Review Article

Extracorporeal membrane oxygenation as rescue therapy for severe hypoxemic respiratory failure

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Abstract: Extracorporeal membrane oxygenation (ECMO) has been used for more than 50 years as salvage therapy for patients with severe cardiopulmonary failure refractory to conventional treatment. ECMO was first used in the 1960s to treat hypoxemic respiratory failure in newborns. On the basis of its success in that population, ECMO began to be used in the early 1970s to treat adult hypoxemic respiratory failure. However, outcomes for adults were, somewhat perplexingly, quite poor. By the 1980s, use of ECMO for severe hypoxemia was rare outside of the pediatric population. ECMO technology, however, continued to evolve and improve. Multiple case reports and small series describing ECMO use as rescue for adults with severe hypoxemia from various lung pathologies have appeared in the literature over the past three decades. Adult respiratory distress syndrome (ARDS) is often the final common pathway of various pathologies affecting adults and causing hypoxemic respiratory failure. It is prevalent in intensive care units throughout the world and has, since it was first described in 1967, carried a high mortality. No specific therapy for ARDS has been found, and current care is supportive, primarily by mechanical ventilation. Results from recent randomized controlled trials, however, suggest that ECMO may have a place in the treatment of these patients. This article reviews these studies and recommends adding severe ARDS to the list of established indications for ECMO in patients with hypoxemic respiratory failure.

Keywords: Extracorporeal membrane oxygenation (ECMO); mechanical ventilation; ventilator-induced lung injury; acute respiratory distress syndrome (ARDS)

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History of extracorporeal membrane oxygenation (ECMO) for hypoxemic respiratory failure

Neonates

ECMO has been used for more than 50 years as salvage therapy for patients with severe cardiopulmonary failure that is refractory to conventional treatment. In the late 1930s, John Gibbon (1), after witnessing a young patient's death from a pulmonary embolism, began experimenting with extracorporeal blood-flow circuits that might temporarily support cardiorespiratory function. He hypothesized that an effective circuit might allow surgical thrombectomy of massive life-threatening emboli and even potentially allow surgery on the heart. After two decades of painstaking experimentation, Gibbon performed the first successful operation using such an extracorporeal

Table 1 Comparison of randomized controlled trials of ECMO in respiratory failure

First author	Publication year	Number of participants (intervention *vs.* control)	Study design	Intervention	Control	Survival	Comments
Zapol (13)	1979	90 (42 *vs.* 48)	Prospective, non-blinded RCT	MV + partial VA-ECMO	MV alone	9.5% ECMO, 8.3% control at 68 days; no statistically significant difference	Outdated devices; prolonged MV before ECMO
Morris (14)	1994	40 (21 *vs.* 19)	Prospective, non-blinded RCT	LFPPV + $ECCO_2R$	Conventional positive-pressure ventilation	33% $ECCO_2R$, 42% control at 30 days; P=0.8	–
Peek (15)	2009	180 (90 *vs.* 90)	Prospective, multicenter, non-blinded RCT	MV + either VA- or VV-ECMO; treatment at ECMO center	Conventional MV; treatment at primary hospital	63% ECMO; 47% control at 6 months; P=0.03	68/90 (76%) received ECMO; 14/17 (82%) in the ECMO arm did not receive ECMO
Combes (16)	2018	249 (124 *vs.* 125)	Prospective, multicenter RCT	ECMO + ultraprotective lung ventilation	Conventional MV with lung-protective ventilation	65% ECMO, 54% control at 60 days; P=0.09	35/125 control patients (28%) crossed over to ECMO; trial was stopped early, at 249/331 (75% of recruitment target)

ECMO, extracorporeal membrane oxygenation; RCT, randomized controlled trial; MV, mechanical ventilation; VA, venoarterial; LFPPV, low-frequency positive-pressure ventilation; $ECCO_2R$, extracorporeal CO_2 removal; VV, venovenous.

circuit, to close a large atrial septal defect in an 18-year-old woman (2). However, his device, and similar ones of that era, required direct contact between blood and gas, which damaged blood constituents and thus could be used for only a few hours at a time. An interesting observation published in 1944 helped to solve that problem and led to the next generation of extracorporeal oxygenators: Kolff and colleagues (3) observed that blood was oxygenated as it crossed the cellophane chambers in their first artificial kidney machine. By 1956, Clowes *et al.* (4) had developed a unique oxygenator with a membrane that separated the gaseous and liquid phases, allowing lengthier extracorporeal circulation of blood. This device was initially used as a "cardiopulmonary bypass" in the burgeoning field of open heart surgery (5).

