Chapter 9

Use of ECMO in Sepsis and Septic Shock

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Abstract

The use of extracorporeal membrane oxygenation (ECMO) has always been controversial in the past. Evidence was mainly build up in neonates and much controversy remained in adults. The main adult indications were mechanical support (e.g., in cardiogenic shock) or respiratory support (e.g., in the field of acute respiratory distress syndrome (ARDS)). Sepsis was historically often considered as a contraindication. As a consequence of several worldwide flu outbreaks, the use of ECMO in infectious diseases increased. Besides in these viral infections, there was also growing interest for its use in bacterial septicemia, although often as escape therapy. In the recent years, other techniques gained increasing interest like for example, immunoadsorption, implemented in dialysis or ECMO circuits. In this chapter, we resume the available literature on the use of ECMO in septic shock including the use of immunoadsorption techniques.

Keywords: ECMO, sepsis, septic shock, immunoadsorption

1. Introduction

Since the publication in the early 1970s of the first successful use of extracorporeal membrane oxygenation (ECMO) in a post-traumatic adult respiratory distress (ARDS) patient [1], ECMO has been used tremendously. The approach can be either by veno-venous cannulation, which is mainly used in hypoxic respiratory failure, or by veno-arterial cannulation, which is the preferred modality for cardiac (or combined) support. This implements that most indications are in the field of ARDS and cardiogenic shock states.

Septic shock is a serious disorder that, despite progress in treatment over the last decades, still has a high mortality (between 20 and 30%) [2]. The ECMO survival in septic neonates [3, 4] and children [5] has improved to ~90 and 75%, respectively. There is however far more controversy

on its use in adult refractory septic shock, although successful salvage cases have been published [6, 7]. In parallel with the reports on its effectiveness during the influenza A (H1N1) outbreaks [8, 9], the interest for using ECMO in noninfluenza-induced sepsis has grown.

This chapter mainly focuses on indications, the difference between children and adults, causative pathogens, outcome and outcome prediction. It will not go into further detail on the technical aspects (cannulation, oxygenators and pumps).

2. Study population

2.1. Adults

2.1.1. Case report

A typical case of refractory septic shock is the following, unpublished, case out of our own ICU. A 42-year-old (type I) diabetic female was found unconscious by her husband and was brought to the emergency department after she was intubated at home by a medical team. She was diagnosed with diabetic ketoacidosis (initial pH 6.96) and was in of severe shock signs, requiring high doses of norepinephrine (0.5 μg/kg/') in the emergency department. The patient was transferred to the ICU and after sampling (respiratory and hemocultures) empirical amoxicillin-clavulanate was started.

Because of refractory shock despite aggressive fluid resuscitation, vasopressin was added as well as low doses of hydrocortisone (3 × 100 mg daily). This led to normalization of blood pressures and pH, but the patient remained oliguric and overnight oxygenation deteriorated despite increasing PEEP and FiO2. Early continuous renal replacement therapy (CRRT) was started.

Approximately 14 h after ICU admission, she suffered cardiac arrest due to sudden onset of ventricular fibrillation. After initial successful resuscitation (after cardiac massage and defibrillation), her oxygenation and hemodynamic status deteriorated further, necessitating peripheral cannulation of the femoral vein and artery and afterward the initiation of veno-arterial ECMO.

Antibiotic therapy was empirically switched to a combination of meropenem and vancomycin and (single shot) amikacin. The initial hemocultures were positive for Gram-positive cocci, later identified as *Enterococcus faecalis*.

Over the following days, the patient suffered no further complications. Hemodynamics and oxygenation stabilized, inflammatory parameters slowly resolved. Seven days after starting mechanical support, ECMO support could be weaned and stopped.

Four days later, she suffered a new bacteremic episode with ***E. coli*** due to the development of empyema of the left hemithorax with. ***E. coli***. This time, however, without the need for mechanical support. After thoracospic drainage and antibiotic switch to cefepime, based on culture results, inflammation went down. After repeat empyema, urokinase in loco was

administered with finally complete resolution of the empyema. The patient was extubated 30 days after hospital admission after 6 weeks she was discharged to the ward.

