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Review

Extracorporeal membrane oxygenation in adult patients with sepsis and septic shock: Why, how, when, and for whom

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ABSTRACT

Sepsis and septic shock remain the leading causes of death in intensive care units. Some patients with sepsis fail to respond to routine treatment and rapidly progress to refractory respiratory and circulatory failure, necessitating extracorporeal membrane oxygenation (ECMO). However, the role of ECMO in adult patients with sepsis has not been fully established. According to existing studies, ECMO may be a viable salvage therapy in carefully selected adult patients with sepsis. The choice of venovenous, venoarterial, or hybrid ECMO modes is primarily determined by the patient's oxygenation and hemodynamics (distributive shock with preserved cardiac output, septic cardiomyopathy (left, right, or biventricular heart failure), or right ventricular failure caused by acute respiratory distress syndrome). Veno-venous ECMO can be used in patients with sepsis and severe acute respiratory distress syndrome when conventional mechanical ventilation fails, and early application of veno-arterial ECMO in patients with sepsis-induced refractory cardiogenic shock may be critical in improving their chances of survival. When ECMO is indicated, the choice of an appropriate mode and determination of the optimal timing of initiation and weaning are critical, particularly in an experienced ECMO center. Furthermore, some special issues, such as ECMO flow, anticoagulation, and antibiotic therapy, should be noted during the management of ECMO support.

Introduction

Sepsis and septic shock are defined as life-threatening organ dysfunction caused by a severely dysregulated host response to infection.[1,2] Despite well-established management guidelines and advances in overall medical care, sepsis, and septic shock continue to cause significant morbidity and mortality globally.[3–6] Sepsis frequently co-occurs with severe acute respiratory distress syndrome (ARDS) and refractory shock, manifesting as insufficient oxygen delivery, tissue hypoxia, microcirculatory dysfunction, and rapid progression to multiple organ failure.[7–10] Even with the advent of the most recent International Sepsis Guidelines, no effective recommendations for such patients are available.[2]

The advancement of extracorporeal membrane oxygenation (ECMO) technology has added a new dimension to the intensive care management of adults with acute respiratory and/or cardiac failure who have not responded to conventional treatment.[11–15] ECMO can increase oxygen delivery, allow adequate rest for the heart and lungs, and provide time for recovery and decision-making. However, the feasibility of ECMO for adult patients with sepsis-induced respiratory and circulatory failure remains debatable. This review examines the theoretical benefits of ECMO in patients with sepsis and septic shock, as well as existing clinical studies to investigate indications, timing, optimal modes of ECMO, and special issues during ECMO management.

Theoretical Benefits of ECMO in Patients with Sepsis and Septic Shock

ARDS

Among the multiple-organ failures caused by sepsis, ARDS is the most common and severe, and it can result from both the

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initial onset and secondary damage from treatment.[16,17] The mortality of severe ARDS was reported to be 46.1%, and the mortality rate of patients with sepsis and ARDS is higher than that of patients with isolated sepsis or ARDS.[18,19] Despite receiving evidence-based practices, such as protective ventilation, prone positioning, fluid management, and recruitment maneuvers, some patients continued to exhibit refractory hypoxemia or hypercapnia. Given its ability to improve hypoxia and acidosis and provide ultra-protective mechanical ventilation, veno-venous (VV) ECMO may be a viable option for patients with refractory severe ARDS.[20,21]

Notably, hemodynamic instability is a common complication of ARDS. On the one hand, hypoxemia, hypercapnia, mechanical ventilation, and acute pulmonary hypertension promote right ventricular (RV) dysfunction. On the other hand, acidosis gradually impairs vascular tone and cardiac contractility.[22–24] If correction of hypoxia and acidosis, protective pulmonary ventilation, and VV ECMO, do not improve RV failure and it is still accompanied by progressive RV failure leading to cardiogenic shock, ECMO for circulatory support should be considered.[20]

Circulatory failure

Several hemodynamic presentations of septic shock, including distributive shock (low systemic vascular resistance and refractory hypotension with maintained cardiac index), [25–27] cardiogenic shock induced by septic cardiomyopathy (SCM) (decreased cardiac index), [28] and RV failure caused by ARDS, have been reported. Notably, hemodynamic patterns of septic shock vary among different individuals and disease processes. Hence, accurate differentiation of the hemodynamic status of each patient is essential.

Distributive shock with preserved cardiac function

The pathophysiological manifestations of distributive shock are overwhelming vasodilation and capillary leakage, which are caused by the release of inflammatory mediators as a result of abnormal host responses to infection, resulting in microvascular damage, insufficient tissue oxygen supply, and abnormal cellular metabolism.[25–27]

The role of venoarterial (VA) ECMO in patients with refractory distributive shock who present with normal or hyperdynamic cardiac function is still debated. One could argue that VA ECMO can increase oxygen delivery and stabilize circulation.[29] Others, however, may argue that VA ECMO is contraindicated. First, VA ECMO supports the failing heart but has little or no direct effect on vasoparalysis and capillary leakage, which are major aspects of sepsis physiology.[30] Second, ECMO treatment does not unaidedly restore microcirculation or oxygen intake in cells. Third, capillary leakage causes fluid extravasation, resulting in difficulty to deliver sufficient flow on ECMO, which is essential for oxygen delivery. Fourth, increasing ECMO flow will reduce preload, increase afterload, and negatively affect left ventricular (LV) performance, eventually decreasing cardiac output in patients with preserved cardiac function.[31,32] Additionally, endovascular catheters and artificial circuits may breed microbes, resulting in severe uncontrolled infections.

