ECMO: beyond rescue therapy for ARDS?

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Abstract

Purpose of review

This article summarizes the results of past and more recent series on venovenous Extracorporeal Membrane Oxygenation (VV-ECMO) and discusses its potential indications beyond the rescue of patients with lung failure refractory to conventional mechanical ventilation.

Recent findings

Successful VV-ECMO treatment in patients with extremely severe H1N1-associated ARDS and positive results of the CESAR trial have led to an exponential use of the technology in recent years. Beyond its currently accepted indication as a salvage therapy in ARDS patients with refractory hypoxemia or unable to tolerate volume-limited strategies, VV-ECMO may improve the outcomes of less severe ARDS patients by facilitating lung-protective ventilation.

Summary

Since initiation of VV-ECMO allows significant decrease in tidal volume, plateau and driving pressures, which has been associated with improved survival in ARDS patients, new trials should evaluate the impact of its early initiation in patients with severe but not refractory ARDS.

Key words: acute respiratory distress syndrome; mechanical ventilation; extracorporeal membrane oxygenation; review article.

Key points

- Success of VV-ECMO as a rescue therapy for the most severe ARDS cases associated with the Influenza A(H1N1) pandemic and positive results of the CESAR trial have led to an exponential use of the technology in recent years.
- Beyond its currently accepted indication as a salvage therapy in refractory ARDS, ECMO may improve the outcomes of less severe ARDS patients by maximizing lung-protective ventilation, with significant decreases in tidal volume, plateau and driving pressures.
- New trials should test the early initiation of VV-ECMO for less severe ARDS patients against standard-of-care mechanical ventilation strategies.

Introduction

Success of venovenous Extracorporeal Membrane Oxygenation (VV-ECMO) as a rescue therapy for the most severe acute respiratory distress syndrome (ARDS) cases associated with the Influenza A(H1N1) pandemic (1-4) and positive results of the CESAR trial (5) have led to an exponential use of the technology in recent years. It is now considered as a reasonable rescue therapy for ARDS patients with refractory hypoxemia or unable to tolerate volume-limited strategies. Alternatively, VV-ECMO may be applied in less severe patients in whom it might allow "lung rest" by lowering airway pressures and tidal volume (VT) rather than improving oxygenation per se.

This article will summarize the current knowledge of the physiology of extracorporeal gas exchange and the results of past and more recent VV-ECMO series and will discuss its potential indications beyond the rescue of patients with lung failure refractory to conventional mechanical ventilation.

Physiological basis of gas exchange under VV-ECMO

CO_2 removal by extracorporeal membrane oxygenators depends on the gas flow through the oxygenator (6). Theoretically, as little as 0.5 to 1.5 L/min of blood flow through modern membrane lungs may allow clearance of 100% of the metabolic CO_2 production (7) and may induce complete apnea. In such conditions, providing 100% oxygen flow into the native lung may allow adequate blood oxygenation (8), while putting the lungs to complete rest and therefore minimizing ventilator-induced lung injury (VILI). However, this dramatic decrease in ventilation might induce lung collapse and it was suggested in animals that 20 cmH_2O positive end-expiratory pressure (PEEP) should be applied to maintain lung volume in this setting (8).

Blood oxygenation through hollow microfibers of membrane oxygenators depends on blood-oxygen saturation in the ECMO drainage cannula, hemoglobin concentration, blood flow in

the ECMO circuit and intrinsic oxygenator properties (9). O_2 transfer through the latest generation oxygenators is theoretically >400 mL of O_2/min when blood flow through the ECMO circuit is >6 L/min, while oxygen saturation in the ECMO drainage canula is 70% and hemoglobin concentration is 15 g/dL (10). However, when highly oxygenated blood reaches the pulmonary artery after the initiation of ECMO, loss of hypoxic vasoconstriction will markedly increase the shunt fraction of the natural lung and will further decrease its contribution to blood oxygenation (7,11). Therefore, patients rescued by VV-ECMO from refractory hypoxemia may become completely dependent on membrane-oxygenator oxygen transfer. In this situation it has been shown that achieving venovenous-ECMO flow >60% of systemic blood flow yielded arterial blood saturation >90% in H1N1-induced ARDS patients with no residual native lung gas exchange (6).