2.1.2. ICU case series

The available literature on ECMO use in adult septic shock patients consists mainly of case reports or (usually single-centered) retrospective case series. In a recent multicenter study [10], the data from 42 Japanese intensive care units were retrospectively collected and propensity score analysis was performed. Out of 3195 patients included in the JSEPTIC DIC study [11], 570 patients suffered from severe respiratory failure and in 285 of them respiratory failure was induced by lung infection. Overall 40 patients were supported with ECMO and these were matched with 150 patients in the control group. Sepsis-related organ failure (SOFA) scores were comparable (12 vs. 13).

A second propensity analysis was performed between the 25 ECMO patients with lung infection-induced respiratory failure and 89 patients in the control group. Overall no marked differences were found in 28-day mortality (47.2% in the control group vs. 32% in the ECMO group, p 0.168) and the in-hospital mortality (60.7% in control group vs. 40% in the ECMO group, p 0.07). However, in the second analysis comparing 89 controls with 25 ECMO patients with lung infection-induced respiratory failure, the survival time in the ECMO group was significantly longer (hazard ratio (HR), 0.498; 95% confidence interval (CI), 0.279–0.889; p 0.018). The numbers of renal replacement therapy and vasopressor-free days were also significantly higher in the ECMO group.

These results are similar with those reported by Nesseler et al. [12], who questioned the use of ECMO in patients with intra-abdominal sepsis-induced ARDS. Although the overall ECMO group (n = 40) received more red blood cell transfusions, there was no significant difference in the rate of severe bleeding complications. The numbers of renal replacement therapy and vasopressor-free days were significantly higher in the ECMO group.

Another retrospective study [13] describes 32 ECMO patients with refractory septic shock. Fourteen patients had undergone cardiopulmonary resuscitation (CPR) in which ECMO was started during CPR (ECPR). The most frequently infected site was the lung and 20 patients had bacteremia. Thirteen patients (40.6%) were successfully weaned of ECMO but only seven (21.9%) survived to discharge. Interestingly, none of the patients in whom ECMO was initiated more than 30 h after the onset of septic shock survived. CPR appeared to be an independent predictor of in-hospital mortality (adjusted HR, 4.61; 95% CI, 1.55–13.69; p 0.006). On the other hand, patients with myocardial injury (higher peak troponin I > 15 ng/ml) had a lower risk of in-hospital mortality (adjusted HR, 0.34; 95% CI, 0.12–0.97; P = 0.04).

The low survival rate was partially due to the ECPR cases, of who only 2 out of 14 survived and they both had return of spontaneous circulation within minutes. One of the conclusions of this trial was evidently that ECMO should be avoided in patients who have received CPR. The fact that patients with signs of myocardial injury had better survival rates could be explained by the reversibility of septic cardiomyopathy. There are two patterns of early death in septic shock: distributive shock or a cardiogenic form of septic shock [14]. ECMO

may be a valuable support in patients with the latter form that is unresponsive to highly dosed cathecholamines [15]. Finally, survivors appeared to have lower SOFA score at day 3 compared with the nonsurvivors (15 vs. 18, p = 0.01).

In another case series [16], 14 patients received ECMO support as salvage therapy for refractory septic shock, 24 h (3–108) after shock onset. Mean simplified acute physiology score (SAPS) III was 84 (75–106) SOFA score was 18 (8–21). Twelve patients (86%) could be weaned off and 10 patients (71%) were discharged home and were alive after a median follow-up of 13 months (3–43) with normalized ejection fraction and a good quality of life.

During a 6-year period, 52 septic shock patients had undergone ECMO support in a South Korean ICU [17]. Almost half of them (n = 21) was receiving CPR at the time of ECMO implantation. Not surprisingly overall outcome data were poor with only 15% survival to discharge. The nonsurvivors were significantly older than survivors (59.3 vs. 43.8 years, P = 0.009) and all patients aged 60 or older died.