Cardiogenic shock caused by septic cardiomyopathy

SCM is common and associated with mortality. The prevalence of SCM reaches up to 83%.[33] SCM consists of two components: the presence of systolic and/or diastolic dysfunction of the left and/or right sides of the heart and the exclusion of other causes of cardiac dysfunction.[28] SCM can lead to cardiogenic shock and deterioration of hemodynamics; several mechanisms, including mitochondrial dysfunction, oxidative stress, complement activation, apoptosis, and autophagy, contribute to sepsis-induced myocardial dysfunction.[34–37]

Among SCM disorders, reduced LV ejection fraction (EF) and impaired contractility are common and associated with increased mortality.[33] LV systolic dysfunction is reversible, and survivors usually recover within 7–10 days.[35] Furthermore, when compared to ischemic cardiomyopathy, LV systolic dysfunction improves faster, and the need for additional support is lower.[32] Notably, RV involvement in sepsis has recently received more attention. Despite having lesser muscle mass than the left, the two ventricles are organized in tandem and are linked by a common interval, resulting in ventricular interdependence. Increased RV afterload combined with decreased RV contractility may reduce LV filling, resulting in a decrease in cardiac output. Independent of the presence of LV systolic and diastolic dysfunction, studies have shown that RV dysfunction is common in patients with sepsis, occurring in 34.7–55.0% of studied patients with sepsis and associated with increased mortality.[38–41]

Given the reversibility of myocardial depression, VA ECMO may be an option in patients with SCM and cardiogenic shock.[42] Patients with sepsis-induced refractory cardiogenic shock may account for up to 10% of patients with septic shock.[43] In this subset of patients, VA ECMO can replace cardiac output, ensure oxygen delivery, and provide additional time for the failing heart's recovery until the cardiac function is restored, resulting in improved survival.[14]

Coronavirus disease 2019 (COVID-19)-related sepsis

COVID-19 spread rapidly, resulting in millions of confirmed cases and deaths globally. Severe COVID-19 can induce respiratory failure, with some patients manifesting signs of multiple organ failure syndrome and satisfying the diagnostic criteria for sepsis and septic shock according to the Sepsis-3 International Consensus.[1] One study reported that the prevalence of COVID-19-related sepsis was 77.9% and 33.3% in the ICU and general ward, respectively.[44] VV ECMO, is recommended in patients with severe COVID-19-related ARDS.[45] According to data from retrospective cohorts (n=1345) of patients with COVID-19 treated with ECMO, 98% and 2% of patients received VV ECMO, and VA/VAV(hybrid) ECMO, respectively.[46]

The Choice of ECMO Mode

Clinical outcomes in patients with sepsis and septic shock receiving ECMO varied due to the lack of established best practices, wide variation in management, and heterogeneity of the study populations [16,17,29,31,47–56] (Table 1).

When ECMO is indicated, the initial configuration should be carefully selected. The decision to use VV, VA, or hybrid ECMO modes is mainly based on the patient's oxygenation and hemodynamics. Furthermore, the primary cause of circulatory collapse should be identified: septic shock with preserved cardiac output, cardiogenic shock caused by LV failure, severe RV fail-

Table 1
Summary of key studies in patients with sepsis and septic shock treated with ECMO.

