Extracorporeal Membrane Oxygenation for ARDS: Optimization of Lung Protective Ventilation

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The use of extracorporeal membrane oxygenation in the management of ARDS has grown considerably in the past decade, largely as a consequence of improvements in extracorporeal technology and management techniques. Recently published data has helped clarify the use of ECMO in ARDS, and its role in optimizing lung-protective ventilation and minimizing ventilator-induced lung injury has the potential to have a substantial impact on ARDS management and outcomes. In the future, novel extracorporeal management strategies may lead to a new paradigm in our approach to patients with ARDS. *Key words: ARDS; extracorporeal membrane oxygenation (ECMO); respiratory failure; extracorporeal life support.* [Respir Care 2018;63(9):1180–1188. © 2018 Daedalus Enterprises]

Introduction

Extracorporeal membrane oxygenation (ECMO) was first used in the management of severe acute respiratory failure in the 1970s, but a lack of proof of clinical benefit beyond the standard of care led to a marked decline in its use. More recent advances in technology and management techniques have led to an improved risk profile and a suggestion of improved survival in patients with severe ARDS who otherwise would be expected to have a high mortality. However, the benefit of ECMO compared with conventional management for ARDS had yet to be demonstrated, until just recently, in rigorously designed, randomized controlled studies by using modern ECMO technology and strict adherence to current standard-of-care mechanical ventilation strategies. As such, ECMO technology has largely remained a rescue therapy for severe refractory ARDS. The potential advantages of ECMO over conventional management may extend beyond its role in supporting patients with refractory gas exchange impairment. The use of ECMO may facilitate and enhance the application of lung-protective ventilation by minimizing ventilator-induced lung injury beyond the current standard of care.

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History of ECMO for ARDS

The first use of ECMO as rescue therapy for severe acute respiratory failure was described in 1972,[1] although a subsequent randomized controlled trial failed to demonstrate a survival benefit of ECMO when compared with conventional mechanical ventilation, with high mortality rates in both groups.[2] Extracorporeal carbon dioxide removal, a variation of ECMO in which the goal is the removal of carbon dioxide without the emphasis on oxygenation, was thereafter investigated as a potential modality[3] to minimize ventilator-induced lung injury by reducing the reliance on invasive mechanical ventilation by pairing extracorporeal carbon dioxide removal with very-low-frequency positive-pressure ventilation.[4-7] Despite its promise, there was no benefit from this strategy over conventional management in a randomized controlled trial.[8] Subsequently, several non-randomized observational studies suggested improved but variable survival rates for subjects with ARDS supported with ECMO (49–81%).[9-17] However, interpretation of these studies is limited both by their methodology and in their use of outdated extracorporeal and mechanical ventilation techniques.

Over the past couple of decades, a number of advancements in clinical management have led to improved outcomes for patients with ARDS, most notably the use of a low-volume, low-pressure ventilation strategy, conservative fluid management, neuromuscular blockade, and prone positioning.[18-23] Innovations in extracorporeal technology have also occurred over this time period.[24,25] The 2009 influenza A (H1N1) pandemic led to a resurgence of interest in the use of ECMO for ARDS, with higher than expected survival rates given the patients' severity of illness.[26-32] However, comparable cohorts at other centers reported equally favorable outcomes without the use of ECMO.[33] Subsequent matched-pairs analyses of subjects with influenza A (H1N1)-associated ARDS managed with and without ECMO also demonstrated conflicting results with regard to mortality benefit,[34,35] which again calls into question the overall benefit of ECMO over optimal conventional management techniques.