2.1.3. Specific populations

2.1.3.1. Obstetrical cases

Maternal sepsis is a predominant cause of maternal death in low-income countries, but also in Western countries maternal mortality from sepsis has increased [18]. In 15 years, the incidence in the UK almost doubled from 0.65 to 1.12 per 100,000 cases [19]. Twenty-one deliveries per 100,000 develop sepsis with a case fatality rate of 7–8%. In the presence of septic shock, mortality goes up to 60%. Pregnant women are not only vulnerable to sepsis because of changes in the immune system, predisposition to pyelonephritis due to ureteral compression and increased invasive interventions. They also tend to decompensate quickly in case of sepsis due to the physiological changes (cardiovascular, respiratory, and metabolic) of pregnancy. These changes can finally also mask the early recognition of sepsis.

Sharma et al. [20] examined 31 published reports (with a total of 67 patients) of ECMO use in pregnancy. Fetal survival was 70% and maternal survival 80% which was comparable to nonpregnant patients requiring ECMO support. Fifteen reports of V-V ECMO, 16 reports of V-A ECMO, and 1 report of a lung assist device. But, indications for ECLS use included mainly severe ARDS, postpartum cardiogenic shock and amniotic fluid embolism. Besides a lot of H1N1 infected patients, only one patient with staphylococcal-induced ARDS and septic shock was included. There was no consensus on an optimal anticoagulation strategy in these patients, though most preferred to keep anticoagulation at lower therapeutic levels. A few cases of vaginal bleeding were reported, but occurrence of catastrophic bleeding was rare.

After this review, several case reports on bacterial septic shock were published [21, 22]. A 24-year-old multiparous woman was admitted with multiple organ failure in the third trimester of pregnancy [21], after suffering from high fever and diarrhea since 1 day. Cesarean section was performed due to fetal distress but the patient remained in refractory circulatory failure with consequent, progressive multiple organ failure. Cateacholamines were increased after ICU admission and low doses hydrocortisone were given.

Continuous hemodiafiltration was initiated 4 h after ICU admission. Piperacillin/tazobactam was started at hospital admission but after the identification of Streptococcus pyogenes, the diagnosis of Streptococcal toxic shock syndrome was made. Antibiotics were switched to penicillin, and clindamycin and intravenous immunoglobulins were added. Despite the abovementioned therapy and the increase of the hemofilter membrane area, multiple organ failure continued to progress. Repeated echocardiography showed left ventricular ejection fraction (LVEF) of 10%. Therefore, veno-arterial ECMO was initiated from the right atrium to the right femoral artery. With blood and oxygen flows of both 3.0 L/min lactate levels decreased from 20 to 8.9 mmol/l after 24 h of ECMO support. On day 7, she was weaned from ECMO; on day 8, vasopressors were stopped; on day 10, ventilation could be stopped and renal function recovered. The patient was discharged after 53 days and cardiac function recovered after 4 months. The patient suffered no bleeding complications.

In a very recent case report [22], another 24-year-old was readmitted to the hospital 2 days after a normal vaginal delivery following an uneventful pregnancy. Despite starting vasopressors and broad-spectrum antibiotics, she continued to decline with intubation 14 h after admission. An echocardiogram revealed an LVEF of 20%. Blood cultures grew Gram-positive cocci (group a streptococcus). The patient was transferred to a tertiary center where the diagnosis of endometritis was made and emergent total abdominal hysterectomy was performed after starting VA ECMO support. The fascia was left open and wound vacuum system was left in place. Vasopressors could be weaned on postoperative day (POD) 1, but she returned to the operating room (OR) for intra-abdominal bleeding. Afterward she suffered no more adverse events until decannulation, which was done on POD 5 in the OR. She was extubated on POD 7 and by POD 12 LVEF had normalized.

Finally, a third case of an 18-year-old nulliparous woman was reported [23]. She was admitted after 26 weeks of pregnancy with high fever, nausea, headache and increasing inflammatory parameters. After blood cultures were taken, empirical cefuroxime (750 mg every hours intravenously). On the second day of hospitalization, contractions started and a preterm low birth weight premature girl was born after urgent C-section. Surgery was uncomplicated but suddenly tachycardia developed and diffuse intravascular coagulation (DIC) with consecutive bleeding problems from wounds and catheter insertion sites started after about an hour after the procedure. Sepsis was supposed to be the cause of the DIC and antibiotics were switched to vancomycin and meropenem after new hemocultures were obtained. The patient was transferred to the ICU because of pulmonary edema, which started 4 h after the bleeding problems.