Reference	Type and period of study, enrollment numbers of patients	Pre-ECMO characteristics	Cardiac arrest before ECMO	Shock-to-ECMO time	ECMO configuration	ECMO duration	LV function at ECMO implantation	Complications	Main results
Huang et al.[16]	Single-center retrospective, 2005–2010, 52	Age: 56.8 (IQR: 42.7–63.6) years SOFA: 16 (IQR: 13–18) Lac: survivors 5.3 mmol/L, non-survivors 8.8 mmol/L	ECPR: 21 (40%)	15 (IQR: 6.1–29.3) h	All VA	1.8 (IQR: 0.4–6.5) days Survivors: 6.8 days, non-survivors: 1.1 days	21% of patients with LVEF <50%, survivors 56.5%, non-survivors 55.5%	Mechanical problems 12 (23%): oxygenator failures 9, a cannula needed to be repositioned 4, blood clots in the circuit 1 Major bleeding complications 4 (7.7%): cannulation sites 2, gastrointestinal hemorrhage 2	Hospital discharge survival: 15% Survival of patients with refractory septic shock receiving ECMO support remains unsatisfactory Age was the only independent factor associated with mortality
Bréchot et al.[47]	Single-center retrospective, 2008–2011, 14	Age: 45 (IQR: 28–66) years SOFA: 18 (IQR: 8–21) Lac: 9 (IQR: 2–17) mmol/L	0	24 (3–108) h	VA (convert to VV 5)	Survivors: 5.5 (2–12) days, non-survivors: 3 (1–7) days	LVEF: 16% (10–30) Aortic VTI: 6.5 (3.0–9.2) cm CI: 1.3 (0.7–2.2) L/(min·m^2)	60% of patients experienced >1 major ECMO-related complication Hemorrhage 4 Arterial ischemia 2 Surgical wound infection 3 Bacteremia 3 Stroke 1 Hemolysis 1	Hospital discharge survival: 71% All 10 survivors had normal LVEF and reported good health-related quality of life at long-term follow-up
Park et al.[48]	Single-center retrospective, 2005–2013, 32	Age: 55 (IQR: 44–63) years SOFA: 16 (IQR: 14–18) Lac: 8.9 (IQR: 5.8–14.6) mmol/L	14 (43.8%) ECPR: 7 (21.9%)	23.5 (IQR 10.3–33.5) h	All VA	3.5 (IQR: 1.8–4.8) days, survivors: 3.9 (IQR: 2.9–5.6) days, non-survivors: 3.2 (IQR: 1.5–4.2) days	LVEF: 25.0% (IQR: 20–41), survivors 23.0% (IQR: 20.0–27.0), non-survivors 25.0% (IQR: 20.5–42.0)	Limb ischemia 5 (15.6%) Gastrointestinal bleeding 1 (3.1%) Brain hemorrhage 1 (3.1%)	Hospital discharge survival: 21.9% Patients who started ECMO more than 30.5 h after the onset of septic shock (31.3%) did not survive CPR was an independent predictor of in-hospital mortality and higher peak troponin I >15 ng/mL was associated with a lower risk of in-hospital mortality
Cheng et al.[17]	Single-center retrospective, 2001–2011, 151	Age: 51 (IQR: 37–63) years SOFA: 12.6±4.6 Lac: 7.2±5.3	37 (24.5%) ECPR: 29 (19.2%)	NA	VA 101 VV 50	7.9±8.6 days, survivors: 9.8±5.9 days, non-survivors: 6.9±9.6 days	CI: 2.1±1.9 L/(min·m^2), survivors: 1.0±0.2 L/(min·m^2), non-survivors: 4.24±2.00 L/(min·m^2)	ECMO circuit clot 64 (42.4%) Major bleeding 25 (16.6%) Post-ECMO neurologic deficit 22 (14.6%) Survived with neurologic disability 14 (9.3) Pneumothorax 11 (7.3%) Post-ECMO dialysis dependence 77 (51%) Hypoglycemia 6 (4%) Peripheral limb ischemia 61 (40.4%)	Hospital discharge survival: 29.8% Patients with door-to-ECMO times of 96 h or less, Gram-positive rather than Gram-negative sepsis, and pneumonia rather than primary bloodstream infections were associated with better outcomes
Yeo et al.[49]	Case series, 2013–2015, 8	Age: 50.9 (IQR: 18–71) years Lac: 7.8 (IQR: 6.3–16.3) mmol/L	NA	NA	All V-VA	3.0 (2.0–4.5) days	LVEF: 42.5% (IQR 23.5–50.0)	NA	Overall survival: 50.0% V-VA ECMO might be an alternative bridging strategy to assist the heart and lungs in patients with combined cardiopulmonary failure

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Table 1 (*continued*)

Reference	Type and period of study, enrollment numbers of patients	Pre-ECMO characteristics	Cardiac arrest before ECMO	Shock-to-ECMO time	ECMO configuration	ECMO duration	LV function at ECMO implantation	Complications	Main results
Choi et al.[50]	Single-center retrospective, 2007–2013, 28	Age: 44.0 (IQR: 33.5–67.0) years SOFA: 15.0 (IQR: 13–17) Lac: 5.9 (IQR: 4.0–9.5) mmol/L	14 (50%) ECPR: 6 (21.4%)	5.5 (IQR: 3.0–9.3) h, survivors: 3.3 (IQR: 3.1–7.6) h, non-survivors: 6.4 (IQR: 3.0–10.4) h	VA 21 VV 4 V-VA 3	3.2 (IQR: 1.1–7.5) days, survivors: 7.1 (IQR: 4.4–9.0) days, non-survivors: 1.8 (IQR: 0.7–6.3) days	NA	Cannula-related complication 5 (21.4%) Cannula site bleeding 2 (7.1%) Leg ischemia 2 (7.1%) Thrombosis 1 (3.6%) Foot drop 1 (3.6%) Acute kidney injury 20 (71.4%) Gastrointestinal bleeding 1 (3.6%) Bed sore 2 (7.1%) Pulmonary hemorrhage 1 (3.6%) CPR-related hypoxic brain damage 2 (7.1%)	Hospital discharge survival: 35.7% A SAPS II score ≤80 may be an indicator of favorable outcomes with the use of ECMO
Takauji et al.[51]	Multicenter retrospective, 2011-2013, 40	Age: 66±12 years SOFA: 13 (IQR: 10-15) Lac: 3.4 (IQR: 1.9-9.0) mmol/L	NA	NA	All VV	NA	NA	Bleeding requiring transfusion 13 (32.5%) Bleeding requiring therapeutic intervention 2 (5.0%)	Hospital discharge survival: 47.5% The survival of overall septic patients with severe respiratory failure between the ECMO group and control group was similar, but in sepsis patients with severe respiratory failure induced by lung infection, ECMO support may improve their survival time.
Vogel et al.[31]	Case series, 2014–2017, 12	Age: 40.5 (IQR: 23.75–50) years SOFA: 10 (IQR: 7.5–11.25) Lac: 5.0 (IQR: 3.85–6.05) mmol/L	5 (41.7%)	NA	V-VA 7 VV convert to V-VA 5	V-AV ECMO: 4 (IQR: 3.0–5.3) days ECMO: 9 (IQR: 7.5–15.5) days	LVEF: 16.25% (IQR: 13.13–17.5)	Right leg ischemia 1 Cerebral edema led to brain herniation 1 Bleeding requiring transfusion 1 Neurologic deficit secondary to ischemic 2 Bilateral below knee amputation 1	Hospital discharge survival: 75% V-VA ECMO is a feasible rescue strategy for a small number of patients with respiratory and cardiac failure secondary to septic shock complicated with septic cardiomyopathy
Kim et al.[52]	Single-center retrospective, 2007–2015, 37	Age: 51.0 (IQR: 35.5–64.5) years SOFA: 15.0: (IQR 13.0–17.0)	18 (48.6%) ECPR: 8 (21.6%)	5.6 (IQR 2.8–9.3) h, survivors: 3.4 (IQR 2.6–9.1) h, non-survivors: 6.0 (IQR 2.7–9.7) h	VA 26 VV 8 V-VA 3	Overt DIC group: 2.9 (IQR: 1.0–12.6) days, non-overt DIC group: 5.5 (IQR: 1.4–9.4) days	LVEF: 40.0% (IQR: 26.3–49.3)	Cannula thrombosis 1 Limb ischemia 6 Cannula bleeding 3 Gastrointestinal bleeding 2 Acute renal failure 25	Hospital discharge survival: 40.5% (VA 26.9%, VV 87.5%, V-AV 33.3%) The pre-ECMO DIC score plus lactate level was the best predictor of hospital death in patients with septic shock
Banjas et al.[53]	Single-center retrospective, 2011–2016, 19	Age: 62 (IQR: 55–73) years SOFA: 8 (IQR: 6–12) Lac: 5 (IQR: 2–11) mmol/L	3 (16%)	NA	All V-VA	14 (IQR: 9–25) days	NA	NA	Hospital discharge survival: 42% Experience of the ECMO center is one factor determining outcome in patients with septic shock receiving ECMO