By the 1960s, ECMO technology had been adapted for extracorporeal perfusion to support patients with cardiac and respiratory failure. In 1965, Rashkind and colleagues (6) made the first attempt to use extracorporeal circulation in a newborn with respiratory failure. Ten years later, Bartlett *et al.* (7) reported the first successful use of ECMO in a neonate with severe meconium aspiration syndrome. As a result of these efforts, the use of ECMO in newborns with refractory respiratory failure increased substantially, supported by results from randomized controlled trials confirming improved survival with ECMO in these infants (8-10). Since 1989, when the Extracorporeal Life Support Organization (ELSO) Registry was established and began collecting data on extracorporeal life support use and survival, more than 31,500 neonates have been treated with ECMO for respiratory failure; of these, 87% survived their ECMO course and 73% were subsequently discharged or transferred (11).

Adults

In 1972, Hill *et al.* (12) reported the first successful use of long-term ECMO in an adult with the newly described acute respiratory distress syndrome (ARDS). Two years later, the National Institutes of Health launched the first multicenter randomized clinical trial of ECMO versus conventional therapy in adults with ARDS (*Table 1*) (13). Of 90 trial participants, 42 received partial-flow venoarterial (VA)-ECMO. Two-week mortality was comparable in the treatment and control groups (90%); no survival advantage was associated with ECMO. In 1994,

INDICATIONS	ABSOLUTE CONTRAINDICATIONS	RELATIVE CONTRAINDICATIONS
Murray score (PaO_2/FiO_2 ratio, PEEP, compliance, chest radiograph) ≥3 Refractory hypoxemia (PaO_2/FiO_2 ratio ≤100) despite lung-protective ventilation (tidal volume 4–6 mL/kg of predicted body weight, plateau pressure ≤30 cmH_2O, neuromuscular blockade, prone positioning considered, Inhaled pulmonary vasodilators Persistent respiratory acidosis (pH <7.20)	Uncontrolled metastatic cancer or terminal disease (life expectancy <6 months Acute intracerebral hemorrhage, infarction, or neurological dysfunction Contraindication to systemic anticoagulation	Immunocompromise Intubation >7 days (preferably <3 days), especially with high pressure/FiO_2 Severe multiorgan failure-increased lactate, increased INR, worsening LFT results, need for CRRT Age >65 years Limited vascular access RESP scores ≤–6 (*www. respscore. com*) or PRESERVE score >7

Figure 1 Indications and contraindications to the use of ECMO in respiratory failure. ECMO, extracorporeal membrane oxygenation; PEEP, positive end-expiratory pressure; FiO_2, fraction of inspired oxygen; ARDS, acute respiratory distress syndrome; INR, international normalized ratio (prothrombin time); LFT, liver function test; CRRT, continuous renal replacement therapy; RESP, Respiratory Extracorporeal Membrane Oxygenation Survival Prediction score; PRESERVE, PRedicting dEath for SEvere ARDS on VV-ECMO score.

Morris *et al.* (14) published a second randomized trial that evaluated mechanical ventilation by using an inverse ratio of inspiratory and expiratory times with low-flow venovenous (VV)-ECMO versus conventional therapy. Of the 40 participants, 21 received VV ECMO. Survival 30 days after randomization did not differ significantly between the control and VV-ECMO groups (42% *vs.* 33%, respectively).