She was intubated and vasopressors were started. Blood cultures grew positive for ***Staphylococcus aureus*** and ***Enterobacter cloacae***. As septic shock and cardiorespiratory failure deteriorated, hysterectomy was performed 4 days after the C-section. Afterward the patient recovered slightly, but respiratory failure further deteriorated and 3 days after the hysterectomy VA ECMO was started between the femoral vein and subclavian artery. She suffered from a hematoma at the arterial insertion point which encapsulated and infected, resulting in a thoracotomy. This had to be repeated several times because of bleeding complications, but finally the ECMO could be weaned 3 weeks after it had been initiated. Respiratory failure regressed and in the end she was discharged home after 105 days.

2.1.3.2. The immunocompromised patient

Several publications [24–27] report on the use of ECMO in immunocompromised patients, mainly kidney and liver transplanted patients. Infections are the leading cause of critical illness and mortality in liver transplant patients. More than half of the patients develop an infection during the first year, almost always ending in ICU admission. Bacteremia associated from 10 to 52%. Mortality is higher in recipients with bacteremia due to 'ESKAPE' pathogens, which stands for *Enterococcus faecium*, ***Staphylococcus aureus***, ***Klebsiella pneumoniae***, *Acinetobacter baumannii*, *Pseudomonas aeruginosa* and *Enterobacter* species [28]. Over a 7-year period, a South Korean university center [24] used ECMO in 8 (of in total 854) liver transplanted patients with refractory septic shock. Primary liver disease in these patients was hepatocellular carcinoma (n = 3), liver cirrhosis due to hepatitis B infection (n = 3), alcoholic liver cirrhosis (n = 1) and toxic hepatitis (n = 1). These patients suffered mainly from intra-abdominal and lung infections. They were infected by a variety of pathogens, but in five out of eight, *Acinetobacter baumannii* was cultured.

ECMO was initiated after a median of 6, 5 h under vasoactive drugs were started and six patients received cardiopulmonary resuscitation (CPR) with initiation of ECMO after a median of 41, 5 min (range, 20–154 min) after onset of CPR. The interval between the transplantation and the onset of infection was not mentioned. Three patients (37.5%) were successfully weaned from ECMO but only 2 (25%) survived until hospital discharge. Illness severity scores at onset were not different between survivors and nonsurvivors. Lactate levels and SOFA scores tended to decrease over the course of treatment in survivors while in nonsurvivors total bilirubin and CRP levels tended to increase.

Another successful use of ECMO support was reported in a 49-year-old male liver transplant [25] suffering from alcoholic liver cirrhosis-induced acute-on-chronic liver failure. Immediately before the emergent liver transplantation, he developed pulmonary tuberculosis and tuberculosis peritonitis. The latter caused intermittent small-bowel obstruction and subsequent ischemia and led to emergency adhesiolysis on POD 114. In the postoperative phase, the patient developed aspiration pneumonia leading to septic shock and ARDS. After 11 days of ECMO support, the patient could be weaned and finally was discharged on day 204.

The largest available series of ECMO in adult liver transplant patients was published by Park et al. [26]. Over a 3-year period, 18 out of 1076 liver transplanted patients required VV ECMO. The main indication, however, was refractory respiratory failure, not necessarily with concomitant septic shock. Eight patients could be weaned.

The electronic medical records of kidney transplanted (KT) patients that received ECMO support were reviewed [27]. Between December 2010 and December 2014, 12 KT patients required ECMO management. In half of them, this was due to bacterial sepsis only or combined viral/bacterial pneumonia or sepsis. The others suffered from viral pneumonia or in 1 case fulminant myocarditis secondary to fungemia. The mean period between the KT and the ECMO support was 44.4 months (range, 1.2–184.3 months) and in three patients ECMO was started during the admission for the transplant.

The mean duration of ECMO support was 9.1 days (range, 3.5–15.1 days) and six patients were successfully weaned from ECMO. However, two of them died after being weaned from ECMO. During ECMO support, all patients needed renal replacement therapy (RRT). Among the six survivors, five could be weaned after a mean period of 53 + 37.5 days (range, 16–97 days). The pH just before the beginning of ECMO appeared to be significantly lower in the nonsurvivors than in the survivors (P = 0.046).

