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Review

Review

Extracorporeal membrane oxygenation combined with continuous renal replacement therapy for the treatment of severe burns: current status and challenges

Huapei Song, Zhiqiang Yuan, Yizhi Peng, and Gaoxing Luo*

State Key Laboratory of Trauma, Burn and Combined Injury, Institute of Burn Research, Southwest Hospital, Third Military Medical University (Army Medical University), 30 Gaotanyan Street, Chongqing 400038, China

*Correspondence. Email: logxw@yahoo.com

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Abstract

Severe burns often cause various systemic complications and multiple organ dysfunction syndrome, which is the main cause of death. The lungs and kidneys are vulnerable organs in patients with multiple organ dysfunction syndrome after burns. Extracorporeal membrane oxygenation (ECMO) and continuous renal replacement therapy (CRRT) have been gradually applied in clinical practice and are beneficial for severe burn patients with refractory respiratory failure or renal dysfunction. However, the literature on ECMO combined with CRRT for the treatment of severe burns is limited. Here, we focus on the current status of ECMO combined with CRRT for the treatment of severe burns and the associated challenges, including the timing of treatment, nutrition support, heparinization and wound management, catheter-related infection and drug dosing in CRRT. With the advancement of medical technology, ECMO combined with CRRT will be further optimized to improve the outcomes of patients with severe burns.

Key words: Severe burns, Extracorporeal membrane oxygenation, Continuous renal replacement therapy, Multiple organ dysfunction syndrome, Acute kidney injury, Acute respiratory distress syndrome

Highlights

- This is the first review of extracorporeal membrane oxygenation combined with continuous renal replacement therapy for the treatment of severe burns, which might help to improve outcomes and reduce mortalities.
- This review is the first to focus on the current challenges of this combined therapy for the patients with severe burns, including timing of treatment, nutrition support, heparinization and wound management, catheter-related infection and drug dosing in continuous renal replacement therapy.

Background

Patients with severe burns are at a high risk of multiple organ dysfunction syndrome (MODS) due to high incidence rates of inhalation injury, shock and systemic infections. The lungs and kidneys are vulnerable organs in patients with MODS. Respiratory failure associated with acute kidney injury (AKI) is very difficult to treat and has a high mortality rate [1,2]. Extracorporeal membrane oxygenation (ECMO) originated from extracorporeal circulation technology, which provides days to weeks of life support for patients with respiratory failure and/or heart failure [3]. Early ECMO technology was mainly used as supportive care for acute respiratory distress syndrome (ARDS) in adults and for critical neonatal conditions [4,5]. With technological advancements, ECMO has become safer and more widely applied, with applications including perioperative bridging therapy in critical cardiothoracic surgical patients, supportive care for cardiogenic shock associated with cardiac emergencies (such as fulminant myocarditis and acute myocardial infarction) and auxiliary care for cardiopulmonary resuscitation [6–8]. Based on different forms of access to patients' vessels, the method used may be venous–venous ECMO (VV-ECMO) or venous–arterial ECMO (VA-ECMO). VV-ECMO provides only respiratory support while VA-ECMO provides both cardiac and respiratory support. In the literature, the complications of ECMO may inflict serious morbidity, which can be classified into complications related to the ECMO device (e.g. circuit clotting, pump or oxygenator malfunction, cannula issues) or physiological complications (e.g. bleeding, haemolysis, infection). The reported mortality for ECMO in severe lung failure ranges from 25% to greater than 60%, while the reported mortality of VA-ECMO remains high and within the wide range of 43–93% [9,10]. It should be noted that the quality control through a learning curve using cumulative sum analysis is essential for improving the outcome of ECMO programme. The prevalence of AKI, a common complication among severely burned patients, has been reported to be close to 25%, with an associated mortality rate of 35%. However, the reported mortality is up to 80% among those requiring renal replacement therapy [11,12]. Continuous renal replacement therapy (CRRT) refers to prolonged use of extracorporeal blood purification for continuous renal replacement to eliminate metabolites and toxins and correct fluid, electrolyte and pH imbalances [13–15]. The application of ECMO and CRRT in patients with burns has been reported in recent decades; however, the literature on ECMO combined with CRRT for the treatment of severe burns is limited. Here, we focus on the current status of ECMO combined with CRRT for the treatment of severe burns and the associated challenges.