Given the discouraging results of these two trials, ECMO was not adopted into algorithms of evidence-based treatment for ARDS for the next 15 years. The results of those early trials, however, may not be relevant to modern ARDS management, because both ECMO deployment and technology, as well as conventional treatments for adult ARDS, have evolved considerably over time. Current ECMO support for hypoxemic respiratory failure is provided by VV (vena cava to right atrium) circuits, which are much less traumatic and better tolerated than the original VA circuits that arose from cardiopulmonary bypass practice. Newer oxygenators provide much more efficient gas exchange, and today's circuits are much less likely to induce clotting, which has reduced the need for anticoagulation and blood products. These advances have enabled more effective, longer-term ECMO support with a lower incidence of complications, and by the late 1990s multiple centers had begun to report encouraging results from VV-ECMO use in respiratory failure caused by various reversible lung pathologies (17-19).

Today, ECMO is an accepted treatment for multiple causes of reversible respiratory failure, including primary graft dysfunction in lung transplant patients, and as a bridge to lung transplant for very select patients (20). Current indications, as well as absolute and relative contraindications for ECMO, are displayed in *Figure 1*.

ARDS and ECMO

ARDS is currently understood as the final common pathway of many, if not most, lung injuries and is often the condition associated with severe hypoxemic respiratory failure in adults. There is no specific cure for ARDS, despite more than a half century of investigation. ARDS treatment is supportive and is based primarily on positive-pressure mechanical ventilation (21). ARDS is prevalent in intensive care units throughout the world, carries a high cost burden, and is associated with substantial mortality (22-24). In the 1980s and 1990s, even as investigators were exploring the utility of ECMO for patients in severe hypoxemic respiratory failure, an understanding of the toxic effects of positive-pressure mechanical ventilation was evolving. Mechanical ventilation was found to potentially injure lungs, primarily by overdistension (volutrauma), high airway pressure (barotrauma), and even underdistension (atelectotrauma) (25). Such trauma was found to induce local and systemic inflammation and to worsen already-impaired alveolar gas exchange. The sum of adverse effects from ventilators was termed "ventilator-induced lung injury" (VILI) (26,27). Unquestionably,

the very foundation of supportive therapy for ARDS, the mechanical ventilator, was actually escalating lung injury and contributing to the high mortality from ARDS. Thus, in the 1990s there began an intense search for techniques and tools to mitigate the toxic effects of mechanical ventilation (28,29).

The landmark ARDSnet trial showed that a tidal volume of 6 mL/kg of predicted body weight and a plateau pressure of 30 cmH_2O lowered in-hospital mortality and the number of ventilation days for patients with ARDS, compared with the traditional tidal volume of 12 mL/kg and plateau pressure of 50 cmH_2O (30). However, further studies found morphological and physiological evidence of VILI despite such lung-protective tidal volumes (6 mL/kg) and plateau pressures (28–30 cmH_2O), suggesting that more-robust lung-protective settings were warranted (31-33). Additionally, in many cases of severe ARDS, recommended ventilator settings do not allow adequate oxygenation or ventilation, forcing providers to use maximal oxygen concentrations and larger tidal volumes with higher airway pressures to adequately oxygenate and ventilate patients. Recent advances in prone positioning (34), positive end-expiratory pressure management, and lung recruitment maneuvers (35) were intended to improve oxygenation and decrease atelectotrauma and appear to have enhanced overall ARDS survival outcomes (36); nonetheless, much more improvement will be needed to mitigate VILI.

Such considerations prompted renewed interest in including ECMO in the treatment algorithm for ARDS. By supporting oxygenation and CO_2 removal in severe ARDS with lung-protective mechanical ventilation, ECMO might achieve the ultimate protection from VILI.

ECMO makes a comeback in ARDS

Two different currents came together in the late 2000s to promote a global increase in the use of ECMO for respiratory failure: (I) the 2009 global swine-origin influenza A (H1N1) pandemic, during which many previously healthy young patients developed severe respiratory failure; and (II) the first major randomized controlled trial of VV-ECMO for respiratory failure [the CESAR (Conventional ventilation or ECMO for Severe Adult Respiratory failure) trial], in which ECMO was shown to have beneficial effects. This landmark trial set the foundation for the recently published EOLIA (Extracorporeal Membrane Oxygenation for Severe Acute Respiratory Distress Syndrome) trial.

