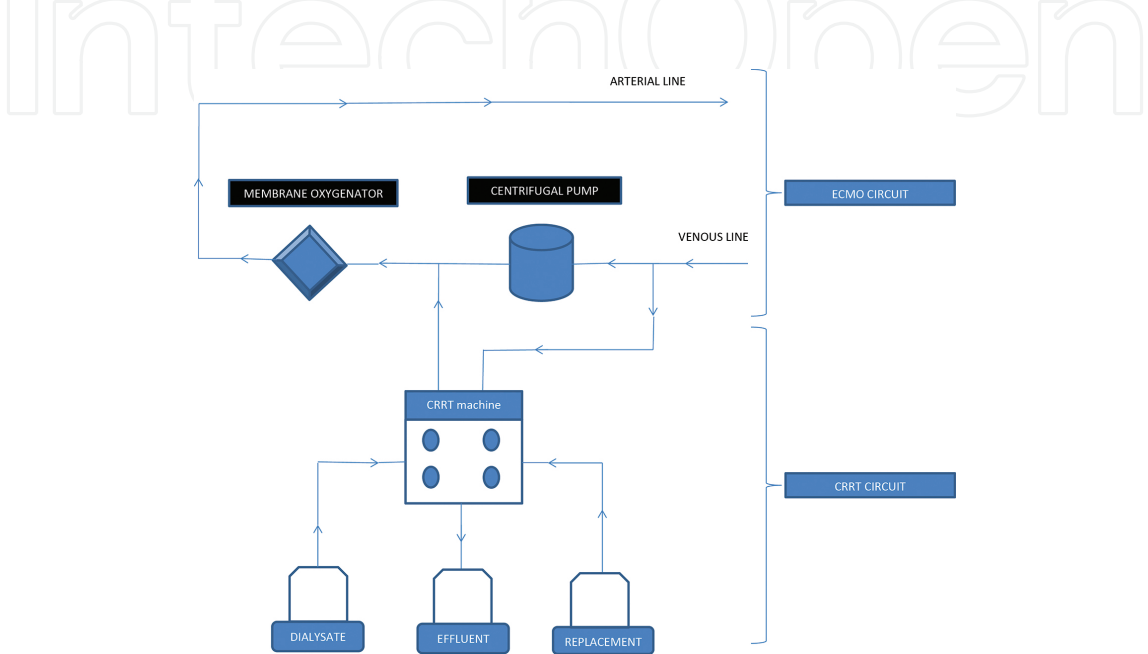

Figure 1. ECMO-CRRT connection with inlet of the CRRT circuit connected to the inlet line of ECMO circuit precentrifugal pump and outlet of the CRRT circuit to the ECMO circuit postcentrifugal pump.
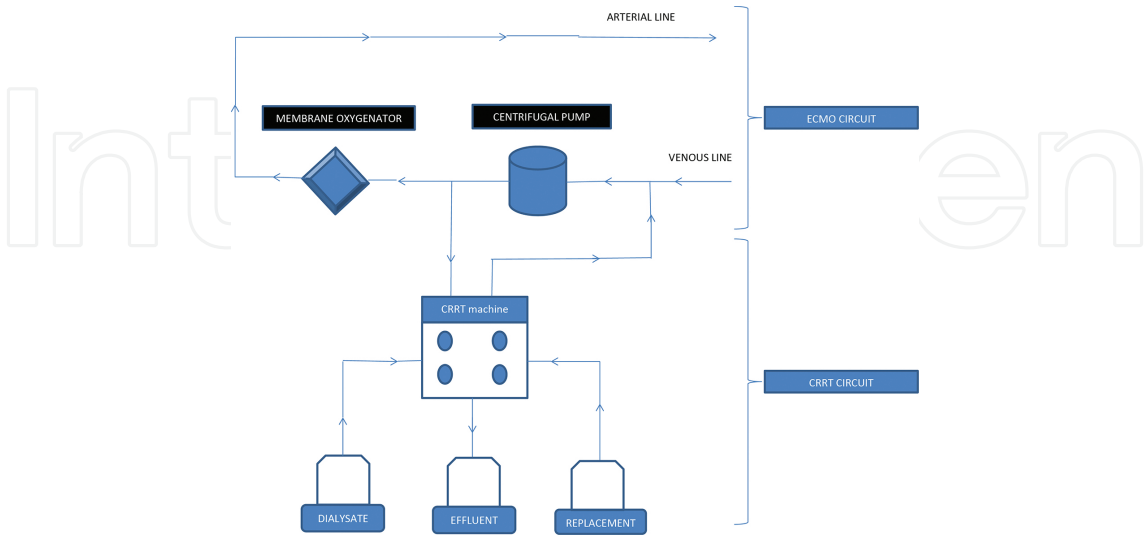