Until just recently, the only multi-center randomized controlled clinical trial of ECMO for ARDS that used relatively modern technology was the CESAR (Conventional Ventilation or ECMO for Severe Adult Respiratory failure) trial,[36] in which 180 subjects with potentially reversible severe, acute respiratory failure were randomized to either conventional management or referral to an ECMO-capable center where they were considered for ECMO after an initial period of standardized conventional management. Subjects referred to a specialty center had a significantly lower rate of the composite outcome of death or severe disability at 6 months compared with conventional management (37% vs 53%; relative risk 0.69, 95% CI 0.05–0.97; $P = .03$). However, only 70% of the subjects in the conventional arm received standard-of-care lung-protective ventilation during the study period, and only 76% of the subjects referred to the ECMO-capable center ultimately were managed with ECMO, which makes it difficult to draw conclusions with regard to the effect of ECMO itself on the management and outcomes of severe ARDS. This study does suggest that referral of patients with severe ARDS to a center capable of providing ECMO and standard-of-care lung-protective ventilation may be beneficial.[36,37] The recently completed randomized controlled trial, EOLIA (ECMO to Rescue Lung Injury in Severe ARDS),[38] which compared standard-of-care management with venovenous ECMO, has helped clarify potential benefits of ECMO for patients with severe forms of ARDS. Eligible subjects, based on either severity of hypoxemia or respiratory acidosis in the context of reduced respiratory system compliance, were randomized to optimal conventional management (including standard of care lung-protective ventilation, neuromuscular blockade, and prone positioning) or ECMO combined with a ventilator strategy that mandated plateau airway pressures even lower than the current standard of care. Notably, the trial was terminated early for futility in achieving the primary endpoint (based on pre-specified stopping rules), which can be attributed, at least in part, to a high rate of crossover from control group to ECMO (28%), along with a lower than expected mortality in the control group (46% vs 60%). Although the results did not meet statistical significance for the primary endpoint of mortality at day 60 (35% in the ECMO group vs 46% in the control group; relative risk 0.76, 95% CI 0.55–1.04, $P = .09$), the overall effect estimate, along with key secondary endpoints and post-hoc analyses, suggest a benefit of ECMO over optimal conventional management, with reassuringly low rates of complications in the intervention group.

The ECMO Circuit and Configurations in ARDS

ECMO consists of an extracorporeal circuit that includes a gas-exchange device, also referred to as an oxygenator, which directly oxygenates and removes carbon dioxide from the blood across a semipermeable membrane. ECMO circuits consist of 2 primary configuration types: venovenous and venoarterial.[39] Venovenous ECMO is a configuration in which deoxygenated blood is drawn from a central vein via a pump, passes through the oxygenator, and is reinfused into a central vein (Figures 1 and 2). Venovenous ECMO provides respiratory support only and is the configuration of choice in the majority of patients with severe forms of ARDS. Venoarterial ECMO, which draws deoxygenated blood from a central vein and reinfuses well-oxygenated blood into a central artery, provides both hemodynamic and respiratory support. A hybrid approach,