ECMO for influenza management

ECMO use as a rescue treatment for severe ARDS and hypoxemic respiratory failure surged during the H1N1 pandemic. Reported results were highly encouraging. The Australia and New Zealand Extracorporeal Membrane Oxygenation Influenza Investigators reported a 75% survival rate among 68 patients who received ECMO for refractory H1N1-induced ARDS (37). Notably, these patients had severe ARDS at the time of ECMO cannulation: Median values were 56 mmHg for the ratio of partial pressure of arterial oxygen (PaO_2) to fraction of inspired oxygen (FiO_2), 18 cmH_2O for the positive end-expiratory pressure requirement, and 3.8 for the Murray score. In a propensity-matched study from the United Kingdom, hospital mortality in patients with H1N1 transferred to an ECMO center was half that of matched non-ECMO-referred patients (38).

CESAR trial

In the UK-based multicenter CESAR trial (15), patients with severe ARDS were randomized 1:1 to receive ECMO or standard treatment (*Table 1*). A total of 180 patients (90 per arm) were enrolled from 68 centers over 5 years (July 2001–August 2006). ECMO patients were transferred to a single center, whereas conventional-care patients remained at their primary hospitals. Inclusion criteria were a Murray score ≥3, uncompensated hypercapnia, and age 18–65 years. Exclusion criteria were peak airway pressure >30 cmH_2O or FiO_2 >0.8 for ≥7 days, signs of intracranial bleeding, or any contraindication to systemic anticoagulation. Pneumonia was the underlying cause of ARDS for approximately two thirds of participants. The mean baseline PaO_2/FiO_2 ratio was 75 mmHg in the control group and 76 mmHg in the ECMO group.

The primary endpoint was death or severe disability within 6 months of randomization. Survival was significantly better in the ECMO group than in the conventional-treatment group (63% *vs.* 47%, respectively); the relative risk was 0.69 [95% confidence interval (CI), 0.05–0.97; P=0.03], and the number needed to treat was 7 patients. The absolute risk reduction for the primary outcome was 16%, and the number needed to treat was 6 patients (*Figure 2*). However, 24% of the patients in the intervention arm (22/90) never received ECMO: 5 died before or during transfer, and of the 17 who received conventional ventilation alone, 82% (14/17) survived without requiring

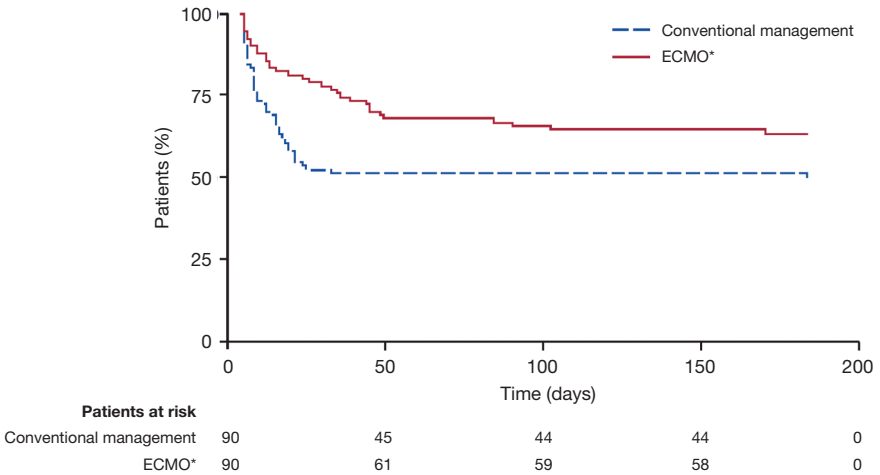

Figure 2 Kaplan-Meier survival estimates from the CESAR trial (Lancet 2009:374:1351-63 with permission). *, patients were randomly allocated to consideration for treatment by ECMO but did not necessarily receive this treatment. CESAR, Conventional ventilation or ECMO for Severe Adult Respiratory failure; ECMO, extracorporeal membrane oxygenation.

ECMO. The trial design did not mandate a specific lung-protective ventilation strategy for the control group; as a result, only 70% of the control patients were managed with a lung-protective strategy, compared with 93% in the ECMO group. Prone positioning was employed comparably in both groups (42% in the conventional medical management group *vs.* 36% in the ECMO group; P=0.58).