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Table 1 (*continued*)

Reference	Type and period of study, enrollment numbers of patients	Pre-ECMO characteristics	Cardiac arrest before ECMO	Shock-to-ECMO time	ECMO configuration	ECMO duration	LV function at ECMO implantation	Complications	Main results
Ro et al.[54]	Single-center retrospective, 2005–2012, 71	Age: 56.0±12.3 years SOFA: 18.2 ± 4.0 Lac: survivors: 5.8 (IQR: 4.3–5.9) mmol/L, non-survivors: 11.6 (IQR: 7.5–15.0) mmol/L	9 (12.7%)	Survivors: 4.0 (IQR: 3.7–4.2) h, non-survivors: 18.0 (IQR: 6.7–53.7) h	All VA	7.9 (IQR: 6.3–10.2) days Survivors: 7.4 (IQR: 5.1–7.9) days, non-survivors: 1.1 (IQR: 0.5–2.3) days	NA	NA	Hospital discharge survival: 7% Elevated arterial lactate levels pre- and post-ECMO were associated with the risk of in-hospital death.
Han et al.[55]	Single-center retrospective, 2007–2017, 23	Age: 56.0±12.3 years SOFA: survivors: 12.0 (IQR: 10.0–13.0), non-survivors: 15.0 (IQR: 13.0–18.3) Lac: survivors 4.4 (IQR: 2.2–7.4) mmol/L, non-survivors 6.8 (IQR: 5.5–8.9) mmol/L	NA	Survivors: 23.5 (IQR: 14.7–26.9) h, non-survivors: 42.2 (IQR: 24.3–80.9) h	All VA	Survivors: 6.1 (IQR: 5.2–6.9) days, non-survivors: 6.6 (IQR: 5.9–8.5) days	NA	NA	Hospital discharge survival: 21.7% $ScvO_2$% at 12 h during ECMO may be risk factor for patient prognosis
Falk et al.[29]	Single-center retrospective, 2012–2017, 37	Age: 55 (IQR: 45–66) years SOFA: 16 (IQR: 15–18) Lac: 7 (IQR: 3.6–10.5) mmol/L	7 (18.9%)	5.5 (IQR: 1.1–14.8) h	VV 10 (convert to VA 6), VA 27	6.9 (IQR: 5.1–11.0) days	LVEF: 35% (IQR: 25–58)	Limb ischemia 2 Cannula bleeding 2 Ventilator-associated pneumonia 3 Intestinal bleeding 1	Hospital discharge survival was 90% for septic shock with LV failure and 64.7% in patients with distributive shock
Myers et al.[56]	Single-center retrospective, 2009–2016, 32	Age: 46 (95% CI: 30 to 58) years SOFA: VV 8.9 (95% CI: 7.7 to 10.1), VA 11.4 (95% CI: 9.7 to 13.0) Lac: VV 7.1 (95% CI: 4.7 to 9.0) mmol/L, VA 7.1 (95% CI: 2.4 to 6.0) mmol/L	12 (38%)	23 (IQR: 6–65) h	VV 21 VA 11	5.8 (IQR: 2.6–11.3) days	LVEF: 51% (IQR: 30–67)	Cardiac arrhythmia 13 (41%) Surgical/cannulation site bleeding 12 (38%) Dialysis 10 (31%) Healthcare-associated infection 8 (25%) Air or clot in membrane 7 (22%) Pneumothorax 3 (9%) Disseminated intravascular coagulation 3 (9%) Brain death 3 (9%) Pulmonary hemorrhage 3 (9%)	Hospital discharge survival: 41% (VA 45%, VV 38%) There was no statistically significant difference in survival by subgroup of ECMO mode
Bréchot et al.[43]	Multicenter retrospective, 2008–2018, 82	Age: 48±15 years SOFA: 16.6±2.9 Lac: 8.9±4.4 mmol/L	NA	1.1 ± 0.9 days	VA 62 V-AV 8 VV convert to VA 12	5.8±5.6 days	LVEF: 17.0±7.3% CI: 1.54±0.54 L/(min·m^2)	Insertion site hemorrhage 17 (21%) Insertion site infection 17 (21%) ECMO-related bacteremia 10 (12%) Critical limb ischemia 4 (5%) Major amputation 2 (2%) Hemolysis 7 (9%) Pulmonary edema 1 (1%)	90 days Survival: 60%. Patients with severe sepsis-induced cardiogenic shock treated with VA ECMO had a large and significant improvement in survival compared with controls not receiving ECMO
Zha et al.[108]	Single-center retrospective, 2017–2021, 31	Age: 55±24 years SOFA: 12±3 Lac: 2.31±2.64 mmol/L	NA	NA	All VV	NA	NA	Acute renal injury 17 (54.8%) Bleeding 9 (29.0%) Hypoglycemia 6 (19.4%)	30-day mortality was significantly lower in the VV ECMO, group than in the control group (38.7% *vs.* 61.3%, *P*=0.043) after propensity score matching