Review

ECMO combined with CRRT for MODS

MODS is one of the systemic complications of severe burns, which is considered as the main cause of death. ARDS is one of the most serious complications of extensive burns, with an incidence of 11.8% to 17% [16,17]. If severe inhalation injury is present, the morbidity of lung failure is substantially higher. In adult patients with burns, the prevalence of AKI is 26.6% to 53.3% [18,19]. For patients with respiratory failure and renal failure, ECMO combined with CRRT improves outcomes and reduces mortality [20,21]. Notably, AKI and fluid overload are common complications during ECMO treatment for respiratory failure and the prevalence of AKI is 70% to 85% in patients undergoing ECMO [22–24]. Some researchers believe that the presence of the ECMO circuit and catheter placement techniques contribute to ECMO-associated kidney injury, which is mainly related to the systemic inflammatory response, renal circulatory disturbances, ischaemia–reperfusion injury and oxidative stress [25–28]. Fluid overload is usually secondary to AKI or improper volume management during ECMO treatment. Research has shown that 40–60% of patients on ECMO who developed AKI were placed on CRRT [29]. Another study from the Extracorporeal Life Support Organization found that the indications for ECMO combined with CRRT include fluid overload (43%), AKI (35%), prevention of fluid overload (16%), electrolyte imbalances (4%) and other complications (2%) [30]. Nevertheless, combined therapy was associated with increased mortality compared with ECMO alone, which ranged from 39.5% to 100% [29,31,32].

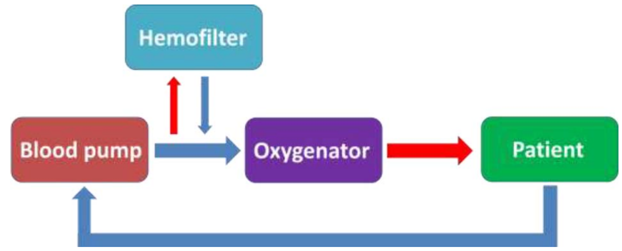

Figure 1. In-line haemofilter connected to the extracorporeal membrane oxygenation circuit

Management of ECMO combined with CRRT

At present, three approaches can be used to combine ECMO with CRRT: connecting the CRRT machine to the ECMO circuit, connecting the filter to the ECMO circuit (Figure 1) and separate circuits (Figure 2) [20,33]. The advantages of the first approach include pressure monitoring and the ability to adjust blood flow or the ultrafiltration volume. However, this approach involves complex procedures and high costs. The advantages of the second approach include low cost and convenience, but it is rarely used in clinical practice because it does not allow pressure monitoring or adjustment of blood flow or the ultrafiltration volume. Moreover, the filter is prone to clogging. The third approach has minimal impact on ECMO but increases the risks of invasive procedures, bleeding and infection and the dosage of CRRT anticoagulants [34–37]. Different methods are available to connect the CRRT machine to the ECMO circuit: pre-pump connection of the CRRT inlet (arterial) and outlet (venous) lines (Figure 3); post-pump connection of the CRRT inlet and outlet lines (Figure 4); post-pump connection of the CRRT inlet line and pre-pump connection of the CRRT outlet line (Figure 5); and post-oxygenator connection of the CRRT inlet line and pre-oxygenator connection of the CRRT outlet line with a Luer lock (Figure 6) [38,39].

ECMO combined with CRRT is an optional regimen for critically ill patients whose condition is refractory to

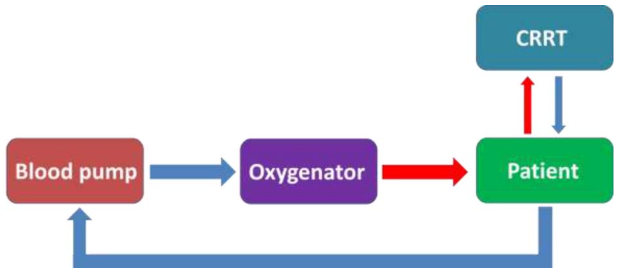

Figure 2. Separate continuous renal replacement therapy (CRRT) and extracorporeal membrane oxygenation circuits