Results of landmark ECMO studies in ARDS patients

Forty years ago, Hill et all reported the first successful use of ECMO for refractory respiratory insufficiency (12). In the following years, a multicenter, randomized trial to evaluate ECMO for ARDS was conducted in the United States on 90 patients with severe ARDS refractory to conventional ventilation (13). However, mortality was >90% in that trial with no improvement with ECMO. Similarly, a randomized controlled trial using a venovenous low-flow CO_2 eliminating device was stopped for futility after only 40 patients had been enrolled in the early 90's (14). The first positive VV-ECMO trial (CESAR) was conducted in the UK from 2001 to 2006 and evaluated a strategy of transfer to a single center which had ECMO capability while the patients randomized to the control group were treated conventionally at designated centers (5). The primary endpoint of 6-month mortality or severe disability was significantly lower for the 90 patients randomized to the ECMO group (37% vs. 53%, p = 0.03). However, 22 patients randomized to the ECMO group did not receive ECMO (e.g.,

died before or during transport, improved with conventional management at the referral center). Moreover, no standardized protocol for lung-protective MV existed in the control group and the time spent with lung-protective MV was significantly higher in the ECMO group.

More recently, VV-ECMO was also successfully used in patients with extremely severe H1N1-associated ARDS. The Australia and New Zealand collaborative group (ANZICS) reported that 75% of 68 ECMO patients survived despite refractory hypoxemia at the time of ECMO initiation (median PaO2/FiO2 ratio 56 mmHg, median PEEP 18 cmH2O, median lung injury score of 3.8) (4). H1N1 patients treated in French ICUs of the REVA network (3) and in the Italian ECMOnetwork (2) had also good outcomes considering disease severity at ECMO initiation. Furthermore, a propensity-matched analysis of the UK collaborative cohort (1) demonstrated lower mortality for patients referred for consideration of ECMO compared to other ARDS patients.

Rationale for applying VV-ECMO to less severe ARDS patients

Lung-protective mechanical-ventilation strategies that use lower end-inspiratory (plateau) airway pressures, lower tidal volumes, and higher PEEPs have been associated with survival benefits in randomized clinical trials involving ARDS patients (15). The so-called ARDSnet protective ventilatory strategy limiting VT to 6 ml/kg and plateau pressure to 30 cm H_2O has been the standard of care to protect the lungs of patients with acute respiratory distress syndrome from ventilator-induced lung injury (VILI) over the last decade. However, it has been demonstrated that up to one-third of the patients under this strategy experienced substantial tidal hyperinflation and increased concentration of inflammatory mediators (16). Pertinently, Hager et all (17) demonstrated that lower Pplat were associated with less mortality and that no safe low Pplat threshold could be identified in patients with ALI/ARDS.

Furthermore, in a prospective series of 485 consecutive mechanically ventilated patients with acute lung injury, Needham et al (18) showed that compared with a mean VT <6.5 mL/kg predicted body weight, the adjusted hazard ratios for two-year mortality for a mean VT of 6.5 to 8.5 mL/kg predicted body weight was 1.59 (1.19 to 2.14, P=0.001). Beyond VT, PPlat and PEEP, Amato (19) recently showed that normalizing VT to C_{RS} and using this ratio as an index indicating the "functional" size of the lung might provide a better predictor of outcomes in patients with ARDS than VT alone. This ratio, termed the driving pressure ($\Delta P=VT/C_{RS}$), can be routinely calculated for patients who are not making inspiratory efforts as the plateau pressure minus PEEP. Analyses indicated that reductions in VT or increases in PEEP driven by random treatment-group assignment were beneficial only if associated with decreases in ΔP. No other ventilation variable had such a mediating effect on mortality. This study suggested that mortality increased significantly when ΔP was >15 cmH_2O, independently of other MV parameters.

