Review Article

Extracorporeal techniques in acute respiratory distress syndrome

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Abstract: Extracorporeal membrane oxygenation (ECMO) was first introduced for patients with acute respiratory distress syndrome (ARDS) in the 1970s. However, enthusiasm was tempered due to the high mortality seen at that time. The use of ECMO has grown considerably in recent years due to technological advances and the evidence suggesting potential benefit. While the efficacy of ECMO has yet to be rigorously demonstrated with high-quality evidence, it has the potential not only to have a substantial impact on outcomes, including mortality, but also to change the paradigm of ARDS management.

Keywords: Acute respiratory distress syndrome (ARDS); extracorporeal membrane oxygenation (ECMO); respiratory failure; extracorporeal life support; extracorporeal carbon dioxide removal ($ECCO_2R$)

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Introduction

Extracorporeal membrane oxygenation (ECMO) has been available to support severe respiratory failure since the 1970s. However, high complication rates, largely due to limitations in technology, lead to poor outcomes early on. In more recent years, advances in technology and management have led to apparently improved survival with reduced complication rates, resulting in increasing use of ECMO for severe acute respiratory distress syndrome (ARDS). While outcomes have improved over time, the benefit of ECMO as compared to conventional, standard of care management for ARDS has yet to be demonstrated in rigorously designed, randomized controlled trials; as such it remains most commonly employed as salvage therapy for the most severe cases of ARDS.

As the field continues to evolve, there is increasing potential for ECMO to enhance the way ARDS is managed, notably through facilitation of lung protective ventilation and minimization of ventilator-associated lung injury. Here we will review the evidence that supports the use of ECMO, the rationale for its use and mechanistic benefits, practical aspects of ECMO initiation and management, and ongoing investigations and future directions.

History of ECMO for ARDS

ECMO is a system that draws blood out of the body through a cannula via a pump, passes the blood through a membrane oxygenator where both oxygen delivery and carbon dioxide removal occur, and reinfuses the well-oxygenated blood back into the body through a cannula, thus providing extracorporeal gas exchange (1).

The first successful use of ECMO as salvage therapy for severe acute respiratory failure was reported in 1972 (2), however, a subsequent randomized controlled trial, published in 1979, failed to demonstrate a survival advantage over conventional mechanical ventilation with low survival rates in both groups (9.5% and 8.3%, respectively) (3). Thereafter, the use of extracorporeal carbon dioxide removal ($ECCO_2R$), which was first observed in the setting of early hemodialysis membranes (4), was recognized as a potential strategy in severe acute respiratory failure,

specifically as a means of facilitating carbon dioxide removal and minimization of invasive mechanical ventilation through low frequency positive-pressure ventilation (5-8). Observed survival rates with this strategy were much higher (48.8%) than previously reported in patients with similar clinical characteristics (9), but in a follow-up randomized controlled trial of $ECCO_2R$ combined with low frequency positive-pressure ventilation, there was no survival benefit over conventional mechanical ventilation (33% *vs.* 42%, respectively, P=0.8) (10). Thereafter, a number of observational studies suggested a survival rate ranging from 49–81% (11-19) for selected patients managed with ECMO for severe ARDS. However, conclusions from these early studies on the efficacy of ECMO for ARDS are limited by study methodology and the use of outdated extracorporeal technology as well as mechanical ventilation practices.

In the last 2 decades, there have been a number of changes in clinical practice that have led to improved outcomes in ARDS, most notably the use of a low-volume, low-pressure ventilation strategy, conservative fluid management, neuromuscular blockade, and prone positioning (20-25). Additionally, a number of advances have been made over time in extracorporeal technology, including the use of centrifugal pumps, polymethylpentene membranes, biocompatible circuit components, and improvements in cannula technology (26,27).

The use of ECMO in severe ARDS during the 2009 influenza A (H1N1) pandemic generated more widespread interest in its use, with high overall survival rates (28-30), including a reported survival of 75% in a cohort of patients in Australia and New Zealand (31,32). However, favorable outcomes were also observed for comparable cohorts of patients with severe ARDS due to influenza A (H1N1) at other centers without the use of ECMO (33), calling into question the benefit of ECMO over optimal conventional management. Two cohort studies that utilized matched-pairs analysis of patients with H1N1-asscoiated ARDS who were managed with or without ECMO demonstrated conflicting results; the first reported a mortality benefit (RR 0.45–0.51, P=0.001–0.006) (34), whereas the second did not (OR 1.48, P=0.32) (35).