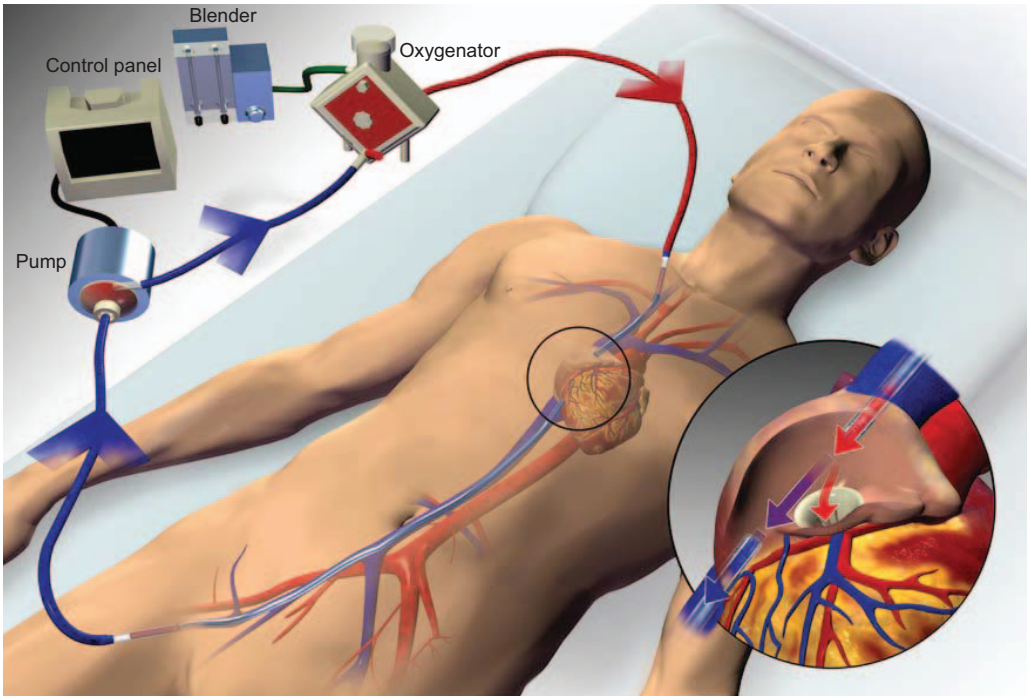

Fig. 1. Two-site approach to venovenous ECMO cannulation. The drainage cannula typically enters a femoral vein and extends into the inferior vena cava. Blood from the cannula is drawn into a pump. This blood is then propelled forward through the oxygenator before being reinfused into the body. The reinfusion cannula typically enters an internal jugular vein and extends into the right atrium, where blood is reinfused. From Reference 80, with permission.

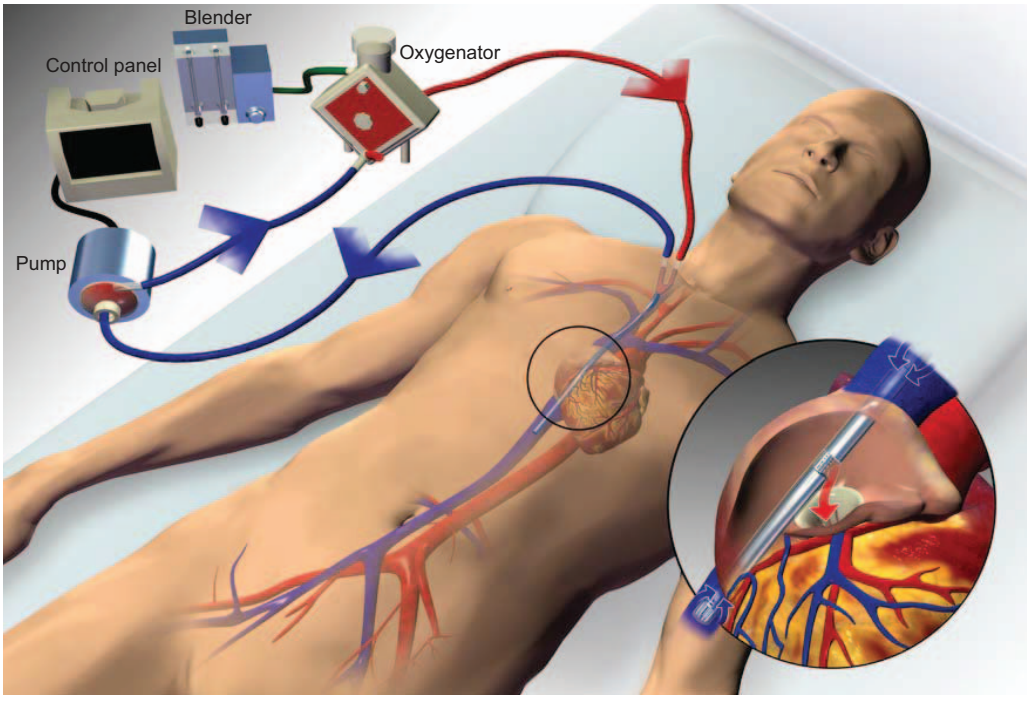

Fig. 2. Single-site approach to venovenous ECMO cannulation. A dual-lumen cannula enters the internal jugular vein and terminates in the inferior vena cava. Blood enters the drainage lumen through ports in the inferior and superior vena cava and is drawn into the pump. This blood is then propelled forward 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. From Reference 80, with permission.

