ABSTRACT

There has been rapid adoption of extracorporeal life support (ECLS) in adult patients with severe acute respiratory failure. Extracorporeal membrane oxygenation (ECMO) is used to rescue patients with severe hypoxic and hypercapnic respiratory failure refractory to optimal therapy and extracorporeal carbon dioxide removal (ECCO₂R) supports hypercapnic respiratory failure and allows very low tidal volume ventilation to minimize the risk of ventilator-induced lung injury. Currently over 3,000 cases of ECLS (ECMO and ECCO₂R) in adults with respiratory failure are reported annually to the Extracorporeal Life Support Organization registry. Advances in the care of patients with acute respiratory distress syndrome, technological innovations in extracorporeal circuitry, and insights from modern clinical trials of ECLS have led to favorable outcomes and a renewed interest in the use of this technology. Significant gaps in knowledge about best practices remain, however. This review will summarize indications for respiratory support in adults, current evidence available from clinical trials and our institution’s experience with adult respiratory ECLS.

KEYWORDS: extracorporeal life support, extracorporeal membrane oxygenation, extracorporeal carbon dioxide removal, acute respiratory distress syndrome, low tidal volume ventilation

INTRODUCTION

The first adult successfully supported with extracorporeal life support (ECLS) was a patient with acute respiratory failure in 1972. Two consecutive negative trials failed to show a benefit of extracorporeal membrane oxygenation (ECMO) or extracorporeal carbon dioxide removal (ECCO₂R) over mechanical ventilation in adults with severe respiratory failure, dampening enthusiasm for the use of ECLS in adults. Widespread adoption of ECLS for acute respiratory failure in adults did not occur until the 2009 influenza A (H1N1) pandemic, which coincided with publication of the Conventional Ventilation or ECMO for Severe Adult Respiratory Failure (CESAR) trial. Consequently ECLS (including ECMO and ECCO₂R) has been rapidly integrated into the management algorithm of adult patients with acute respiratory failure, most commonly acute respiratory distress syndrome (ARDS). Over 3,000 cases are reported annually to the Extracorporeal Life Support Organization (ELSO). Common respiratory indications for adults in cases reported to ELSO include ARDS, bacterial and viral pneumonia.

We will review common respiratory indications for ECLS and discuss three modern randomized trials that have compared ECLS to standard therapy in patients with severe ARDS: the CESAR trial, the ECMO to Rescue Lung Injury in Severe ARDS (EOLIA) trial and the Xtravent trial. The Strategy of Ultra-Protective lung ventilation with Extracorporeal CO₂ Removal for New-Onset moderate to seVere ARDS (SUPERNOVA) trial, a feasibility trial of ECCO₂R support to achieve very low tidal volume ventilation (LTVV) for moderate ARDS will also be highlighted. Finally, we will present our institution’s experience using ECLS in the management of adult patients with acute respiratory failure.

INDICATIONS

The goal of ECLS in acute respiratory failure is to permit lung rest while maintaining adequate gas exchange and oxygen delivery as a bridge to recovery or as a bridge to destination with transplantation. The use of ECLS to reduce the injurious effects of positive pressure mechanical ventilation is the greatest potential of this technology. A LTVV strategy that targets a tidal volume of 6 mL/kg of ideal body weight and plateau pressures < 30 cm H₂O improves outcomes in ARDS. However even higher plateau pressures (i.e., < 30 cm H₂O) in patients with severe ARDS increases the risk of mortality, suggesting there may be no safe plateau pressure limit. An aggressive strategy to protect the lungs on ECLS in which airway pressures and alveolar overdistention are minimized may therefore be beneficial.

The degree of respiratory support and configuration of ECLS used is determined by the severity of the patient’s respiratory failure and the primary gas exchange abnormality. In patients with isolated respiratory failure that do not require concurrent hemodynamic support, veno-venous (VV-) ECMO is the most common configuration used. In VV-ECMO, blood is drained from a central vein, passed through a blood pump and oxygenator and then returned to a central vein. Lower flow ECCO₂R (which requires smaller
cannulae with target flows of 10–20 mL/kg/min compared to flows of 60–80 mL/kg/min in ECMO) can be used to support adult patients with less severe respiratory failure including hypercapnic respiratory failure from airways exacerbations. ECCO,R can also be used to support very LTVV (< 6 mL/kg) strategies to maintain plateau pressures below 30 cm H₂O in ARDS and to overcome permissive hypercapnia. In patients supported with ECCO,R, blood is drained via a central vein and passed through a blood pump and oxygenator before it is returned to the venous system; an arteriovenous (AV) configuration which drains blood from an artery and uses the patient’s systemic blood pressure gradient without a blood pump may also be used. Dual lumen cannulas, which offer single site cannulation to increase mobility, are available for both ECMO and ECCO,R.