The only multicenter randomized controlled trial utilizing relatively modern techniques in ECMO for ARDS is the Conventional Ventilation or ECMO for Severe Adult Respiratory Failure (CESAR) trial, in which 180 patients with severe acute respiratory failure were randomized to either receive conventional mechanical ventilation or be referred to a specialized center where they were considered for ECMO after an initial period of optimal conventional management. A significant reduction was seen in the composite outcome of death or severe disability at 6 months in patients who were referred to a specialty center for consideration of ECMO versus conventional management (37% *vs.* 53%; RR 0.69, 95% CI 0.05–0.97, P=0.03). Of note, only 76% of patients referred to a specialty center were ultimately managed with ECMO, and a large portion of patients in the conventional management arm (30%) never received lung protective ventilation at any time, making it difficult to draw conclusions about the benefit of ECMO itself on outcomes. Despite these and other limitations, referral of patients with severe forms of ARDS to a center that has the capability of performing ECMO, and adheres to standard of care mechanical ventilation, may be beneficial (36,37).

Indications and contraindications for ECMO in ARDS

ECMO may be considered as a salvage therapy for patients with ARDS in those who have severe gas exchange abnormalities in the setting of potentially reversible acute respiratory failure. Proposed thresholds for the initiation of ECMO include severe hypoxemia [e.g., partial pressure of oxygen in arterial blood (PaO_2) to the fraction of inspired oxygen (FiO_2) ratio less than 80], uncompensated hypercapnia with acidemia (e.g., pH less than 7.15) or excessively high end-inspiratory plateau pressures (e.g., greater than 35–45 cmH_2O) despite standard of care low-volume, low-pressure ventilation (1). When available, adjunctive therapies that have a proven or suspected benefit in severe ARDS (e.g., neuromuscular blockade and prone positioning) should be strongly considered prior to the initiation of ECMO.

Patients who have been exposed to high-pressure ventilation (end-inspiratory plateau pressure of greater than 30) or high FiO_2 for more than 7 days may be less likely to benefit from ECMO, although clearly this is only a relative contraindication and may simply reflect enrichment of the population for more severe cases. Other relative contraindications include limited vascular access options for cannulation and any condition that does not allow the use of systemic anticoagulation, which is strongly preferred to minimize thrombosis formation in the ECMO circuit (1). Additionally, there are conditions that should

exclude patients from receiving ECMO due to the limited overall benefit anticipated from its use. Such patients include those with advanced, untreatable underlying conditions (e.g., irreversible brain injury or metastatic cancer). An absolute contraindication is the use of ECMO in patients with end-stage lung disease and severe acute-on-chronic respiratory failure who are not candidates for lung transplantation when recovery to baseline is not deemed possible (1).

ECMO cannulation and configuration in ARDS

ECMO configurations include venovenous, where deoxygenated blood is drained from a central vein and oxygenated blood is reinfused into a central vein (*Figure 1*), and venoarterial, where blood is drained from a central vein and reinfused into a central artery. Venovenous ECMO provides respiratory support, whereas venoarterial ECMO provide both respiratory and hemodynamic support. The majority of ARDS cases involve severe respiratory failure alone, for which a venovenous configuration is most appropriate, and is the primary focus of this review. Some cases of ARDS may present with concomitant severe cardiogenic shock. In such circumstances, a hybrid approach, where blood is drained from a vein and reinfusion is split between a central artery and vein (*Figure 2*), may be necessary to provide both hemodynamic support and adequate upper-body oxygenation (1,38-40). Of note, when ARDS presents with an acute elevation in pulmonary vascular resistance (PVR) with right ventricular dysfunction from severe hypoxemic- or hypercapnic-induced pulmonary vasoconstriction, venovenous ECMO is often effective in improving PVR and unloading the right ventricle such that venoarterial ECMO can be avoided (41).