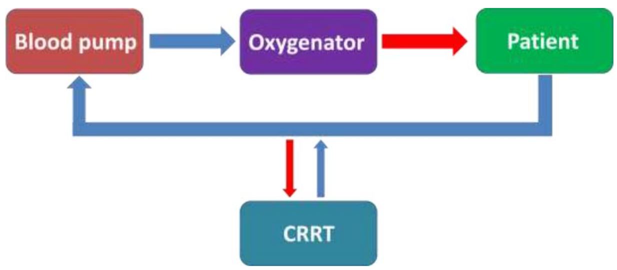

Figure 3. Integrated continuous renal replacement therapy (CRRT) and extracorporeal membrane oxygenation circuit: pre-pump connection of the CRRT inlet (arterial) and outlet (venous) lines

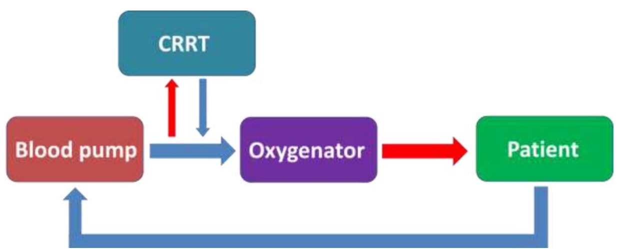

Figure 4. Integrated continuous renal replacement therapy (CRRT) and extracorporeal membrane oxygenation circuit: post-pump connection of the CRRT inlet (arterial) and outlet (venous) lines

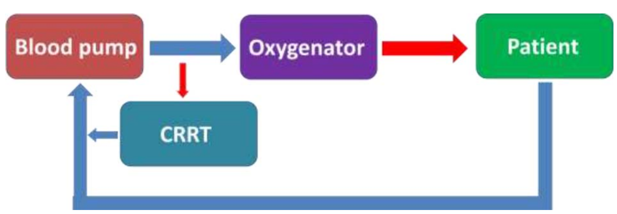

Figure 5. Integrated continuous renal replacement therapy (CRRT) and extracorporeal membrane oxygenation circuit: post-pump connection of the CRRT inlet (arterial) line and pre-pump connection of the CRRT outlet (venous) line

conventional treatments [40,41]. The timing of CRRT in ECMO patients is generally based on kidney function and/or fluid load. Researchers believe that early use of CRRT is more beneficial [42]. Yetimakman *et al.* concluded that CRRT is warranted if fluid overload has reached 10% of patient weight within 24 hours [39]. Schmidt *et al.* showed that 42% of 172 patients received CRRT within three days after the start of ECMO and that the indications for CRRT included potassium > 6.5 mmol/L, pH < 7.2, urea > 25 mmol/L, creatinine > 300 μmol/L or organ oedema (e.g. pulmonary oedema) [43].

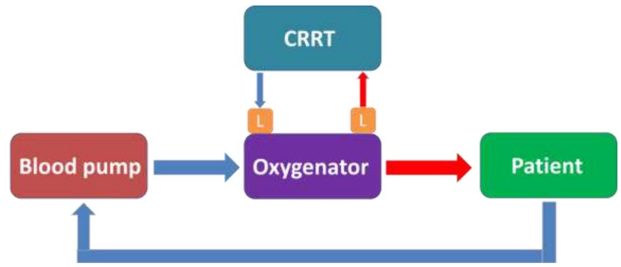

Figure 6. Integrated continuous renal replacement therapy (CRRT) and extracorporeal membrane oxygenation circuit: post-oxygenator connection of the CRRT inlet (arterial) line and pre-oxygenator connection of the CRRT outlet (venous) line with a Luer (L) lock

The application of ECMO combined with CRRT requires a multidisciplinary treatment team, including experienced burn surgeons, cardiothoracic surgeons, intensivists, nurses, nutritionists and psychotherapists [44]. During combined therapy, measures, including circuit management, haemodynamic monitoring, fluid management, anticoagulation management and respiratory monitoring, should be implemented to prevent complications such as intracranial haemorrhage, gastrointestinal haemorrhage, haemolysis, infection and limb ischaemia [45,46]. Dado *et al.* concluded that early integration of combined therapy with experience and expertise might contribute to improved outcomes [29].