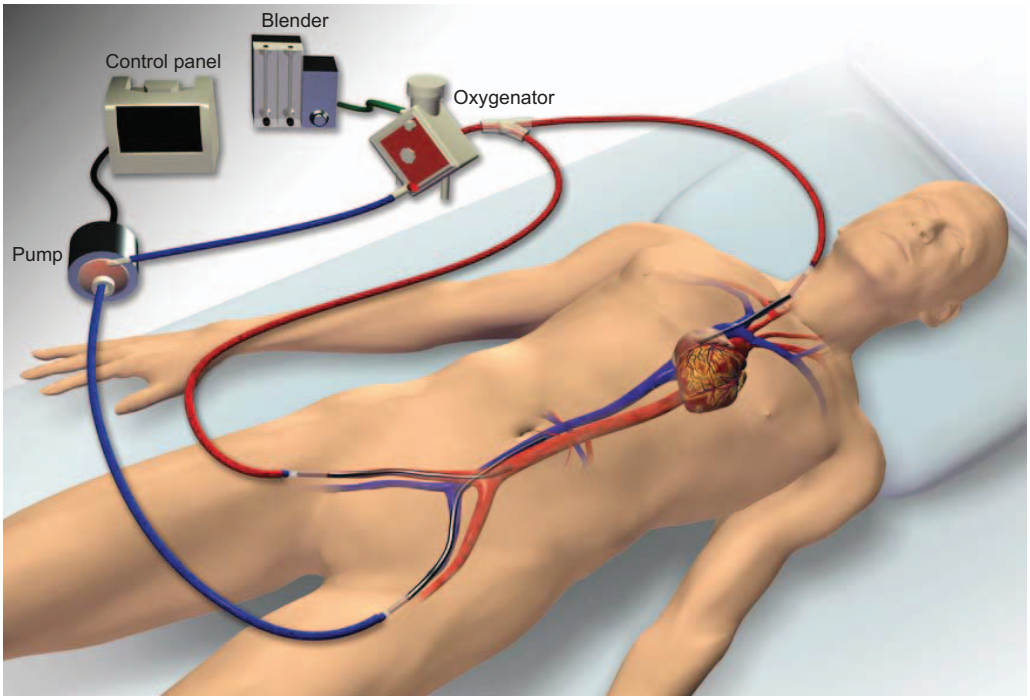

Fig. 3. Venovenous-arterial ECMO cannulation. The venous drainage cannula enters a femoral vein and extends into the inferior vena cava. This blood is then drawn into a pump and propelled forward through the oxygenator before being reinfused into the body. The reinfusion of blood is split between a venous cannula, typically placed in an internal jugular vein, and an arterial cannula, typically placed in a femoral artery. From Reference 80, with permission.

which draws deoxygenated blood from a central vein and reinfuses oxygenated blood into both a central vein and artery, referred to as venovenous-arterial ECMO (Figure 3), may be beneficial for patients with ARDS and concomitant severe cardiogenic shock to provide both hemodynamic support and adequate upper body oxygenation.[39-42]

Cannulation approaches for venovenous ECMO may be performed with either dual- or single-site techniques. The dual-site approach draws blood, for instance, from a femoral vein and reinfuses blood into either an internal jugular or contralateral femoral vein (Figure 1). Alternatively, a single-site approach, which involves placement of a bicaval dual-lumen cannula, typically into an internal jugular or femoral vein, permits both drainage and reinfusion through a single vascular access point (Figure 2). Although this approach often requires either fluoroscopic or transesophageal echocardiographic guidance for placement, it may avoid femoral cannulation, which can help optimize mobilization in select patients.[39,43,44]