Venovenous ECMO can utilize either a dual-site or single-site cannulation approach. The dual-site approach most commonly drains blood from a femoral vein and reinfuses into an internal jugular or contralateral femoral vein. This approach may be complicated by recirculation of blood, which occurs when reinfused blood is drawn back into the circuit without passing through the systemic circulation, thereby reducing the effectiveness of gas exchange. A single bicaval dual-lumen cannula can also be used (*Figure 3*), which, when properly positioned, minimizes the likelihood of recirculation and does not require femoral cannulation, allowing for improved mobility of patients when appropriate. However, it does require either transesophageal echocardiography or fluoroscopic guidance to ensure proper positioning, notably directing the reinfusion jet across the tricuspid valve (1,26,42,43).

An alternative configuration for gas exchange support is a pumpless, arteriovenous circuit (arterial drainage and venous reinfusion via femoral artery and vein, respectively), which relies upon the patient's native cardiac output to generate extracorporeal blood flow through the membrane oxygenator. However, the lack of control over extracorporeal blood flow, which tends to be relatively low and thus less effective for oxygenation, and the need for arterial cannulation make this approach less desirable than a pump-based venovenous configuration in most circumstances (44-46).

Management of ECMO in ARDS

Control of oxygenation and carbon dioxide removal

Once a patient is cannulated with venovenous ECMO, a gas supply typically consisting of a mixture of oxygen and air is connected to the membrane oxygenator, with the fraction of delivered oxygen (FDO_2) set via a gas blender. This gas, referred to as sweep gas, passes along one side of a semipermeable membrane, while blood flows along the other side, with the membrane allowing for diffusion of oxygen and carbon dioxide down their respective gradients. The sweep gas flow rate is the main determinant of carbon dioxide removal at high blood flow rates, and can be titrated to $PaCO_2$ or pH (*Table 1*). The level of $PaCO_2$, blood flow rate and properties of the membrane lung also affect carbon dioxide removal.

The major determinants of blood oxygenation in patients receiving venovenous ECMO include the amount of blood flow through the circuit relative to cardiac output, FDO_2 through the circuit, the contribution of native lung gas exchange (which is largely impaired in severe ARDS), and the characteristics of the membrane lung. As such, establishing adequate blood flow based on a patient's size and predicted cardiac output is an important determinant in choosing the appropriate cannula sizes, with blood flow largely being limited by the size of the drainage cannula. An increase in cardiac output at a given extracorporeal flow rate will decrease systemic oxygenation because of a relative decrease in the contribution of the ECMO circuit to oxygenation. In a small study that evaluated various ECMO parameters with regard to blood oxygenation and decarboxylation in patients with ARDS, it was noted

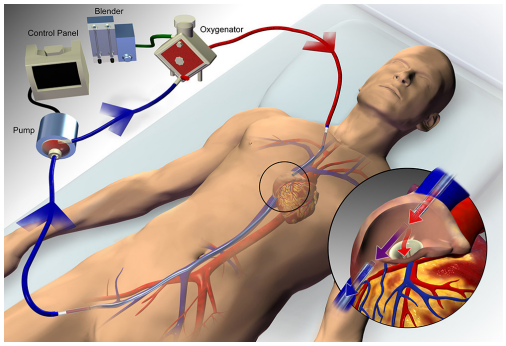

Figure 1 Two-site approach to venovenous ECMO cannulation. The venous drainage cannula typically enters a femoral vein and extends into the inferior vena cava. Blood from the cannula is drawn into a pump. This blood is then propelled forward through the oxygenator before beng reinfused into the body. The venous reinfusion cannula typically enters an internal jugular vein and extends into the right atrium, where reinfusion occurs. Reproduced with permission from collectedmed.com, previously published in ASAIO (Agerstrand CL, Bacchetta MD, Brodie D. ECMO for adult respiratory failure: current use and evolving applications. ASAIO J 2014;60:255-62. Figure 1).