Pertinently, data collected in a multicenter study of 140 severe ARDS patients showed that VT was reduced from 5.9 to 2.8 ml/kg, PPlat from 32 to 24 cm H_2O and ΔP from 22 to 14 cm H_2O in the hours following VV-ECMO initiation (20). Such "ultraprotective" MV settings also reported in other series of severe ARDS patients on VV-ECMO (21-24) might allow lung rest with less VILI, facilitated lung healing and ultimately lower ARDS-associated mortality.

Patients selection for successful ECMO results

According to the Extracorporeal Life Support Organization (ELSO), "ECMO initiation should be considered in hypoxic respiratory failure when the risk of mortality is 50% or greater, identified by PaO_2/FiO_2 <150 mmHg on FiO_2 > 90% and/or Murray score 2-3, and is indicated when this risk exceeds 80%, i.e. when PaO_2/FiO_2 is <80 mmHg on FiO_2 >90% and

Murray score is 3-4 or hypercapnia with a PaCO2 > 80 mmHg or inability to achieve safe inflation pressures (Pplat ≤ 30 cm H2O) "(25). Alternatively, guidelines from the New South Wales department of Health in Australia recommended immediate consultation for venovenous ECMO in case of refractory hypoxemia (PaO_2/FiO_2 <60 mmHg) or hypercarbia ($PaCO_2$ >100 mmHg, with PaO_2/FiO_2 <100 mmHg) (26). Since complications associated with ECMO support are still common and potentially life-threatening, more stringent selection of patients for ECMO should be applied. Most experts agree on absolute contraindications to ECMO such as moribund patients with multiple organ failure, those with active and rapidly fatal malignancy or other advanced comorbidities such as chronic cardiac or respiratory insufficiency with no indication for transplantation, cirrhosis with ascites, irreversible neurological pathology, or recent allogeneic stem cell transplantation (27). Independent risk factors of death in ECMO patients were also determined in recent retrospective series (20-23,28,29). Older age was almost consistently associated with poorer outcomes, with patients younger than 45 years of age (20) having higher survival rate than those aged over 60 years (30). Other factors associated with worse outcomes were a duration of mechanical ventilation ≥ 7 days and more organ failing prior to ECMO initiation, pre-ECMO comorbidities, such as an immunocompromised status, very low pre-ECMO pulmonary compliance (i.e, plateau pressure <30 cmH_2O and inability to increase PEEP above 10 cmH_2O). On the opposite, prone positioning and the use of neuromuscular blocking agents prior to ECMO were protective in two studies (20,29). Interestingly, lower PaO_2/FiO_2 indicating the severity of hypoxemia which is a frequent indication for ECMO in ARDS patients was not retained as an independent mortality predictor in these series.

Based on the results of these analyses, predictive survival models have been constructed to help physicians select appropriate candidates for ECMO (20,22,23,28,29). The Respiratory ECMO Survival Prediction (RESP) score was created using bootstrapping

methodology with internal and external validation on 2,355 patients extracted from the Extracorporeal Life Support Organization (ELSO) international registry, of whom 1,338 (57%) were discharged alive from hospital (29). Pre-ECMO variables composing the score included age, immunocompromised status, duration of mechanical ventilation before ECMO, ARDS etiology, central nervous system dysfunction, acute associated nonpulmonary infection, neuromuscular blockade agents or nitric oxide use, bicarbonate infusion, cardiac arrest, PaCO2, and peak inspiratory pressure. External validation of the score, performed on the 140 patients of the PRESERVE cohort, exhibited excellent discrimination. An online calculator available at www.respscore.com allows rapid estimation of patients survival at the time of ECMO decision. Lastly, it should be mentioned that since these scoring systems were constructed on populations of patients who all received ECMO, they may less accurately predict mortality on a broader population of ARDS patients only considered to receive VV-ECMO.