CI: Cardiac index; CRP,: Cardiopulmonary resuscitation; DIC: Disseminated intravascular coagulation; ECPR: Extracorporeal cardiopulmonary resuscitation; ECMO: Extracorporeal membrane oxygenation; IQR: Interquartile range; Lac: Lactate; LV: Left ventricular; LVEF: Left ventricular ejection fraction; NA: Not available; SOFA: Sequential organ failure assessment; VTI: Velocity time integral; VA: Venoarterial; V-AV: Veno-arterialvenous; VV: Venovenous; V-VA: Veno-venoarterial.

ure, or a combination of these factors. Notably, the clinician's experience of managing patients using ECMO is essential, because the clinical management of such critical and complex patients is particularly difficult.[56,57]

Sepsis with severe ARDS

Sepsis with severe ARDS and hemodynamic stability

In patients with sepsis and severe ARDS but no severe shock, VV ECMO, may be an option. Several retrospective and observational studies with small sample sizes have shown that adult patients with sepsis and severe ARDS treated with VV ECMO, have survival rates ranging from 30% to 60%.[17,29,50,51,56] Takauji et al.[51] found no difference in in-hospital survival between the ECMO and control groups among all patients with sepsis and severe respiratory failure. However, during subgroup analysis, ECMO support improved survival time in patients with sepsis caused by lung infection. Falk et al.[29] showed that the commencement of VV ECMO, had a worse outcome, in terms of hospital (11% *vs*. 50%; *P*=0.011) and long-term survival (29.6% *vs*. 70%; *P*=0.026), than VA ECMO. However, Myers et al.[56] found no statistically significant difference in ECMO mode (VV *vs*. VA, 38% *vs*. 45%).

As in previous studies, early VV ECMO, reduces 90-day mortality in patients with refractory severe ARDS (36% *vs*. 48%).[58–60] However, whether patients with sepsis and refractory severe ARDS benefit from VV ECMO is unknown and needs to be investigated further. Due to a lack of direct evidence, the Surviving Sepsis Guidelines 2021 suggested that for adults with sepsis-induced severe ARDS, VV ECMO can be used in experienced centers when conventional mechanical ventilation fails (weak recommendation, low quality of evidence).[2]

Sepsis with severe ARDS and hemodynamic instability

Notably, hemodynamic instability is not a contraindication to VV ECMO, support if shock is caused primarily by RV failure.[22] One study described the use of VV ECMO, in 17 patients with refractory hypoxemia due to ARDS and hemodynamic instability. ECMO did not only improve oxygenation but also decreased the need for vasoactive agents in almost all patients.[21] Furthermore, a review of the extracorporeal life support organization registry revealed that survival to discharge was 58% and 43% for VV ECMO and VA ECMO, respectively (*P*=0.002), in adult patients with ARDS requiring pre-cannulation hemodynamic support, suggesting that initiation of VV ECMO, first may be reasonable, with VA ECMO reserved for conversion for refractory hypotension.[61]

In patients with ARDS and progressive RV failure, reversible causes, such as fluid overload, pulmonary emboli, and alveolar atelectasis, should be addressed first. Interestingly, an intra-aortic balloon pump has the potential to be used as an adjunct to VV ECMO, to improve RV function. One study observed a decrease in central venous pressure and a reduction in inotropic score after inserting an intra-aortic balloon pump, which was likely due to an increase in myocardial oxygen supply, a decrease in myocardial oxygen demand, and an improvement of RV pressure-induced failure.[62] If the disease progresses and is accompanied by significantly reduced cardiac output, a VA or V-VA configuration (an arterial cannula is added to a VV configuration) may be considered, which will increase venous drainage, resulting in right heart unloading and thus increased perfusion.

Recently, in patients with pre-ECMO evidence of RV injury, the role of a percutaneous right ventricular assist device (RVAD) in severe ARDS refractory to conventional management was investigated, showing a promising benefit in improving survival. However, the evidence is insufficient because these studies were observational with small sample sizes, and mainly enrolled patients with COVID-19-associated ARDS.[63,64] RVAD-ECMO configuration with the Protek Duo single dual-lumen cannula, which is placed through the right internal jugular vein, drains blood from the right atrium and returns it to the pulmonary artery, resulting in lung and RV function support.[65,66] RVAD-ECMO appears to be a promising treatment option in selected patients with sepsis, ARDS, and RV dysfunction. Therefore, future studies on RVAD-ECMO will be worthwhile.