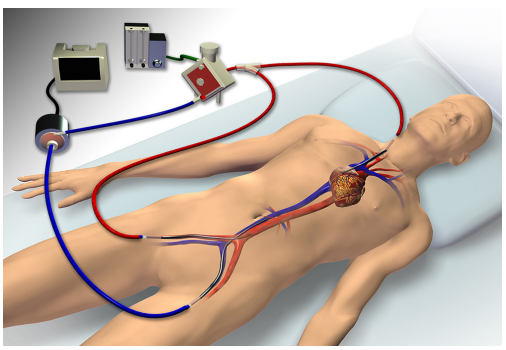

Figure 2 Venovenous-arterial ECMO cannulation. The venous drainage cannula enters a femoral vein and extends into the inferior vena cava. This blood is then drawn into a pump and propelled forward through the oxygenator before being reinfused into the body. The reinfusion of blood is split between a venous cannula, typically placed in an internal jugular vein, and an arterial cannula, typically placed in a femoral artery. Reproduced with permission from collectedmed.com, previously published in ASAIO (Biscotti M, Lee A, Basner RC, *et al.* Hybrid configurations via percutaneous access for extracorporeal membrane oxygenation: a single-center experience. ASAIO J 2014;60:635-42. Figure 3).

that when blood flow was greater than or equal to 60% of

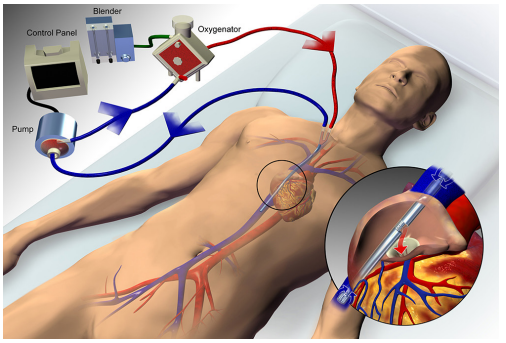

Figure 3 Single-site approach to venovenous ECMO cannulation. A dual-lumen cannula enters the internal jugular vein and terminates in the inferior vena cava. Blood enters the drainage lumen through ports in the inferior and superior vena cava and is drawn into the pump. This blood is then propelled forward through the oxygenator before being reinfused via the second lumen of the cannula, which has a port positioned in the right atrium and blood flow is directed across the tricuspid valve. Reproduced with permission from collectedmed.com, previously published in ASAIO (Agerstrand CL, Bacchetta MD, Brodie D. ECMO for adult respiratory failure: current use and evolving applications. ASAIO J 2014;60:255-62. Figure 2).

cardiac output, patients were able to maintain an arterial saturation of greater than 90% (47).

Anticoagulation

Systemic anticoagulation is required for all ECMO circuits to minimize the risk of thrombus formation, with unfractionated heparin being the most commonly used anticoagulant. Although there are no universally accepted anticoagulation goals for ECMO, an activated partial thromboplastin time of 40 to 60 seconds has been used by some centers as a target that provides adequate anticoagulation of the circuit while minimizing potential bleeding complications (1,48). Retrospective data suggests that a low level anticoagulation strategy, coupled with conservative transfusion thresholds and reinfusion of circuit blood at the time of decannulation, results in favorable outcomes while minimizing transfusion requirements (49).

Ventilator strategies

While a low-volume, low-pressure strategy is the hallmark of ventilator management in ARDS, (21,50-53) the ideal

Table 1 Determinants of oxygenation and carbon dioxide removal

Determinants of oxygenation
Amount of extracorporeal blood flow relative to total cardiac output
Fraction of oxygen delivered through oxygenator
Hemoglobin
Membrane properties
Recirculation
Native gas exchange
Determinants of carbon dioxide removal
Rate of gas flow (sweep gas) through oxygenator
Contribution of native lung function
Extracorporeal blood flow
Membrane properties
Native gas exchange

ventilator settings for patients managed with ECMO are unknown. Secondary analysis of the data from the ARDSNet ARMA trial of low tidal volume ventilation in ARDS suggests patients with even lower end-inspiratory plateau pressures than the targeted 30 cmH_2O on day one, had lower mortality rates as compared with those with higher values, regardless of tidal volume assignment, suggesting a lower target may be more protective (53,54). However, the ability to achieve very low plateau airway pressures—below those targeted with a standard of care low-volume, low-pressure ventilation strategy—in patients with ARDS and severely reduced lung compliance, is often limited by unacceptable levels of respiratory acidosis. The concurrent use of ECMO may provide sufficient additional gas exchange support to allow for further reductions in ventilator volumes and pressures while managing the hypercapnia and acidemia that accompanies the reduction in minute ventilation. Whether this strategy is superior to standard of care low-volume, low-pressure ventilation is unknown.