Current status of ECMO combined with CRRT for severe burns

A few studies have investigated the effects of ECMO for burns with inhalation injury and it has been demonstrated that early implementation of ECMO is of benefit in the treatment of severe refractory ARDS [47,48]. CRRT can be used to treat AKI to alleviate fluid overload, improve renal recovery and reduce inflammation and it has been widely used in clinical practice for severe burns [49,50]. However, the literature on ECMO combined with CRRT for the treatment of burns is limited (Table 1) [51–56]. The results of these studies demonstrate encouraging survival rates in the range of 50–100% with combined therapy, indicating that this should be considered to improve outcomes in cases of worsening ARDS and AKI with unsuccessful conventional treatment.

Nevertheless, studies on the application of combined treatment in patients with burns affecting a total body surface area (TBSA) >80% have not been reported. Previously, three patients (TBSA: 85%, 91%, 95%) with refractory respiratory failure and renal insufficiency received VV-ECMO combined with CRRT in our department; two patients were successfully withdrawn from the combined treatment after recovery of respiratory and renal functions. However, we were unable to perform early debridement and skin grafting due to wound bleeding and limited device portability. All three patients died of MODS resulting from wound infection followed by severe sepsis. Some issues, especially the influence of combined

Table 1. Selected studies reporting treatment of ECMO combined with CRRT in burn patients

Study	Year	Patient No.	TBSA (%)	Type of ECMO	ECMO duration (hours)	CRRT duration (hours)
Askegard-Giesmann *et al.* [51]	2010	13	NA	VV-ECMO VA-ECMO	NA	NA
Pu *et al.* [52]	2017	1	60	VA-ECMO	224	624
Hsu *et al.* [53]	2017	1	50	VV-ECMO	401	NA
Ainsworth *et al.* [54]	2018	9	1–76	VV-ECMO	63–539	NA
Szentgyorgyi *et al.* [55]	2018	4	12–51	VV-ECMO	264–840	NA
Dadras *et al.* [56]	2019	4	15–75	VV-ECMO	48–984	96–1824

ECMO extracorporeal membrane oxygenation, *CRRT* continuous renal replacement therapy, *TBSA* total body surface area, *NA* not available, *VV-ECMO* venous–venous extracorporeal membrane oxygenation, *VA-ECMO* venous–arterial extracorporeal membrane oxygenation

therapy on the treatment outcomes of extensive wounds, must be addressed.

Challenges of ECMO combined with CRRT for severe burns

Timing of treatment During the shock stage, patients with severe burns often have hypovolemia and hypoperfusion, which are contraindications for ECMO and CRRT as these treatments may interfere with fluid resuscitation. Therefore, ECMO combined with CRRT is usually used after the shock stage at the discretion of burn physicians [57,58]. In addition, the key to treating patients with extensive burns is early wound closure and most patients require prompt debridement and skin grafting [59,60]. ECMO and CRRT are indicated for patients with refractory ARDS and AKI before surgery. In such cases, surgery may be delayed or even cancelled for safety reasons. While ECMO combined with CRRT can replace lung and kidney functions and improve outcomes, deep, extensive wounds may still cause severe systemic infection and worsen a patient's condition. With the advancement of medical technology and the optimization of treatment regimens, patients with extensive burns may promptly receive ECMO combined with CRRT, even during the shock stage, to improve outcomes. Likewise, they may receive combined therapy synchronized with early surgery to close the wounds to minimize sources of infection.

Nutritional support Severe burn injury leads to a hypermetabolic state, especially hypercatabolism, resulting in the consumption of more nutrients and oxygen than usual, which causes severe malnutrition, low immunity and high morbidity from infection and organ dysfunction [61–63]. Furthermore, ECMO itself causes hypercatabolism, and CRRT depletes some intravenous nutrients [64,65]. Patients with extensive burns usually require both enteral and parenteral nutrition. Lipid emulsion is an integral part of parenteral nutrition. Studies have shown that lipid emulsion infusion during ECMO causes lipid emulsion layering, aggregation and coagulation, thereby affecting haemodynamics and energy delivery [66]. To ensure the safety of ECMO, lipid emulsions are often removed from parenteral nutrition, which causes energy deficiencies in patients with severe burns. Buck *et al.* showed that the incidence of adverse reactions is lower if lipid emulsion is infused through a separate venous line instead of the ECMO circuit, indicating that this approach should be used when possible [67]. It is noteworthy that enteral nutrition is the primary approach for nutritional support during ECMO combined with CRRT in patients with severe burns [68]. In addition, a nasogastric or nasojejunal tube may be placed before the treatment and drugs that improve gastrointestinal motility should be administered to promote nutrient digestion and absorption. Further research is needed to explore improved regimens of sufficient nutritional support for patients with severe burns undergoing ECMO combined with CRRT.