Septic shock with preserved cardiac function

The role of VA ECMO in adult patients with refractory distributive shock and preserved cardiac function is still being debated. Some studies have shown that ECMO improves local blood flow and oxygen delivery, even when mean arterial pressure and cardiac output are not fully restored to baseline in a porcine model of early endotoxin shock.[30,67] However, the majority of evidence suggests that VA ECMO may not be a viable option in patients with distributive shock. According to one study, using VA ECMO in a porcine model of peritonitis-induced refractory vasodilatory septic shock did not only not improve mortality but also exacerbated hemodynamic deterioration.[68] Recently, two systematic reviews reported in-hospital mortality rates of 63.6%-76.7% in patients with refractory septic shock receiving VA ECMO, regardless of cardiac function.[57,69] However, when compared to previous literature that reported 28-day mortality rates of 60% in patients with sepsis receiving conventional treatment, VA ECMO did not improve clinical outcomes.[70] Furthermore, Falk et al.[29] found that patients with distributive shock had lower hospital mortality (35.3%), but their initial modes were all VV ECMO, indicating less severe shock. Notably, six of them were then converted to VA ECMO, but none survived to discharge.

Sepsis with SCM

SCM presenting left heart failure and cardiogenic shock

VA ECMO has been proposed as a rescue therapy in neonates and children with refractory septic shock, most likely due to heart failure being the primary cause of shock.[71–75] In adults, several retrospective studies have shown that VA ECMO is feasible in patients with SCM who have left heart failure and cardiogenic shock. Kim et al.[76] revealed that VA ECMO may help improve survival in patients with septic shock and cardiogenic shock. Cheng et al.[17] showed that survivors of VA ECMO for refractory septic shock had more severe myocardial dysfunction than non-survivors (mean cardiac index: 1.0 L/(min·m^2) *vs*. 4.24 L/(min·m^2). Recently, a retrospective, multicenter, international cohort study found that patients with sepsis-induced refractory cardiogenic shock treated with VA ECMO had a significant improvement in survival, compared to controls who did not receive ECMO (60% *vs*. 25%), despite having more severe

myocardial dysfunction (mean cardiac index: 1.5 L/(min·m^2) *vs.* 2.2 L/(min·m^2), left ventricular ejection fraction [LVEF]: 17% *vs.* 27%), more severe hemodynamic impairment, and more severe organ failure.[15] Consistent with these studies, a systematic review and meta-analysis found that survival among patients with septic shock and severe sepsis-induced myocardial depression supported by VA ECMO with LVEF of 20% was significantly higher than that among those with LVEF >35% (62.0% *vs.* 32.1%).[57] The link between poor cardiac function and improved survival could be explained by reversible myocardial dysfunction.

When patients receive VA ECMO in combination with Harlequin syndrome or differential hypoxia, if conventional management to improve respiratory function, such as reducing pulmonary edema and adapting ventilator settings, is ineffective, extension to V-AV (a re-entry vein cannula is added to a VA configuration) ECMO mode may provide adequate hemodynamic and oxygenation support.[77] Notably, converting the ECMO circuit from VA to V-AV mode may be ineffective in patients with severe right cardiac function failure because the failing RV is unable to cope with the increased preload, whereas increasing venous drainage (VV-A) may be preferable to traditional V-AV configuration, resulting in right heart unloading and thus increased RV output.[78]

SCM presenting right/biventricular heart failure and cardiogenic shock

Unfortunately, most current studies focus on sepsis-induced left cardiac systolic dysfunction. No study has assessed the value of VA ECMO in sepsis-induced right and whole heart dysfunction. VA ECMO may be a rescue option in patients with SCM who have right/biventricular heart failure and refractory cardiogenic shock. Whether VA ECMO can confirm its beneficial effect on clinical outcomes in such patients would necessitate future carefully designed prospective studies.[79]

Sepsis with simultaneous cardiopulmonary failure

In patients with sepsis and simultaneous cardiopulmonary failure, V-VA (physiologically, V-VA is the same as V-AV) ECMO could be considered. V-VA ECMO provides cardiac and respiratory support by draining blood from the vein and returning blood from the pump through a “Y” connector to two lines connected to the vein and artery to deliver oxygenated blood to the right atrium and retrogradely into the aorta via the artery.[80]

Several studies discussed their experiences with using V-VA ECMO. Two studies with small sample sizes reported similar mortalities of V-VA ECMO treatment in patients with severe ARDS and septic shock. Survival-to-hospital discharge was 50% in the study by Yeo et al.[49] and 42% in that by Banjas et al.[53] Of these two studies, one had an average LVEF of 42.5%, [49] and the other did not mention cardiac function.[53] However, Vogel et al.[31] showed that V-VA ECMO was initially used in patients with severe respiratory failure and SCM (at baseline, the median LVEF was 16.25%, and the median PaO_2/FiO_2 ratio was 67.50 mmHg), with a median of 4 days and a favorable survival rate of 75% (9/12) to hospital discharge. The disparity in clinical outcomes between these studies could be attributed to differences in the study population. Furthermore, except for one patient with LV dilation who received an intra-aortic balloon pump for 5 days while on V-VA ECMO, no one received mechanical cardiac support or LV decompression.[31] V-VA ECMO has the potential to be a viable rescue strategy for a subset of patients with sepsis, severe respiratory, and sepsis-induced cardiogenic shock. However, notably, initiation and management of V-VA ECMO are difficult and require extensive experience.