Figure 2. ECMO-CRRT connection with inlet of the CRRT circuit connected to ECMO circuit postcentrifugal pump and outlet of the CRRT circuit to the ECMO circuit precentrifugal pump.
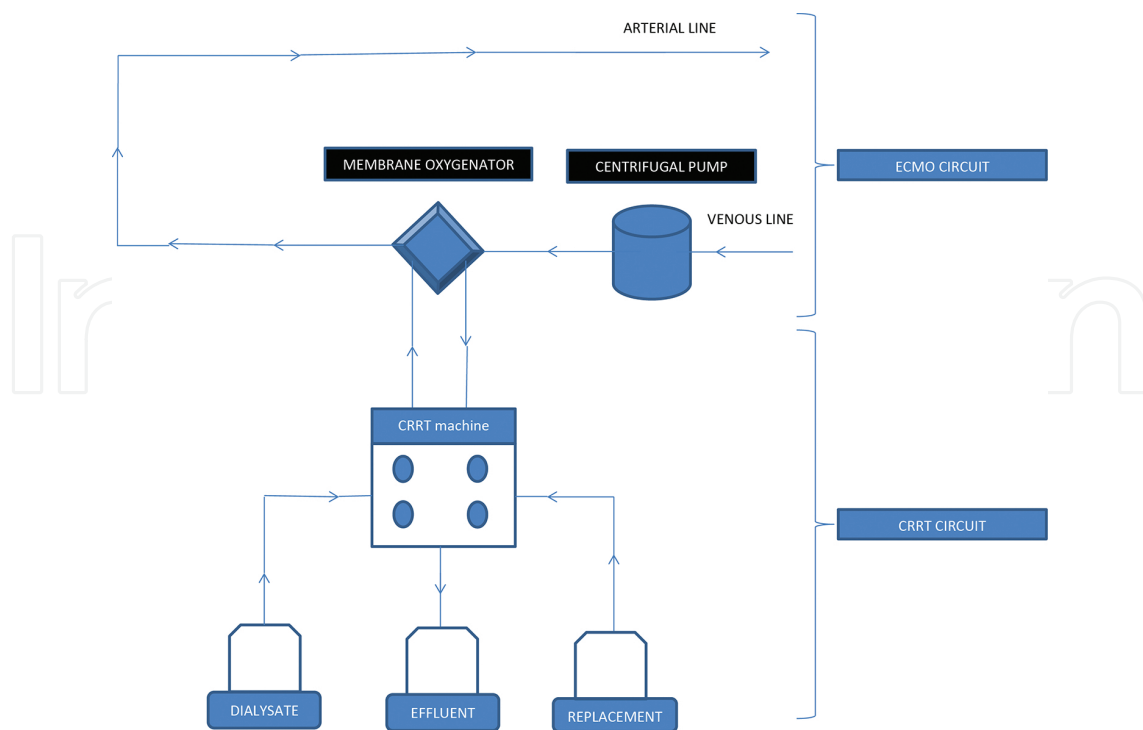
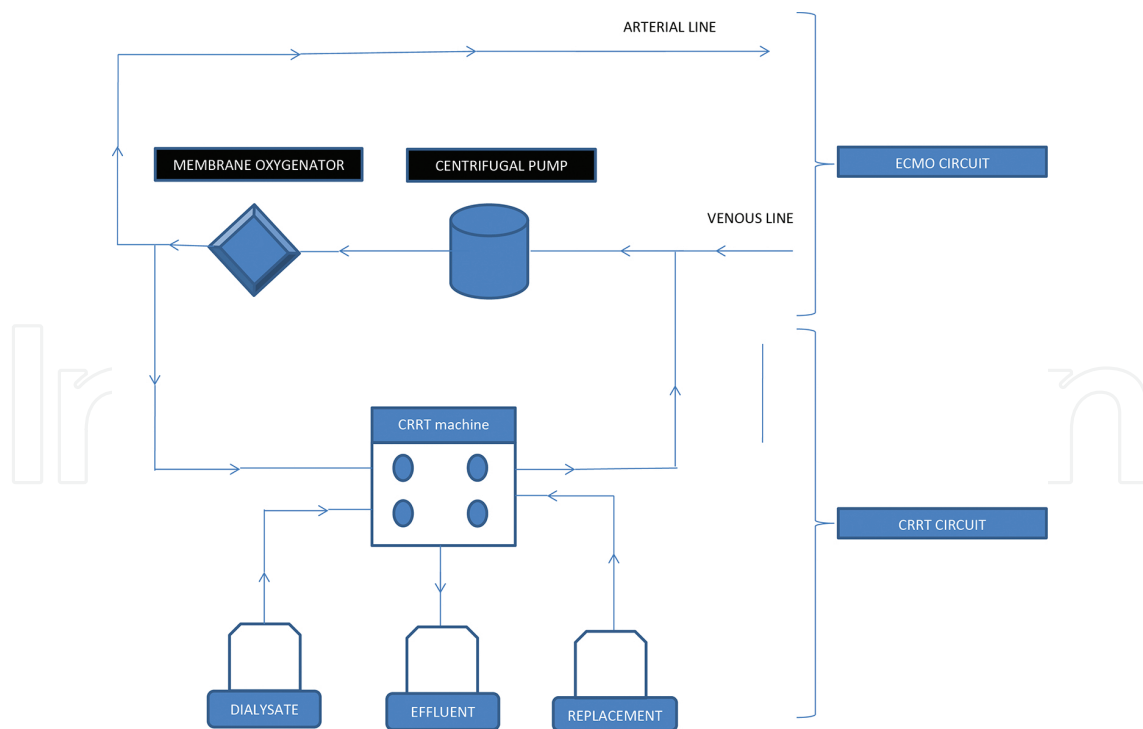**Figure 3.** ECMO-CRRT connection with inlet and outlet of the CRRT circuit connected to ECMO oxygenator.