The most common indication for respiratory support in adults reported to the ELSO registry remains ARDS. Respiratory support can be considered for all patients with a treatable underlying condition resulting in refractory hypoxic or hypercapnic respiratory failure despite optimal care, massive air-leak syndromes, or as a bridge to transplantation.

In all four ‘modern’ trials of ECLS discussed here, patients on mechanical ventilation for 7 days or longer were excluded. While the ideal timing to consider ECLS after the initiation of mechanical ventilation remains unclear, prolonged mechanical ventilation is an independent predictor of in-hospital mortality. The Respiratory ECMO Survival Prediction (RESP) Score is a validated risk assessment tool created to guide candidate evaluation for ECMO in adults with acute respiratory failure. In addition to younger age and the presence of single organ failure, patients supported with ECMO within 48 hours of initiation of mechanical ventilation had the most favorable outcomes while those supported after 7 days had a significantly higher mortality. Our institution’s practice is to consider ECLS if a patient has not reached optimal ventilator targets after LTVV, early paralysis, and (in appropriate cases) a trial of proning and ideally within 48–72 hours of mechanical ventilation.

**MODERN ECLS TRIALS**

Early randomized trials of ECMO and ECCO,R for acute respiratory failure in adults with severe ARDS showed no benefit of ECLS. These trials were problematic in their design, their execution, and limited by the available ECLS technology and prevailing clinical practices at the time. The last two decades have been marked by advances in extracorporeal technology including miniaturized, heparin-coated circuits, more durable solid hollow fiber oxygenators that are less prone to shear stress, and dual lumen cannulas. General medical care and ventilator strategies in patients with ARDS have also evolved. For these reasons, there has been a renewed interest in ECLS clinical trials.

**ECMO TRIALS**

The first modern trial of ECLS for acute respiratory failure in adults with severe ARDS, the single-center CESAR trial, was similar in design to an earlier successful trial in neonates. CESAR enrolled 180 adults with severe ARDS randomized to conventional mechanical ventilation versus transfer to a highly experienced ECMO center. Once transferred, subjects in the ECMO group were managed using a standardized ARDS protocol including lung protective LTVV, diuresis and prone positioning. If a subject did not improve within twelve hours they were cannulated for VV-ECMO. CESAR demonstrated that subjects in the ECMO group had a significantly higher composite of survival without severe disability at six months compared to the control group, 63% versus 47% respectively [RR 0.69, 95% CI 0.05–0.097, p = 0.03]. Of note, only 75% of subjects transferred for ECMO actually received it. The major criticism of CESAR is that the management of subjects in the conventional mechanical ventilation arm was not standardized and those in the intervention arm who were transferred for ECMO were more likely to receive LTVV for longer periods of time.

The CESAR trial demonstrated that care at an ECMO-center including a standardized ARDS protocol may improve outcomes in ARDS. Experience from this pragmatic trial guided the design of the EOLIA trial. Published in 2018, EOLIA was the first international, multicenter randomized trial of ECLS for acute respiratory failure in adults with severe ARDS. Adults with severe ARDS were randomized to VV-ECMO and very LTVV versus standardized LTVV. To account for the ethical quandary of potentially withholding a life-saving therapy within the control group, the study design permitted crossover to ECMO for patients in the control group with refractory hypoxemia. Unlike in the CESAR trial, subjects in both arms were treated with a standardized lung protective ARDS protocol including adjunctive therapies such as inhaled nitric oxide, prone positioning and recruitment maneuvers. The primary end point was 60-day mortality. After enrolling 249 subjects the trial was terminated early for statistical futility after the preplanned fourth interim analysis. While the ECMO group had a lower 60-day mortality compared to the control group [35% versus 46% respectively], this difference was not statistically significant [RR 0.76, 95% CI 0.55–1.04, p = 0.09]. Given the high crossover rate (28%), the trial would not have achieved a statistically significant difference in the primary outcome between the two groups, defined a priori as an absolute reduction in mortality of 20% in favor of ECMO. It should be noted that the time of crossover for the 35 subjects in the control group were extremely ill. With rescue ECMO, 15 (43%) of these crossover subjects survived. Taking this into account, there was a significant reduction in the relative risk of treatment failure defined as death by 60 days in the ECMO group, crossover to ECMO or death in the control group [RR 0.62,
95% CI 0.47–0.82, \( p < 0.001 \), a predefined key secondary end point. While EOLIA was a negative trial, it is difficult to draw definitive conclusions given these results. A post-hoc Bayesian analysis found it highly probable that ECMO reduced mortality in EOLIA.\(^{16} \) Taken together, these results suggest that ECMO is effective but the size of the benefit and the risk/benefit ratio in individual candidates is yet to be defined.