Despite its limitations, the CESAR trial showed the importance of transferring patients with potentially reversible respiratory failure to centers that specialize in ARDS management. The trial also supported lung-protective ventilation and VV-ECMO as effective treatments for severe ARDS, leading to expanded use of ECMO in clinical practice and further ECMO research. Nevertheless, because ECMO skeptics could question whether patients in the ECMO arm benefitted more from ECMO or from superior medical management, additional investigation to attempt to answer that question was warranted, and hence the EOLIA trial was undertaken.

EOLIA trial

The EOLIA trial was a multicenter, international, prospective, randomized trial for adults with severe ARDS that compared early VV-ECMO with standard lung-protective ventilation (16) (*Table 1*). The trial was designed to remedy the methodological limitations of the CESAR trial with strict mechanical ventilation control, ECMO initiation before transportation, and better adherence to the mechanical ventilation protocol in the control group. Inclusion criteria were severe hypoxemia with a PaO_2/FiO_2 ratio of <50 mmHg for >3 hours or <80 mmHg for >6 hours, or pH <7.25 and a partial pressure of arterial CO_2 of ≥60 mmHg for >6 hours. Crossover to ECMO was allowed for control-group patients with refractory hypoxemia (defined as oxygen saturation of <80% for at least 6 hours) and no irreversible multiorgan failure. The primary endpoint was 60-day mortality.

At randomization, this high-risk cohort had a mean PaO_2/FiO_2 ratio of 73 mmHg and a mean sequential organ failure assessment score of 10.7; 59% had previously used prone positioning, 94% had had neuromuscular blockade, and 53% had used inhaled nitric oxide or prostacyclin. An 11% absolute reduction in 60-day mortality was found for the ECMO group (35% *vs.* 46%, P=0.07), with a relative risk reduction of 0.76 (95% CI, 0.55–1.04; P=0.09). (That this difference was not statistically significant may be due to the study's being underpowered, discussed below.)

In contrast, the 60-day mortality rate for the 28% (35/125) of control patients who crossed over to receive rescue ECMO was 57%. The original ECMO group began ECMO approximately 34 hours after intubation and 3 hours after randomization, whereas the rescue ECMO group crossed over later (6.5±9.7 days after randomization, approximately 5 days after the original group commenced ECMO). These results suggest an advantage for earlier versus later ECMO. Secondary analysis revealed a relative

risk for treatment failure (defined as death by day 60 for the ECMO group and as either crossover to ECMO or death for the control group) of 0.62 (95% CI, 0.47–0.82; P<0.001) and a treatment-failure rate of 35% in the ECMO group versus 58% in the control arm. ECMO support lasted for 15±13 days. Delayed ECMO initiation and the high crossover rate may have confounded the 60-day mortality results.

ECMO has traditionally been associated with a high incidence of adverse events. However, in the EOLIA trial, the incidence of stroke was actually lower in the ECMO group (2% *vs.* 6%). Although the ECMO group had higher rates of massive transfusion (2% *vs.* 1%) and severe thrombocytopenia (27% *vs.* 16%), these rates were not prohibitively excessive, given the severity of the underlying respiratory illness. Notably, the targeted anticoagulation level was an activated partial thromboplastin time of 40–55 seconds, lower than the 60–80 seconds often used in other centers. Moreover, in an intention-to-treat analysis of secondary outcomes, the ECMO group had 20 fewer days of mechanical ventilation, 9 fewer days of vasopressor requirement, and 18 fewer days of renal replacement therapy. These data suggest that ECMO somehow decreases circulatory and renal dysfunction and may even protect against multiple organ dysfunction syndrome. In addition, during ECMO there was a 43% reduction in tidal volume and a 23% reduction in respiratory rate, while the positive end-expiratory pressure remained unchanged. This indicated a 66% reduction in mechanical power to the lungs (28 to 10 J/min), which may have promoted earlier lung recovery (39).