Ventilator Strategies With ECMO

Lung-Protective Ventilation

ECMO may be considered a salvage therapy for patients with severe, refractory ARDS (Figure 4). The essence of ECMO support in these cases is 2-fold: first, to ensure adequate oxygenation and ventilation, and, second, to minimize ventilator-induced lung injury by facilitating at least standard-of-care, low-volume, low-pressure ventilation, which may otherwise be difficult to achieve with conventional management alone.[39] Although a lung-protective strategy is the hallmark of ventilator management in ARDS,[19,45-48] the optimal targets for such a strategy remain unknown. Secondary analysis of the ARDS Network Low Tidal Volume Trial[19] found that the subjects with the lowest end-inspiratory plateau airway pressures on day 1 had lower mortality than those with higher plateau airway pressures, which indicates that a lower target may be more protective.[48,49] However, the ability to achieve these lower-than-standard plateau airway pressures in patients with severe forms of ARDS and with severely reduced lung compliance is often limited by prohibitive respiratory acidosis that results from the reduction in minute ventilation. ECMO can manage the hypercapnia and respiratory acidosis that accompany reductions in tidal volumes and plateau airway pressures by directly removing carbon dioxide from the blood. However, it is unknown if such a strategy of ECMO-facilitated very-low tidal volume ventilation is superior to conventional low tidal volume ventilation or other rigorously studied adjunctive therapies, for example, prone positioning.[19,23]