Heparinization and wound management Anticoagulation is usually required during ECMO combined with CRRT and may cause wound bleeding or increase intraoperative blood loss [69]. Therefore, anticoagulation requirements have limited the application of ECMO in patients with severe burns. Local citrate anticoagulation is commonly used during CRRT to prevent heparin-induced bleeding [70,71]. Short-term, heparin-free ECMO may be an effective transitional treatment for patients in whom anticoagulation is contraindicated, but it requires careful monitoring and management by an experienced multidisciplinary treatment team [72,73]. For patients with extensive burns, ECMO can feasibly be administered during wound dressing and surgery as long as wound bleeding is controlled. At present, heparin is often applied via the ECMO oxygenator and monitored by the activated clotting time or anti-Xa activity [74,75]. Recently, research on anticoagulation with heparin has focused on determining the optimal heparin doses for ECMO, which will yield a more reliable and effective heparin assessment system and minimize the effect of heparinization on wound management. Lai *et al.* showed that fibres that release nitrogen oxide may be used on gas exchangers to reduce platelet activation and thrombosis without causing bleeding, which provides new insight into anticoagulation improvement during ECMO [76].

Catheter-related infection Patients receiving ECMO and CRRT are prone to catheter-related infections due to prolonged indwelling of deep venous catheters [77,78]. Catheters inserted through the burn wounds of patients with extensive burns pose a high risk of infection [79]. To prevent catheter-related infection, daily wound dressing changes and even the use of topical antibiotics are required. The intervals for catheter replacement should be minimized, especially when a catheter is inserted through burn wounds. Moreover, patients should be withdrawn from treatment as soon as possible after recovery of respiratory and renal functions. Likewise, to decrease the risk of infections in these patients, further study is necessary to investigate the proper timing and dosage of antibiotics during combined therapy.

Drug dosing in CRRT Most severely burned patients undergoing CRRT for AKI are treated with antimicrobials. Optimizing antimicrobial treatment in these patients can be challenging because pathophysiological changes after burns and concomitant CRRT can influence the pharmacokinetics and pharmacodynamics of antimicrobials [80,81]. Appropriate antimicrobial selection and drug dosing are essential to improve clinical outcomes, avoid overdosing-related toxicity and underdosing-related treatment failure and/or potential pathogen resistance [82–84]. Drug dosing during CRRT are recommended by literatures, including meropenem, cefepime, levofloxacin, tigecycline, polymyxin B, vancomycin, voriconazole and amphotericin B [80,82,85]. However, the antimicrobial regimen should be administered cautiously and individualized by considering factors such as the site of infection, the severity of illness, residual renal function, comorbidities, renal replacement modalities, etc. [80,86–88]. It should be noted that drug dosing adjustments with the therapeutic drug monitoring could improve the outcomes of patients with severe burns undergoing CRRT [89,90].

Conclusions

For patients with severe burns, when refractory ARDS and concomitant AKI occur, treatment using ECMO combined with CRRT may be complementary and effective, helping to improve outcomes and reduce mortality. However, various challenges remain in terms of the timing of treatment, nutritional support, anticoagulation, catheter-related infections and drug dosing in CRRT, which will be gradually addressed with the rapid development of medical technology. At present, clinical studies on ECMO combined with CRRT for severe burns are limited and multicentre clinical studies in large populations are necessary to improve the outcomes of severe burns.

Authors' contributions

HS drafted the manuscript. ZY and YP helped in the drafting of the manuscript. GL revised the manuscript. All authors reviewed the final manuscript for important intellectual content. All authors read and approved the final manuscript.

Abbreviations

AKI: acute kidney injury; ARDS: acute respiratory distress syndrome; CRRT: continuous renal replacement therapy; ECMO: extracorporeal membrane oxygenation; MODS: multiple organ dysfunction syndrome; VA-ECMO: venous–arterial extracorporeal membrane oxygenation; VV-ECMO: venous–venous extracorporeal membrane oxygenation.

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Conflicts of interest

The authors have no conflict of interest in connection with the work submitted.

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