2.2. Children

In contrast with the adult population, there is far more acceptance for using ECMO in pediatric cases of septic shock. In a French study [29], the use of VA ECMO in 14 neonates and 9 children with refractory septic shock was reported. The mean age of the pediatric population was 30 months. Overall, in more than half of the cases septic shock was due to streptococcal or ***E. coli*** bacteremia. Fifty-seven percent of the neonates suffered from Streptococcus B infection. All patients were ventilated and received vasopressors before ECMO initiation.

In two patients, cannulation was performed during chest compressions because of cardiac arrest. The mean duration of support was 7.43 days (range, 1–17) and 5.9 days (range, 3–10) in neonates and children, respectively. Six neonates (42%) and three children (37%) had mechanical (mainly clotting) complications with the ECMO circuit. One neonate and three children required renal replacement therapy.

The overall survival rate was 59.1%, with 64.% of the newborns (n = 9) surviving to discharge and 50% (n = 4) of the pediatric population. So survival was significantly higher in the newborns (p = 0.02), although ECMO weaning rates were comparable (64 and 66% respectively).

These results are somewhat lower than those reported in older trials [3, 4, 30, 31], with survival rates up to 80% in neonates and 74% in older children. But in the French cohort [29], the patients seemed to have more severe cardiovascular failure with higher inotropic scores and lower pH. The authors conclude that ECMO can be safely used to resuscitate children with refractory shock and propose to transfer infants to an ECMO referral center in case of persisting oliguria and without decrease of lactate levels within 6 h after the initiation of maximum drug therapy.

In some of the older trials [5], central cannulated ECMO (atrio-aortal cannulaton) was used in 23 children, almost all (96%) having at least three organ failures and eight (35%) suffered cardiac arrest and required massage during ECMO placement. All had microbiological evidence of infection and meningococcemia was the most common causative pathogen. Despite the severe setting at onset, 18 patients (78%) could be weaned of ECMO and 17 (74%) survived to hospital discharge.

More recently, several case reports of pediatric ECMO use were published in specific indications [32] like liver transplanted infants or with more rare pathogens [33] like community-acquired Legionella infection.

Finally, a Taiwanese group [34] recently published their retrospective single center review of 55 pediatric septic shock patients. In this cohort, overall survival to discharge was 31%. However, 25 patients were immunocompromised, in whom mortality was 75%. Mean ECMO duration was 9 days (range, 0–103) with a duration in survivors that doubled the one in non-survivors (14 vs. 7 days, $p = 0.09$). In 17 of them, causal pathogens could be identified of which 7 were bacterial and 1 was an invasive fungal infection. In the previously healthy kids, in 18 cases with an identified pathogen 10 were bacteremic (mainly pneumococcal).

3. Adjunctive therapies

The mainstay of etiological treatment in septic shock remains source control and the administration of anti-infective agents. Especially with regard to the latter, dosing issues are extremely important. Finally, there is also some emerging literature, unfortunately mainly anecdotal, on the use of immunoadsorptive strategies.

3.1. Source control

Resection or drainage of an infectious inoculum is important. Due the necessity of anticoagulating ECMO treated patients, this is not without risk of bleeding during or after (at restart of anticoagulation) the procedure. However, as mentioned in previous sections of this chapter, performing surgical procedures in ECMO patients is feasible [22, 23].

3.2. Dosing of anti-infective agents

In the last decade, the interest in pharmacodynamics and therapeutic drug monitoring (especially for antibiotics) has grown tremendously. With regard to prescribing antibiotics, several reports have dealt with therapeutic drug monitoring in ICU patients in the absence [35] or in the presence [36] of concomitant use of renal replacement therapy.

However, there are no clear guidelines for dosing antibiotics in ECMO-treated patients. Therefore, the interest on the matter increased in the latest years and several publications investigated this topic [37–39], mainly in the class of beta-lactam antibiotics.

In ECMO patients, the volume of distribution increases tremendously, but clearance is usually lower than controls [37]. Although pharmacokinetic variability is high, decreased meropenem clearance usually compensates for ECMO and critical illness-related increases in the volume of distribution. With standard 1 g IV dosing 8-hourly, target concentrations of >2 mg/L are usually met, but an increase in dose may be appropriate in patients with elevated creatinine clearance or when higher concentrations are needed for less susceptible microorganisms.