Indication and Timing

To date, the indications and timing for initiating ECMO support for sepsis and septic shock are unknown. The decision to begin ECMO should be made individually for each patient. We propose indications for using ECMO based on the literature with high levels of evidence thus far. ECMO for respiratory support is considered in patients with sepsis, severe ARDS (partial pressure of oxygen [PaO_2] /fraction of inspired oxygen [FiO_2] <50 mmHg for >3 h, PaO_2/FiO_2 <80 mmHg for more than 6 h, arterial blood pH <7.25 with $PaCO_2$ ≥60 mmHg for >6 h despite ventilator optimization [FiO_2 ≥0.80, PEEP ≥10 cmH_2O]), and less severe shock who are unresponsive to conventional treatment (etiological treatment, lung-protective ventilation, neuromuscular blockade with deep sedation, recruitment maneuvers, inhaled nitric oxide, fluid administration, and prone positioning).[2,51,58] ECMO for circulatory support is considered in patients with sepsis-induced cardiogenic shock. According to the criteria of the largest multicenter retrospective study to date, the timing to initiate ECMO can be defined as follows: after adequate therapy (early effective anti-infection, infectious source control, optimized fluid resuscitation, high-dose vasoactive drugs, etc.), LVEF ≤35%, cardiac index ≤3 L/(min·m^2), lactatemia ≥4 mmol/L, and inotrope score {calculated as dobutamine dose [μg/(kg·min)] + (epinephrine dose [μg/(kg·min)] + norepinephrine dose [μg/(kg·min)]) × 100} at least 75 μg/(kg·min).[43]

Additionally, grasping the optimal timing of the initiation of ECMO is essential. When compared to patients who receive conventional ventilatory support, patients with ARDS who receive VV ECMO, early have a lower 90-day mortality and treatment failure.[59] No study has, however, been conducted to investigate the relationship between shock-to-ECMO initiation timing and clinical outcome in patients with refractory sepsis-induced cardiogenic shock. According to some studies, receiving ECMO sooner improves outcomes. One study discovered that ECMO was used early (mean of 1.1 days) after the onset of sepsis-related cardiogenic shock, with a higher survival of 60%, and that after receiving ECMO, patients had significantly faster lactate clearance and a decrease in the inotrope score.[7] Another study discovered that patients with septic shock and LV failure who underwent ECMO had a higher hospital survival of 90%, likely due to the short time from shock onset.[29] As a result, ECMO should be considered earlier when indications are noted.

Special Issues During ECMO Management

ECMO flow

Ensuring appropriate flow is crucial in the implementation of ECMO. ECMO flow is an important factor in ensuring tissue

oxygen delivery.[81] Patients with sepsis and distributive shock typically have a high metabolic oxygen demand, necessitating a high ECMO flow and even exceeding the rated flow of the oxygenator. High ECMO flow can cause complications, such as hemolysis and renal failure.[82] Peripheral femoro-femoral VA ECMO provides non-physiological, retrograde blood flow, which may reduce LV function and substantially decrease LV stroke volume while increasing myocardial oxygen consumption and favoring the development of pulmonary edema.[83] The optimal ECMO flow is dictated by the balance of oxygen delivery and consumption. Especially during VA ECMO, ECMO flow should be tuned to decrease LV afterload while preserving peripheral perfusion.

Before starting ECMO, an appropriate cannula and optimal ECMO flow should be selected by a thorough examination of the individual patient's situation, including the patient's oxygen consumption and demand and physiologic vessel measurements. Notably, patients with sepsis frequently have vascular paralysis, venous stasis, and capillary leakage, resulting in decreased venous return and insufficient ECMO flow.[84] When inadequate ECMO flow occurs during ECMO support, the displacement, distortion, or obstruction of ECMO cannulation should be investigated first. Second, while blood volume expansion can be used to increase ECMO flow, excessive fluid infusion can cause pulmonary edema and thus oxygen deficiency. Third, patients with VA ECMO who do not have enough venous cannulas for adequate venous drainage may require a second or even third venous drainage cannula to achieve adequate blood flow.[85] Furthermore, central ECMO appears to provide adequate blood flow; however, its clinical application is limited due to its invasiveness and patient comorbidities.

Anticoagulation

Coagulation activation is a critical step in the development of sepsis, resulting in extensive microvascular thrombosis and secondary multiple-organ dysfunction.[86] ECMO is associated with an inflammatory response that promotes a hypercoagulable state once blood interacts with non-endothelial surfaces, necessitating anticoagulation to prevent thrombosis. Moreover, coagulation factor consumption and secondary hyperfibrinolysis can result in coagulopathy, which is frequently associated with thrombocytopenia.[87] Severe thrombocytopenia is an independent predictor of mortality in patients with sepsis.[86,88] The complexity of managing anticoagulation during ECMO is increased by abnormal coagulopathy caused by sepsis. It is complicated to balance the risk of thrombosis and bleeding in such patients.

Complications

Studies on patients with sepsis and septic shock treated with ECMO revealed a range of complications, including bleeding, thrombosis, neurological injury, infections, limb ischemia, hemolysis, and renal damage (Table 1).