Patients management and center organization for successful ECMO programs

Neuromuscular blocking agents may be used in the early phase after ECMO implantation (31) and sedation and analgesia titrated to the lowest dose. The impact of different ventilator settings in ARDS patients undergoing ECMO remains uncertain and optimal MV settings has yet to be determined in this situation. Data from 123 patients admitted for (H1N1)-associated ARDS collected from 2009 to 2011 through the national REVA registry showed that higher Pplat the first day of ECMO (mean Pplat 25 vs. 29 cm H_2O, $p < 0.01$, in survivors and non-survivors, respectively) was associated with higher mortality (3). Alternatively, in a retrospective observational study of 168 patients treated with ECMO for severe ARDS in 3 international high volume ECMO centers (32), higher PEEP levels during the first 3 days of ECMO support were associated with lower mortality (OR, 0.75, 95% confidence interval

[0.64-0.88]; p=0.0006). Potential benefits of higher PEEPs in VV-ECMO patients include reduced atelectasis (33,34) and improved ventilation/perfusion matching, especially when VT is < 4mL/kg (34). The most recent data derive from individual patient data metaanalysis of 9 observational studies including 545 patients on ECMO (21). This study confirmed that initiation of ECMO was accompanied by significant decreases in VT, PEEP, plateau and driving pressures, and respiratory rate and minute ventilation, and resulted in higher PaO_2/FiO_2, higher arterial pH and lower $PaCO_2$ levels. Interestingly, results of mediation analyses suggested that the driving pressure was the only ventilatory parameter during ECMO that was independently associated with in-hospital mortality, consistent with data recently published in ARDS patients on conventional MV (19). This decrease in ΔP after ECMO initiation was largely obtained by VT and plateau pressure changes, as there were only minor changes in PEEP settings.

Systemic anticoagulation should be titrated to very low levels (40-55 s for aPTT and 0.1-0.2 IU/ml for heparinemia) since ECMO circuits and oxygenators are coated with heparin or with a biocompatible material (7,35-37). As transfusion of blood products might cause specific lung injuries (38), the hemoglobin threshold for red cell transfusion should be 7-8 g/dl (some centers consider increasing to 10 g/dl if persistent hypoxemia) and platelet transfusion should be discouraged except when severe thrombocytopenia is accompanied by bleeding (27,35).

In patients for whom prolonged respiratory support is anticipated, early tracheostomy to facilitate patient comfort and ease of care might be performed (39,40). Tracheostomy may also facilitate mobilization of critically ill patients on ECMO, a strategy that is now recognized as an important intervention to improve patient outcomes (41). ECMO has traditionally been viewed as a barrier to physical activity; however, more compact circuits, in conjunction with configurations that avoid femoral cannulation, have created the opportunity

for early mobilization and rehabilitation in ARDS patients receiving ECMO (42). An observational study established safety and feasibility of early rehabilitation in 100 ECMO patients during their ICU stay (43).

International guidelines and position of experts have recently been published on the organization of ECMO centers (25,27). For optimal management of ARDS patients on ECMO, a structured national or regional organization should be organized, with referral centers located in tertiary hospitals. These centers should possess all the resources needed for the care of ARDS patients and the safe provision of ECMO, such as critical care, cardiothoracic surgery. Data have indeed demonstrated a robust effect of center case volume on outcome, suggesting that fewer than 20 cases/year may not be safe and cost effective and result in a loss of expertise (44,45).

Each ECMO network should ideally create mobile ECMO teams to retrieve patients on ECMO to the tertiary ECMO referral center (27). This mobile team should be available 24 hours a day, 7 days a week, and employ experienced personnel trained in the transport of critically ill patients, insertion of ECMO cannulae, as well as circuit and patient management. Highly successful transportation of patients on cardiopulmonary support has been described for short and long distances by ambulance, helicopter, and airplane (46,47).

Conclusion

The use of ECMO for severe ARDS remains controversial, with conflicting data regarding its impact on survival compared with conventional ventilatory management. Beyond its currently accepted indication as a salvage therapy in refractory ARDS, ECMO may improve the outcomes of less severe ARDS patients by facilitating lung-protective ventilation. The ongoing trial international multicenter randomized Extracorporeal Membrane Oxygenation for Severe Acute Respiratory Distress Syndrome (EOLIA) trial, which will test the efficacy of

early VV-ECMO in patients with severe ARDS with tight control of mechanical ventilation in the control group may help to resolve such controversies (48).

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Conflicts of interest

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* In this international, case-mix-adjusted analysis, higher annual hospital ECMO volume was associated with lower mortality.