Figure 4. ECMO-CRRT connection with inlet of the CRRT circuit connected to ECMO circuit postoxygenator and outlet of the CRRT circuit to the ECMO circuit precentrifugal pump.
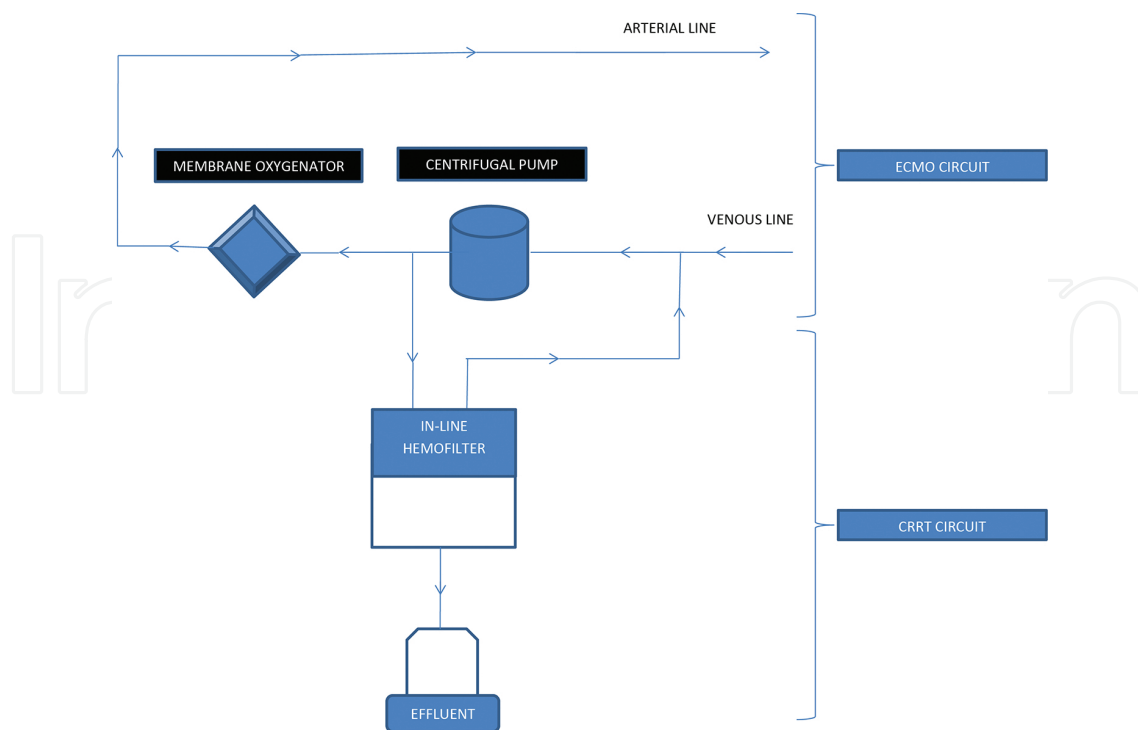
Figure 5. ECMO-hemofilter connection in an ECMO machine with centrifugal pump. The inlet of the hemofilter circuit is connected to ECMO circuit postcentrifugal pump and the outlet of the hemofilter circuit is connected to the ECMO circuit precentrifugal pump.