The use of continuous infusions of carbapenems might be useful in this regard [38]. In a pediatric ECMO case, a bolus of 40 mg/kg meropenem followed by a continuous infusion of 200 mg/kg/day resulted in target attainment of 100% for serum and lung concentrations above the MIC.

Also, other beta-lactam antibiotics [39] were investigated. For piperacillin/tazobactam insufficient concentrations were more frequent than with meropenem therapy in the treatment of *Pseudomonas aeruginosa* infections.

Also while prescribing antifungal agents, caution is warranted for subtherapeutic exposure. In pediatric ECMO case [40], insufficient plasma levels were measured despite the administration of normal to high doses of caspofungin.

3.3. Immunoadsorption

In the last decade, several publications report on the use of cytokine adsorption techniques [41–46]. In several case reports [41–43], the Cytosorb hemoadsorption column (Linc Medical, Leicestershire, United Kingdom) was installed either in the ECMO circuit or in the CRRT circuit in order to stabilize septic shock patients more rapidly and to improve their outcome. Cytosorb removes the proinflammatory cytokines and has been shown to reduce vasopressor doses and serum inflammatory markers in septic patients. A similar device is the polymethylmethacrylate membrane hemofilter is also available for clinical use and a report on its use has been published [46]. Although promising, the addition of these immunabsorption techniques is costly and still under investigation.

4. Outcome prediction

Giving the debatable indication (at least in adults), the high cost and the invasive nature of ECMO treatment and the consequent complications, outcome prediction before treatment initiation is important. In **Table 1**, the outcome predictors of the previously cited publications

Predictor	cut off	impact on survival	Reference
ADULTS			
SAPS II	< 80	increased	50
ECPR at implementation		decreased	13
Pneumonia induced septic shock		increased	51
Gram-positive vs. Gram-negative septicemia		increased	51
Door-to ECMO time	< 96 hours	increased	51
	> 30 hours	decreased	24
Age	> 60	decreased	10, 24
Troponin I levels	> 15 ng/ml	increased	13
lower SOFA score at day 3 of support		increased	15
CHILDREN			
Arterial blood gas pH	< 7,2	decreased	37
Arterial blood gas CO2	> 56,9 mm Hg	decreased	37
Glasgow Coma Scale	<9	decreased	37
SOFA	< 15	increased	37
Central cannulation		increased	34

Table 1. Outcome predictors for ECMO use in septic shock.

are listed and a few other publications [47–49], that have investigated survival predictors for septic shock patients under mechanical support, were added.

In a Korean case series [47], 28 patients were treated with ECMO, of whom 21 with VA ECMO. The overall survival to discharge rate was 35.7% and predictors of survival appeared to be: a simplified acute physiology score II (SAP II) of 80 or less and pre-ECMO albumin levels.

In another report [48], better outcomes were seen if door-to ECMO times were < 96 h. Furthermore, survival was better in case of Gram-positive infections rather than Gram-negative septic shock. Finally, outcome was better for pneumonia rather than primary bloodstream infections.

The same group [49] also published that the implementation of ECMO during CPR is not beneficial for septic shock patients.

5. Conclusions

Although the use of VA ECMO has been controversial in adults with septic shock, it is commonly used in the pediatric population, with good results. Despite the ongoing controversy, VA ECMO has seen increased use in septic adults with SICM, with survival and complete cardiac recovery in as high as 70% of patients. However, outcomes vary enormously and VA ECMO seems especially beneficial in certain subsets, like, for example, lung infection-induced septic shock. On the other hand, survival rates are poor when ECMO is initiated in a CPR setting. Other currently reported, negative predictors (at ECMO onset) are SAPS II scores >80, Gram-negative septicemia, age > 60 years, SOFA scores >15. Also in immunocompromised patients, mortality rates are high and ECMO, which does not exclude its use in escape therapy (e.g., after liver transplantation). The use of ECMO does not prohibit other surgical interventions, with the aim of infectious source control. Procedures like hysterectomy, laparotomy, all have been performed under or immediately before ECMO therapy.

Conflict of interest

The author has no conflicts of interest to be declared.

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