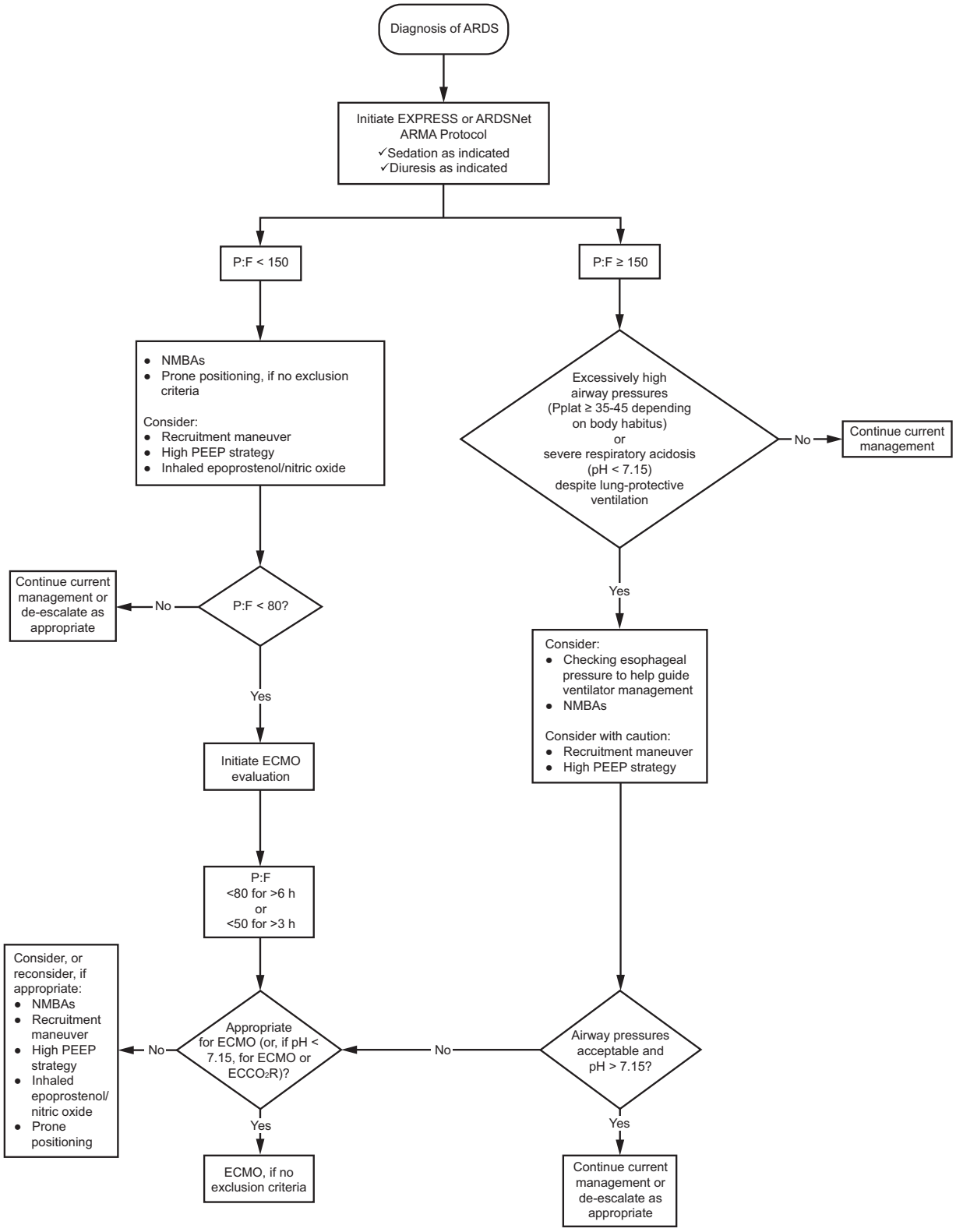

Fig. 4. Management algorithm for patients with ARDS. Initial management for patients diagnosed with ARDS should include a low-volume, low-pressure ventilation strategy, with sedation and diuresis, as appropriate. Further interventions should be considered based on the severity of the ARDS. ECMO = extracorporeal membrane oxygenation. From Reference 81, with permission.

Ventilator Management With ECMO

The CESAR trial[50] managed subjects who received ECMO with pressure-controlled ventilation with a target peak inspiratory pressure of 20–25 cm H_2O, a frequency of 10 breaths/min, PEEP of 10–15 cm H_2O, and a F_{IO_2} of 0.3. This ventilator management strategy, or one that aims to optimize lung protection, has often been adopted by ECMO centers, although current practices vary widely.[51,52] It is unknown if these settings are optimal because this strategy has not been directly compared with any other ventilator strategy during ECMO, including volume-controlled modes with or without particular airway pressure targets. As mentioned, the optimal target plateau airway pressure is unknown, and analysis of prospective data indicates that targeting even lower volumes and pressures may be beneficial.[48] Given the findings of the EOLIA trial, which used a plateau airway pressure limit of 24 cm H_2O, PEEP of at least 10 cm H_2O, F_{IO_2} of 0.3–0.5, and a breathing frequency of 10–30 breaths per minute in the ECMO group, it would be reasonable to consider these parameters as the new standard in ventilator management for patients receiving ECMO support.[38]

Analysis of combined data from large-volume ECMO centers also indicates that higher PEEP during the first few days of ECMO support for ARDS is associated with reduced mortality (odds ratio 0.75, 95% CI 0.64–0.88; $P < .001$).[53] In addition, there are data that the breathing frequency may also be a significant contributor to ventilator-induced lung injury and that targeting lower respiratory rates may be beneficial.[54,55] Analysis of pooled data of patients managed with mechanical ventilation with or without venovenous ECMO indicates that driving pressure (end-inspiratory plateau airway pressure minus PEEP) is independently associated with mortality (adjusted hazard ratio 1.06, 95% CI 1.03–1.10; $P < .001$) and that perhaps targeting a lower driving pressure would improve outcomes.[56,57] However, the strategy of reducing driving pressure has not been well studied in a prospective, randomized fashion, which limits its adoption for the time being. Furthermore, a recent randomized controlled trial of recruitment maneuvers and titrated PEEP strategies demonstrated an increased mortality despite reductions in driving pressure, which called into question the performance of driving pressure as a suitable biomarker in ventilatory management in ARDS.[58]