The flow of blood from and into the ECMO circuit can interfere with blood flow in the ECMO circuit. The support for a patient with severe hypoxemia often requires high blood flow with a pump speed of above 3000 rpm and the flow of blood into CRRT circuit may generate very low pressure particularly when the inflow to the ECMO circuit is limited. This may have clinical consequences in patients with severe hypoxemia where even small fluctuations in the ECMO flow can lead to significant drop in the arterial blood oxygenation [2, 3].

4. Indications and benefits of combined ECMO-CRRT treatment

Classic indications for initiation of renal replacement therapy in patients on ECMO include uremia, acidosis, electrolyte abnormalities, and fluid overload. The most frequently reported indications were fluid overload (43%), prevention of fluid overload (16%), AKI (35%), electrolyte disturbances (4%), and other (2%). Combined use of ECMO and CRRT has many benefits. ECMO by itself is an effective means of providing cardiorespiratory support for these patients. Similarly, provision of ECMO support may prevent the myocardial damage that can be caused by inotropic agents or hypoxia and promote hasty recovery of myocardial function. Both these factors can improve oxygenation and perfusion of organs including the kidneys which in turn may promote early recovery of renal failure. Correction of hypoxia using the ECMO machine can result in the reduction of lactic acidosis. The addition of CRRT (with bicarbonate-based solutions) efficiently manages severe lactic acidosis avoiding fluid overload

and hypocalcemia in hemodynamically unstable patients. Hence combining ECMO with CRRT might result in rapid reversal of the metabolic sequelae of lactic acidosis [4–6].

Another major advantage of combining CRRT with ECMO is the establishment of favorable volume status. Improvement in fluid overload or improving fluid balance has been found to be associated with improved lung function, faster recovery of left ventricular function, better diastolic compliance, better contractility and less myocardial edema and time to weaning off ECMO and ventilator support. In addition to the above-mentioned advantages, initiation of renal replacement therapy (RRT) also allows for the administration of adequate nutrition, medications, and blood products, while avoiding further fluid accumulation. It can correct azotemia, electrolyte imbalance and decrease levels of inflammatory cytokines as well as systemic inflammatory response syndrome induced by ECMO. The latter might be beneficial in terms of decreasing ECMO-induced renal injury [4–6].

5. Timing of initiation of CRRT in ECMO patients

The timing of initiation of CRRT on ECMO is not well defined. Clinical studies have shown a beneficial role of early initiation of CRRT and better outcomes in patients on ECMO. The benefits of early initiation of CRRT in these studies were mostly related to maintenance of fluid balance. Excessive fluid has been found to be associated with prolonged ECMO duration, mechanical ventilation, longer length of stay in the ICU, and mortality. CRRT is an important tool for managing fluid overload in these patients since it enables goal-directed maintenance of fluid balance. Hence, early initiation of CRRT before the onset of fluid overload should be considered in patients on ECMO. Blijdorp et al. observed that initiating preemptive CRRT during ECMO in neonatal patients improved outcomes by decreasing time on ECMO due to improved fluid management [6, 7]. It has also been shown that odds ratio for death was higher when CRRT was started later and longer it was performed.

6. Complications of ECMO and CRRT

Complications of CRRT are related to placement of vascular access, cardiac arrhythmias, electrolyte disturbances, nutrient losses, hypothermia, and bleeding complications from anticoagulation. Common vascular access-related complications include arterial puncture, hematoma, hemothorax, pneumothorax, formation of arteriovenous fistulas, aneurysms, thrombus formation, pericardial tamponade, and retroperitoneal hemorrhage. Electrolyte imbalances commonly encountered include hypokalemia and hypophosphatemia, which may lead to complications such as hemolysis and rhabdomyolysis. In unstable patients with multiple organ failures and fluid overload, although ECMO alone can improve hemodynamic stability by increasing cardiac output via an ECMO pump (in venoarterial ECMO) and improved myocardial oxygenation, the presence of fluid overload can nullify these advantages. Hence, maintenance of fluid balance is very essential in the treatment of critically ill patients