An often-cited, likely shortcoming of the EOLIA trial was that its power calculation was based on an expected 20% survival advantage for ECMO versus conventional medical management. This is probably an unrealistic expectation for any supportive intervention in ARDS. In the trial's design, failure to achieve such a reduction was considered evidence of futility; thus, when a 20% reduction in mortality was not projected as an outcome after 75% (249/331) of the planned cohort was enrolled, trial recruitment was stopped early, per protocol. The underpowering of the study has been cited as the reason that the mortality difference between the ECMO and control groups did not achieve statistical significance (P=0.07) (40). Indeed, 624 patients would be required for adequate power to detect an 11% mortality reduction in the ECMO patients from the 46% mortality in the non-ECMO patients. Given EOLIA's enrollment rate, it would have taken 9 years to complete the trial (39).

Other inherent difficulties make another EOLIA-style trial unfeasible. First, it would have been unethical to withhold crossover ECMO from patients in the non-ECMO control arm. Nonetheless, there may be value in seeking to characterize predictors of non-ECMO recovery in severe ARDS, so as to identify those patients who will not require ECMO and those patients who are at risk for conventional (non-ECMO) treatment failure and should begin ECMO earlier rather than later. Future studies could investigate whether, in patients with less-severe ARDS (PaO_2/FiO_2 ratio of 75–125 mmHg), earlier ECMO would improve survival and reduce dependence on ventilatory support, vasoactive medication, and renal replacement. Moreover, if lower anticoagulation levels were feasible, then some of the intrinsic risks of ECMO could be reduced, tilting the risk-to-benefit ratio in favor of earlier ECMO. Second, recruitment for the EOLIA trial was difficult, given that only 249 (24.5%) of 1015 eligible patients were enrolled. Indeed, 23% of the patients screened for EOLIA were eliminated because they had already begun ECMO, which may reflect widespread clinician acceptance of the procedure. That ECMO has a role in treating respiratory failure and severe ARDS is now well accepted; the ongoing debate centers on when ECMO should be initiated.

Mortality risk models

The use of VV-ECMO is increasing as it evolves as a therapeutic option for patients with severe ARDS. In the January 2019 ELSO registry report, 59% of adults on VV-ECMO survived to discharge (11). However, identifying the best candidates for ECMO remains challenging for clinicians. When several clinicians discuss the same patient, using a mortality risk score provides an objective assessment of the patient's survival prospects. Moreover, identifying patients for whom treatment is likely to be futile reduces unnecessary resource utilization and helps to provide family members with a more realistic prognosis.

Several predictive mortality risk models are available to help clinicians identify those patients most likely to survive. These include the ECMOnet score developed during the H1N1 epidemic (41), the PRESERVE (PRedicting dEath for SEvere ARDS on VV-ECMO) mortality risk score (42), and the RESP (Respiratory Extracorporeal Membrane Oxygenation Survival Prediction) score developed from ELSO registry data (43) (*Table 2*). In our experience, the RESP score, which has a convenient online calculator and appears to be the most thoroughly validated of these

Table 2 Comparison of survival scores from existing respiratory-failure risk models for ECMO

Risk model	First author	Publication year	Criteria	Score	Survival	Comments
ECMOnet	Pappalardo (41)	2013	Bilirubin level	0.0–2.5	Score of 4.5 is the most appropriate cutoff for mortality risk prediction	Survival to hospital discharge was strongly correlated with extrapulmonary organ function before ECMO initiation
			Systemic MAP	0.0–1.0		
			Hematocrit	0.5–2.0		
			Pre-ECMO length of stay	0.5–2.0		
			Creatinine level	0.0–3.5		
PRESERVE	Schmidt (42)	2013	Age <45, 45–55, >55 years	0, 2, 3	Total score, survived 6 months: 0–2, 97%; 3–4, 79%; 5–6, 54%; ≥7, 16%	Cumulative probabilities of survival 6 months after ECMO initiation
			BMI >30 kg/m^2	2		
			Immunocompromise	2		
			SOFA >12	2		
			MV >6 days	1		
			No prone positioning before ECMO	1		
			PEEP >10 cmH_2O	2		
			Plateau pressure >30 cmH_2O	2		
RESP	Schmidt (43)	2014	Age 18–49, 50–59, >60 years	0, –2, –3	Score (risk class), survived to hospital discharge: >6 (I), 92%; 3 to 5 (II), 76%; –1 to 2 (III), 57%; –5 to –2 (IV), 33%; ≤–6 (V), 18%	External validation, performed on 140 patients, exhibited excellent discrimination (c=0.92; 95% confidence interval, 0.89–0.97)
			Immunocompromise	–2		
			MV before ECMO:			
			<48 hours	3		
			48 hours to 7 days	1		
			>7 days	0		
			Diagnosis:			
			Viral, bacterial, asthma	3, 3, 11		
			CNS dysfunction	–7		
			Acute non-pulmonary infection	–3		
			Before ECMO:			
			Cardiac arrest	–2		
			Nitric oxide	–2		