Coagulopathy-related complications are common due to insufficient or excessive anticoagulation. Close monitoring is required to reduce the occurrence of those complications; both patients and the device must be monitored concurrently. First, patients' bleeding symptoms, coagulation status, thromboelastogram, platelet count, and platelet function should be closely monitored before, during, and after ECMO support. Second, the system, particularly the oxygenator, should be externally inspected for the presence of thrombosis, which may necessitate component replacement. Additionally, monitoring the pressure drop between pre- and post-oxygenator measurements at a constant flow rate can assess clot formation within the oxygenator.[89] Besides the coagulopathy-related reasons, neurologic injury may be caused by a sudden increase in blood PaO_2, decrease in blood $PaCO_2$, and disease-related variables (including prolonged severe hypoxia and pre-ECMO cardiac arrest). To detect neurologic injury, multimodal neurologic monitoring (neurologic examination, near-infrared spectroscopy, electroencephalography, cerebral ultrasound, biomarkers, and neuroimaging) is beneficial.[90] Additionally, infections, such as insertion site infection, surgical wound infection, and ventilator-associated pneumonia, are frequently reported as complications. The detection, management, and prevention of infections during ECMO are challenging.[91] Limb ischemia is caused by insufficient perfusion of the cannulated limb during peripheral femoral cannulation, and it can lead to lower extremity ischemia or even limb amputation. Capillary refill, temperature, and limb color are all beneficial for identifying ischemia. Additionally, limb regional oxygen saturation monitoring is useful.[92]

Pharmacokinetics and pharmacodynamics of antibiotics

Effective antimicrobial treatment is essential for reducing mortality in patients with bacterial sepsis, as delayed treatment has been related to increased mortality.[1,2] Sepsis, due to capillary leakage, hypoproteinemia, and multiorgan failure, will affect the pharmacokinetics (PK)/pharmacodynamics (PD) of antibiotics, which will be affected when combined with other *in vitro* support techniques, such as renal replacement therapy.[93–96]

Antibiotic PK/PD may be affected during ECMO support due to increased drug distribution volume and drug sequestration in the ECMO circuit. However, due to the complexity and large individual differences of such patients, data on the PK/PD of antibiotics during ECMO therapy are limited.[97–99] Some authors believe that PK changes in most antibiotics in patients with critical sepsis receiving ECMO are primarily caused by the pathophysiological state of the disease.[100–104] However, some studies found that ECMO treatment was associated with significantly lower serum concentrations of specific antibiotics.[105–107]

To select optimal doses and infusion methods for patients, clinicians must consider patient characteristics (including age, liver and kidney function, and fluid balance condition), pathogen drug resistance (minimal inhibitory concentration), antimicrobial drug characteristics (including molecular size, degree of ionization, physical and chemical properties, and protein binding rate), and the presence of ECMO or other *in vitro* support techniques.[99,100] Inappropriate anti-infective treatment can lead to the generation of resistant bacteria and poor clinical outcomes. Thus far, therapeutic drug monitoring has been suggested, and the principle of individualization should be followed.

Appropriate Timing for ECMO Weaning

The duration of ECMO in patients with sepsis varies due to patient heterogeneity, ECMO mode, and ECMO center experience (Table 1). Notably, due to the potentially fatal complications of ECMO, frequent assessments are required to make the best decision for ECMO weaning. Weaning can be decided based on the state of recovery of respiratory and cardiac function. However, no adequate criteria for ECMO weaning in patients with sepsis are available. The guidelines of the extracorporeal life support organization can be followed for weaning and decannulation of patients with respiratory and cardiac failure.[12,13]

In most cases, respiratory failure persists after heart recovery, necessitating a switch from V-VA or VA to VV mode. Five patients in one study with 24 cases had their VA ECMO converted to VV ECMO, after a median of 5 days due to persistent severe respiratory failure.[47] Bréchot et al.[43] found that 30 patients with persistent respiratory failure received immediate VV ECMO, for an average of 13.4 days after weaning from VA ECMO, with no recurrence of myocardial dysfunction. Vogel et al.[31] demonstrated that V-AV ECMO was used on 12 adult patients with simultaneous cardiopulmonary failure, and 9 of them survived. Cardiac support was required for a median of 4 days, whereas respiratory support was required for a median of 9 days. Notably, re-cannulation during ECMO support should be approached with caution, because the ECMO run undergoes anticoagulation, which increases the risk of bleeding. In addition to vascular complications, re-cannulation may lead to another infection or thrombosis.[80]

Conclusions

For patients with sepsis and septic shock, early effective antimicrobial therapy, infectious source control, fluid resuscitation, and vasoactive drug use are crucial. In carefully selected adult patients with sepsis-induced refractory respiratory and/or cardiac failure, ECMO may be a viable salvage therapy. Since current studies are retrospective and observational, the role of ECMO in adult patients with sepsis has not yet been fully established. Numerous issues, such as indications, appropriate timing for ECMO initiation and weaning, and optimal modes, need to be addressed. Future prospective studies with careful designs are required to investigate the feasibility, outcome benefit, and, importantly, cost-benefit of ECMO in adult patients with sepsis. Additionally, the use of novel mechanical assistive devices in patients with sepsis and refractory respiratory and/or cardiac failure warrants further investigation.

Author Contributions

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Ethics Statement

Not applicable.

Conflict of Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

The data sets generated during and/or analyzed during the current study are available from the corresponding author upon reasonable request.

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