supported with ECMO and CRRT. Experimental and observational data have shown that ECMO itself can have hemodynamic consequences and can interfere with the accurate assessment of volume status. Traditional markers of volume assessment like CVP can be unreliable in these patients. Larsson et al. in his experiments in swine model showed that venoarterial ECMO can decrease systemic venous pressure while maintaining systemic perfusion leading to diminution of central venous pressure measurement [8]. Additionally, volume assessment can be made difficult by the myocardial dysfunction secondary to use of ECMO. Numerous mechanisms have been proposed for the pathogenesis of this phenomenon including low ionized calcium at the onset of cardiac bypass, effect of reactive oxygen species, toxic substances related to the ECMO circuit, various cytokines involved in inflammation during ECMO on the myocardium, retrograde nonpulsatile blood flow, particularly, in the background of underlying left ventricular dysfunction, coronary hypoxia due to higher oxyhemoglobin saturation in the lower extremities compared to upper body (exclusively seen with use of femoral arterial catheter placement in a VA ECMO configuration), and increase in left ventricular afterload. ECMO can additionally result in cardiac stunning as reported by Martin et al. [9]. Pyles et al. [10] in their experiment on Dorset lambs found that initiation of ECMO is associated with decreased hemodynamic and echocardiographic measures of LV function despite accounting for changes in afterload.

The incidence of AKI in patients on ECMO is estimated to be up to 70%. AKI with the need for renal replacement therapy (RRT) occurs in 50% of patients on ECMO and it is one of the most frequent additional organ failures in this patient population. ECMO initiation by itself can lead to acute kidney injury; the mechanisms include ischemia/reperfusion injury from rapid hemodynamic fluctuation in renal blood flow secondary to adjustments in vasopressors or inotropes, pigment nephropathy due to hemoglobinuria resulting from hemolysis secondary to exposure of blood to artificial surfaces, nonpulsatile retrograde renal perfusion, activation of complement system, and accumulation of cytokines. Development of renal failure is a reflection of progression to multisystem organ failure. Moreover, it can predispose to the accumulation of fluid and subsequent volume overload worsening heart and lung disease.

7. Renal recovery and combined ECMO-CRRT

Renal recovery outcome data are limited in patients who have received ECMO and CRRT. Paden et al. [11] in his study of 154 patients on ECMO and CRRT showed that renal recovery was seen in 96% of the patients who survived. Similarly, Meyer et al. [12] in a series of neonatal and pediatric survivors renal recovery was seen in 14/15 (93%) patients. In the study by Thajudeen et al., the renal recovery was found in all patients who survived. In his study, a key observation was that all those patients who had renal recovery were on VA ECMO and they hypothesized that the increased oxygen supply to renal vessels due to its close proximity to heart in the cases of VA ECMO might have played a role in the renal recovery [13]. All these studies show a favorable renal outcome in patients who survive.

8. Mortality in patients on combined ECMO and CRRT

Clinical studies have shown the association between ECMO, CRRT, and high mortality. In a retrospective study of 200 patients who underwent ECMO 60% (120/200) required renal replacement therapy (RRT) for AKI and the survival of patients requiring RRT was only 17%. Wu et al. [14] made a similar observation where the need for RRT was found to be an independent risk factor for mortality. Although survival in ECMO patients has improved tremendously over the years, the addition of CRRT portends a worse prognosis eliminating this advantage. Severity of illness has been suggested as a cause of high mortality in these patients. It is also speculated that in the presence of multiple organ dysfunction syndromes (MODS), the presence of AKI itself rather than the requirement for CRRT is the independent risk factor for mortality in critically ill patients undergoing ECMO.

There are data supporting an association between delayed start of CRRT and mortality. Kielstein et al. [15] observed that the 90-day survival of patients on ECMO needing CRRT was only 17%; however, at the same time they found that the cohort of patients who had delayed the start of CRRT had higher mortality. Randomized controlled studies comparing early vs. late initiation of CRRT before and after the occurrence of the fluid overload in patients on ECMO would be needed to further address this issue.

9. Antibiotic dosing in CRRT and ECMO

While ECMO and CRRT are important modes of therapy that can sustain life, little is known about the independent effects of ECMO and CRRT on antibiotic pharmacokinetics. Clear data on the dosing of medications are lacking at this point. Patients on extracorporeal circuit usually will have increased volume of distribution and variable clearance. Clinical studies have shown significant alterations in the pharmacokinetics which can result in suboptimal dosing of medications (both under- and overdosing). Inadequate or underdoing of antibiotics can lead to inadequate treatment of sepsis and subsequent increase in morbidity and mortality. Similarly, too high dosing can lead to systemic toxicity. This is significant in these patients who already have high infection-related mortality. Guidelines for dosing of medications should take into consideration the mode of RRT, dose of RRT delivered, blood flow rate, filter material, and surface area of the filter [16–18].

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