The CESAR trial managed patients with pressure-controlled ventilation with a target peak inspiratory pressure of 20–25 cmH_2O, a rate of 10 breaths per minute, PEEP of 10–15 cmH_2O and FiO_2 of 0.3 (36). This strategy has often been adopted in the practice of ECMO. However, the ventilator strategy itself was not tested. Multiple approaches may be acceptable, including the use of volume-cycled ventilation to target a particular plateau airway pressure, although the optimal plateau airway pressure has yet to be determined. Prospective ARDS studies suggest that there may not be a safe upper limit of tidal volume or plateau airway pressure (53). In addition, recent reports highlight the role of respiratory rate as a contributor to ventilator-associated lung injury (55,56) and that lower respiratory rates (e.g., lower than 10 breaths per minute) should be considered. Analysis of pooled data of patients managed with mechanical ventilation alone for ARDS and those managed with venovenous ECMO have also suggested that driving pressure (plateau airway pressure minus positive end-expiratory pressure) is independently associated with increased mortality; while this relationship has not been validated in a prospective or randomized fashion, perhaps targeting a lower driving pressure could also be beneficial (57,58).

In light of the significant mortality benefit seen with the use of prone positioning in patients with ARDS (25), prone positioning should be strongly considered prior to the initiation of ECMO, when possible (59). Prone positioning might also be considered in selected patients managed with ECMO. However, little is known about the effects of combining these strategies. One small case series reviewed the outcomes in patients with ARDS who were managed with the combination of ECMO and prone positioning. The authors noted improved oxygenation and general safety of the procedure with no complications attributable to prone positioning (60).

Extubation during extracorporeal support

Given that the fundamental goals for ventilator management in ARDS are geared towards minimizing ventilator-associated lung injury, removing the ventilator entirely may theoretically be the preferred strategy. Additionally, it could optimize other intensive care-based management strategies, including minimization of sedation, reductions in nosocomial infections (particularly ventilator-associated pneumonia) and maximization of mobilization and enteral nutrition. However, there is potential concern over exacerbating mechanical stress with spontaneous breathing in ARDS (61-65). Although $ECCO_2R$ has been shown to have the ability to control ventilatory drive in select patients with severe, chronic respiratory failure (e.g., COPD), data suggests that it may not be able to sufficiently control the spontaneous and potentially injurious respiratory efforts of patients with severe ARDS (66,67).

Mobilization during extracorporeal support

Physical and occupational therapy has been shown to not only be feasible, but also have a number of favorable outcomes in patients with acute respiratory failure, notably improving functionality, reducing delirium, and increasing ventilator-free days (68-70). The mobilization of patients with respiratory failure requiring ECMO has been increasing overall, but this data is largely limited to patients who are awaiting lung transplantation (71-74). While patients requiring ECMO for ARDS may often be too critically ill to participate in active rehabilitation, it may be possible in appropriate patients who are at centers that have a multidisciplinary approach to physical therapy (75-77). The benefit of mobilizing ARDS patients on ECMO has not been well defined and must be weighed against the potential risks of physical therapy in this population.

Complications

Potential risks or complications of ECMO include hemorrhage, thrombosis, hemolysis, and infection, among others, and must be weighed against the potential benefits when selecting appropriate patients for ECMO support (78-82). A lower anticoagulation goal has been adopted by many centers in an attempt to minimize the risks of hemorrhage while still maintaining circuit patency (1). Advances in extracorporeal technology and techniques and increasing experience have reduced the rates of these complications over time, however, the risks of ECMO remain considerable (78).