**ECCO\(_{R}\) TRIALS**

Xtravent is the first modern trial of ECCO\(_{R}\) for acute respiratory failure in adults with ARDS. In this multicenter trial, 79 adult patients with ARDS were randomized to pumpless ECCO\(_{R}\) and very LTVV (3 mL/kg) versus standardized LTVV (6 mL/kg).\(^{6} \) Patients with significant hemodynamic instability were excluded. The results of this trial published in 2013 revealed that very LTVV with ECCO\(_{R}\) was feasible and safe. The ECCO\(_{R}\) group had higher 28- and 60-day ventilator-free days (the primary end point) compared to the control group but the difference was not clinically nor statistically significant, 10.0 ± 8 days versus 9.3 ± 9 days (\( p = 0.78 \)) at 28 days and 33.2 ± 20 days versus 29.2 ± 21 days (\( p = 0.469 \)) at 60 days respectively. While Xtravent is a negative study, subjects in this trial were not as ill as those in the CESAR and EOLIA trials and the overall mortality was only 16.5%. In a post-hoc analysis of sicker patients (\( \text{PaO}_2/\text{FiO}_2 \leq 150 \)), subjects in the ECCO\(_{R}\) group had a significantly higher number of ventilator-free days at 60-days (40.9 ± 12.8 versus 28.2 ± 16.4, \( p = 0.03 \)).

The recently published SUPERNOVA trial is the largest international, multicenter feasibility and safety trial to date of ECCO\(_{R}\) and very LTVV (4 mL/kg and plateau pressures ≤ 25 cm H\(_2\)O) for acute respiratory failure in adults with moderate ARDS. SUPERNOVA enrolled 95 patients with moderate ARDS expected to require mechanical ventilation for more than 24 hours into this single-arm trial. In the first 24 hours, sedation and paralysis was used to maintain LTVV. After initiation of ECCO\(_{R}\), the tidal volume was lowered incrementally from 6 mL/kg to 4 mL/kg, while titrating the positive end-expiratory pressure to maintain target plateau pressures of 23–25 cm H\(_2\)O. The primary outcome, very LTVV without a rise in \( \text{PaCO}_2 \) > 20% above baseline and an arterial \( \text{pH} > 7.30 \) at 8 hours, was achieved in 78% subjects while 82% achieved these goals at 24 hours. Subjects were supported on ECCO\(_{R}\) for a mean of 5 days [range of 3–8 days] with an in-hospital survival of 62%. Adverse events occurred in 39% of subjects with two serious adverse events attributed to ECCO\(_{R}\). Like the Xtravent trial, this trial showed that ECCO\(_{R}\) and very LTVV for acute respiratory failure in adults with moderate ARDS is feasible. The randomized portion of the SUPERNOVA trial will help determine if a strategy to protect the lungs from ventilator-induced lung injury using ECCO\(_{R}\) and very LTVV is beneficial over conventional LTVV in ARDS. A similar randomized trial, the ongoing pRotection vEntilation with veno-venousS lung assistT in respiratory failure [REST] trial will also address this question by randomizing adults with moderate ARDS [\( \text{PaO}_2/\text{FiO}_2 < 150 \text{ mm Hg} \)] to ECCO\(_{R}\) and very LTVV (3 mL/kg or less and a plateau pressure ≤ 25 cm H\(_2\)O) versus LTVV alone.\(^{17} \) The primary outcome of the REST trial is mortality at 90-days following randomization [NCT02654327].

**LOCAL EXPERIENCE**

The Lifespan ECLS program was started in 2010 with the first adult patient supported for acute respiratory failure the same year. It has been recognized as a Gold Center of Excellence by ELSO since 2015 and is the only ECLS center in Southern New England. Mirroring a global trend, acute respiratory failure is no longer the most common indication for ECLS in adults in our region. To date, 162 patients have been treated with ECLS, including 107 adults, of whom 57 were supported for acute respiratory failure. The overall survival to discharge or transfer in this subset of patients was 66%, while 75% of patients survived ECLS, comparable to similar-sized ECMO-centers. Rhode Island Hospital is one of the U.S. sites of the international, multicenter VENT-AVOID trial, the first randomized trial of ECCO\(_{R}\) in chronic obstructive pulmonary disease (COPD), which compares ventilator free days at day 60 in patients with severe COPD exacerbations randomized to ECCO\(_{R}\) versus standard of care [NCT03255057].

**SUMMARY**

ECLS has been widely adopted to rescue adult patients with refractory respiratory failure and support patients with respiratory failure to minimize ventilator-induced lung injury. Two modern randomized trials suggest a possible benefit of rescue ECMO in adults with severe ARDS, while the role of ECCO\(_{R}\) and very LTVV in patients with moderate ARDS remains unclear based on current evidence.\(^{4,6} \) While significant questions remain regarding patient selection, optimal care strategies, and cost effectiveness, this potentially life-saving therapy is best deployed by centers who are expert in its use.
References


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