ECMO, extracorporeal membrane oxygenation; BMI, body mass index; SOFA, sequential organ failure assessment; MV, mechanical ventilation; PEEP, positive end-expiratory pressure; CNS, central nervous system.

models (44), provides clinical utility.

Complications of VV-ECMO

Neurological complications

Neurological complications of VV-ECMO include seizures, ischemic stroke, intracranial hemorrhage, and brain death; any of these could increase morbidity and mortality. Using ELSO registry data from 1992–2015, Lorusso *et al.* (45) reported a 7.1% overall incidence of neurological injury, including intracranial hemorrhage (42.5%), brain death (23.5%), ischemic stroke (19.9%), and seizures (14.1%). (The ELSO registry is voluntary, and as such is subject to the intrinsic limitations of self-reporting and consistency of definitions as interpreted by individual

centers.) Pre-ECMO cardiac arrest, continuous venovenous hemofiltration, and severe hyperbilirubinemia during ECMO were associated with higher risk for neurological complications. Mechanisms of brain injury include pre-ECMO hypoxic injury, embolism, reperfusion injury, and deranged coagulation. Unless the patient has undiagnosed intracardiac shunting, the risk of embolic stroke from the circuit is lessened when the ECMO cannula is placed in the venous system instead of the venoarterial system.

Nonetheless, the incidence of neurological injury has decreased over the past two decades, possibly as a result of better patient selection, improved technology, consistent monitoring, increased clinician experience, and the need for less anticoagulation. This is consistent with findings from the EOLIA trial that showed a lower incidence of stroke in the ECMO group (16).

Bleeding/thrombosis

Bleeding is one of the most common complications in patients on VV-ECMO, occurring in approximately 16% of cases analyzed in a systematic review of 18 studies and 646 patients (46). Bleeding risk is heightened by systemic anticoagulation and coagulopathy from interaction between blood and the ECMO circuit. The 2019 ELSO Registry International Report (47) noted cannula hemorrhage in 7.8% of adults who received ECMO from 2014 to January 2019, surgical hemorrhage in 6.8%, pulmonary hemorrhage in 3.9%, and cerebral hemorrhage in 2.5%. Transfusion necessitated by bleeding also is associated with greater mortality risk. In addition, the systematic review cited above (46) found that thrombosis occurred in 53% of patients, although not all study results were clinically significant. This demonstrates the need to balance the risks of bleeding and thrombosis for each patient.

Conclusions

Over the course of several decades, survival in patients placed on ECMO for hypoxemic respiratory failure has grown from 10% in the 1970s to approximately 60% today. Extracorporeal technology has become much safer and more effective in the past five decades. Additionally, the use of ECMO for hypoxemic respiratory failure has dramatically increased in the past 10 years, owing to its success in the H1N1 pandemic and the CESAR trial. Although ECMO's exact role and optimal timing in ARDS, and even its effect on the pathophysiology of ARDS, have not been fully determined, the recently published EOLIA trial suggests that ECMO's role in the treatment algorithm for ARDS—and certainly severe ARDS—should be expanded, producing significantly better outcomes. The results of the studies cited here suggest that in cases of ARDS, often the final common pathway for lung injuries that cause severe hypoxemia, ECMO should be deployed early, before VILI occurs and possibly even before the onset of multiple organ dysfunction syndrome.

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Footnote

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