Economics of ECMO for ARDS

There are limited data evaluating the cost-benefit profile of ECMO in ARDS. The CESAR trial incorporated an economic evaluation within their study, which noted more than a two-fold increase in cost per patient who received ECMO as compared to standard management, with a gain of 0.03 quality-adjusted life-years (QALYs) at 6 months. However, this was limited to one health care system in the context of a randomized controlled trial (36,83). Further economic assessments will be important as the use of this technology continues to widen.

Ethical considerations

ECMO has the ability to support gas exchange for patients with severe respiratory failure. However, ethical dilemmas have arisen, most notably when patients are unable to be weaned from extracorporeal support and are deemed not to be candidates for lung transplantation. There are currently no available devices that would offer a "destination therapy" or more portable extracorporeal devices that would allow such a patient with persistent respiratory failure the option of residing outside the ICU. As such, families and patients may find themselves in a situation with no clear endpoint to their clinical course (84). Careful selection of patients who have a higher likelihood of a favorable outcome from ARDS may help avoid some of these dilemmas (85-87). Potential future technological advances in device therapy may one day help remedy such situations by providing a durable destination device.

Ongoing areas of investigation

$ECCO_2R$ for less severe ARDS

While the use of $ECCO_2R$ was first described in the 1970's as an alternative means of providing ventilation, pursuit of novel management strategies incorporating $ECCO_2R$ have become more popular in recent years in response to the increasingly recognized importance of lung-protective ventilatory strategies and advances in technology that have improved the risk-benefit profile of extracorporeal support. Venovenous ECMO has largely been reserved as salvage therapy for cases of the most severe forms of ARDS (1,88), the incidence of which is low compared to less severe forms of ARDS (89). As such, there is increasing interest in the possible utilization of $ECCO_2R$ in less severe cases of ARDS in an attempt to facilitate or extend low-volume, low-pressure ventilation, which is often otherwise limited by hypercapnia with acidemia. The removal of carbon dioxide via an extracorporeal circuit, notably with lower flow and smaller cannulae (which is more feasible in patients with less severe hypoxemia), could permit the optimization of lung protective strategies, including lower tidal volumes, plateau airway pressures, and respiratory rates, by maintaining pH within an acceptable range. This concept of $ECCO_2R$-assisted very-low tidal volume ventilation in patients with ARDS was studied in a prospective trial that used $ECCO_2R$ to reduce tidal volumes from 6 mL/kg of predicted body weight to approximately 4 mL/kg with a goal of reducing plateau airway pressure from 28–30 cmH_2O to 25–27 cmH_2O. In doing so, inflammatory markers (including interleukin 6, interleukin 8, interleukin 1b, and interleukin 1 receptor antagonist) were significantly

reduced from baseline, suggesting potential mitigation of ventilator-associated lung injury (90). A subsequent randomized controlled trial compared the use of $ECCO_2R$-assisted very-low tidal volume ventilation (tidal volume of 3 mL/kg predicted body weight) to a standard lung protective ventilation strategy in patients with moderate to severe ARDS. Although there was no difference in the primary outcome of ventilator free days at 28 and 60 days between the two groups (33 *vs.* 29, P=0.469), there was a suggestion of benefit among those with more severe hypoxemia (91). Based on the limited literature that exists, extending lung protective ventilation to very-low tidal volume ventilation is achievable with the assistance of $ECCO_2R$. The overall clinical benefits of such a strategy are still uncertain and need to be further elucidated in randomized-controlled trials.

Conclusions

Despite a lack of rigorous, high-quality evidence, modern-day ECMO is increasingly becoming accepted as a reasonable salvage therapy for patients with severe ARDS (92), and has the ability to maximize lung-protective ventilation in these patients, albeit with uncertain benefit. The application of $ECCO_2R$ may, in the future, also play an important role in the mitigation of ventilator-associated lung injury in less severe forms of ARDS. Randomized controlled trials are needed to assess the potential impact of extracorporeal technology on the management of ARDS.

Acknowledgements

None.

Footnote

Conflicts of Interest: Dr. Brodie is currently on the medical advisory boards of ALung Technologies and Kadence. All compensation for these activities is paid to Columbia University. Dr. Parekh and Dr. Abrams have no conflicts of interest to declare.

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