Extracorporeal Carbon Dioxide Removal for Less-Severe Forms of ARDS

Although ECMO has largely been reserved as a salvage therapy for patients with severe, refractory ARDS, there is increasing interest in the use of extracorporeal carbon dioxide removal, which can be achieved with lower blood flows, smaller cannulae, and a potentially more favorable risk/benefit profile, to facilitate or extend lung-protective ventilation. Because the lower blood flows of extracorporeal carbon dioxide removal do not significantly contribute to oxygenation, this approach may be best suited for less-severe forms of ARDS. The concept of extracorporeal carbon dioxide removal assisted very-low tidal volume ventilation in patients with ARDS was studied in a prospective trial that reduced tidal volumes from 6 mL/kg of predicted body weight to 4 mL/kg, with a goal reduction in plateau pressure from 28–30 cm H_2O to 25–27 cm H_2O. Inflammatory markers, interleukin-6, interleukin-8, interleukin-1b, and interleukin-1 receptor antagonist, were reduced, which indicated a biologic mitigation of ventilator-associated injury.[59] Thereafter, a randomized controlled trial that compared extracorporeal carbon dioxide removal assisted very-low tidal volume ventilation (3 mL/kg predicted body weight) with standard low-tidal volume ventilation in subjects with moderate ARDS did not demonstrate a difference in the primary outcome of ventilator-free days between groups but did indicate a reduction in ventilator-free days among subjects with more-severe hypoxemia.[60] Although analysis of data that supports the use of extracorporeal carbon dioxide removal for facilitation of very-low tidal volume ventilation in a wider range of patients with ARDS are currently limited, extracorporeal carbon dioxide removal remains an area of active investigation.[61,62]

Prone Positioning During ECMO

The significant improvement in mortality achieved with prone positioning when combined with low-volume, low-pressure ventilation[23] makes this a foundational strategy for patients with moderate-to-severe forms of ARDS in centers where there is experience with the technique and should be performed, whenever possible, before consideration of ECMO. Prone positioning may have a benefit when combined with ECMO, with case series that indicate it is safe and feasible.[63] However, more data are needed before such an approach can be recommended.

Mobilization During Extracorporeal Support

Active physical and occupational therapies have been shown to be both feasible and favorable for patients with acute respiratory failure by improving delirium and functionality, and increasing ventilator-free days.[64-66] Mobilization of patients with respiratory failure who require ECMO has largely been limited to patients with chronic respiratory failure awaiting lung transplantation[67-70] but may also be appropriate in select patients with ARDS.[71-73] However, little is known about the efficacy or safety in

patients with ARDS who receive ECMO. Any attempt at active physical therapy in these patients would ideally be performed at centers with a carefully designed, multidisciplinary approach to ensure safety.

Endotracheal Extubation During ECMO

As previously stated, a fundamental goal of mechanical ventilation strategies during ECMO is to minimize ventilator-induced lung injury, a major contributor to morbidity and mortality in ARDS.[19] As such, endotracheal extubation and liberation from invasive mechanical ventilation, when ECMO support is sufficient to manage oxygenation and ventilation, could be an optimal strategy. Additional ventilatory support could also be provided by noninvasive means in addition to ECMO, namely noninvasive positive-pressure ventilation or high-flow nasal cannula, in an attempt to facilitate extubation. Extubation could also potentially minimize additional complications associated with ventilator dependence, including the need for sedation, ventilator-associated pneumonia, critical-illness–related weakness due to immobilization,[71-74] and malnutrition. However, spontaneous breathing may exacerbate lung injury by increasing mechanical stress, which may be difficult to predict or control.[75-78] Although extracorporeal carbon dioxide removal has been shown to aid in controlling ventilatory drive in patients with chronic respiratory failure, it may not be sufficient in reducing the potential injurious effects of spontaneous breathing in patients with severe ARDS.[64,76,79] More data are needed to determine in whom such a strategy might be considered and whether this approach is superior to optimal invasive mechanical ventilation.

Summary

Minimizing ventilator-associated lung injury is the hallmark of current management strategies for patients with ARDS. The concurrent use of ECMO facilitates lung-protective ventilation in patients with severe ARDS and may create the opportunity to achieve lung-protective ventilation beyond the current standard of care. Emerging data from a recent randomized controlled trial have helped to clarify the role of ECMO in ARDS, though much remains to be determined about the optimal ventilator management for patients receiving ECMO support.

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