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What is new in extracorporeal membrane oxygenation for ARDS in adults?

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Introduction

The use of extracorporeal membrane oxygenation (ECMO) in severe acute respiratory distress syndrome (ARDS) has increased considerably over the last several years, attributable to advances in extracorporeal technology, renewed interest, and accumulating evidence. Yet the role of ECMO in severe ARDS is still being defined. Looking ahead, the future of ECMO for ARDS may potentially involve an expanding role.

Impact on short- and long-term outcomes

There remains a lack of high-level evidence from controlled clinical trials that demonstrate definitive efficacy for ECMO in severe ARDS [1]. Although the CESAR (efficacy and economic assessment of conventional ventilatory support versus extracorporeal membrane oxygenation for severe adult respiratory failure) trial, a randomized, multicenter study, demonstrated improved outcomes from referral to an ECMO-capable center for severe ARDS [2], methodological flaws limit its practical application. An ongoing international randomized controlled trial (ECMO to rescue lung injury in severe ARDS (EOLIA), ClinicalTrials.gov Identifier: NCT01470703) will attempt to clarify the role of ECMO in severe ARDS, with all subjects randomized to the intervention arm receiving ECMO and standardized ventilation protocols in both arms (Table 1).

Despite a paucity of randomized data supporting ECMO for ARDS, advances in extracorporeal technology have led to a significant rise in its use [3], particularly in the setting of the 2009 influenza A (H1N1) pandemic. Several years later, data is now emerging regarding both short-term and long-term outcomes for ECMO recipients. Initial reports from the UK, using multiple matching methods to compare ECMO-referred patients with non-ECMO-referred patients from a comparable cohort, suggested a survival benefit of ECMO over conventional management (24 vs. 47 %, relative risk 0.51; 95 % CI 0.31–0.84, $p = 0.008$) [4]. Caveats to interpretation of these results include a lack of standardized ventilation management and duplicate inclusion of control subjects in order to match all ECMO patients. More recent propensity analyses by the French Réseau Européen de Recherche en Ventilation Artificielle (REVA) research network demonstrated no difference in intensive care unit mortality between patients who received ECMO for H1N1-related ARDS and non-ECMO control subjects (odds ratio 1.48; 95 % CI 0.68–3.23, $p = 0.32$), without duplication of control subjects in the matching process. Of note, 51 ECMO patients who could not be matched were younger, had more severe hypoxemia, higher plateau pressures, and lower mortality than the ECMO patients

Table 1 Major current and future potential trials for ECMO or extracorporeal carbon dioxide removal ($ECCO_2R$) in ARDS

Current trials	ECMO to rescue lung injury in severe ARDS (EOLIA); ClinicalTrials.gov Identifier: NCT01470703
Trials in planning phases	$ECCO_2R$ for ARDS
Areas of potential exploration	Low tidal volume vs. very low tidal volume ventilation
	Assessment of long-term neurocognitive and psychiatric outcomes
	Effect of early mobilization on functional outcomes
	Cost-effectiveness studies
	Effect of ECMO on pharmacokinetics of medications

matched to controls (22 vs. 50 %, $p < 0.01$) [5]. In an analysis of the long-term outcomes of survivors in the REVA registry, those supported by extracorporeal lung assist (ECLA), compared to non-ECLA-supported patients, had a higher rate of returning to work at 1 year, but had similar rates of anxiety, depression, and PTSD, with lower health-related quality of life (HRQoL) scores in both groups compared to sex- and age-matched healthy controls. An Australian cohort study that assessed long-term outcomes among ECMO-supported ARDS survivors, not only revealed low HRQoL scores across all domains compared to healthy controls, but also lower mental health, general health, vitality, and social functioning scores, compared with survivors from other ARDS cohorts in which ECMO was not used. However, the ECMO patients were sicker, on average, than the patients in the non-ECMO cohorts. With the inherent limitations of observational studies, prospective randomized trials with long-term physical, psychological, and neurocognitive assessments would provide more insight into the impact of ECMO on these clinically relevant outcomes. Likewise, prediction models, including assessment of extrapulmonary organ dysfunction, may help risk stratify patients before the initiation of ECMO [6].

Maximization of lung-protective ventilation: getting beyond severe ARDS

A volume- and pressure-limited ventilation strategy is the only intervention that has proven survival benefit in ARDS. However, animal data, post hoc analyses of ARDS trial data, and prospective studies using $ECCO_2R$ have suggested a reduction in ventilator-associated lung injury by achieving tidal volumes and plateau airway pressures below the currently accepted standard of care; volumes and pressures that may only be achieved reliably with the addition of $ECCO_2R$ to correct the low tidal volume-induced respiratory acidosis [7, 8]. The Xtravent study, a randomized trial comparing $ECCO_2R$-assisted very low tidal volume ventilation (approximately 3 mL per kg predicted body weight) to standard of care low tidal volume ventilation in patients with moderate to severe ARDS, demonstrated a non-significant increase in the number of ventilator-free days within 60 days in the intervention arm (33 vs. 29, $p = 0.469$) [9]. Post hoc analysis revealed significantly more ventilator-free days in those subjects with more severe hypoxemia (40.9 vs. 28.2, $p = 0.033$). These findings are provocative, adding further support to the concept that a very low tidal volume ventilation strategy may lead to reduction in lung injury beyond current practice. Larger, prospective trials are needed to determine whether such a strategy will translate into a survival benefit.

Because $ECCO_2R$ could facilitate lung-protective ventilation with low blood flow rates, similar to continuous venovenous hemodialysis, using smaller cannulae than are traditionally needed for oxygenation, there is considerable potential to expand the use of ECMO and $ECCO_2R$ beyond severe ARDS [10, 11]. Further trials evaluating such a strategy are in the planning phases.

Physical therapy

Mobilization of critically ill patients is recognized as an important intervention to improve patient outcomes [12]. 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 patients receiving ECMO [13, 14], including patients with ARDS [15]. Although some patients with ARDS may be too hypoxemic to tolerate physical therapy, those receiving $ECCO_2R$ for low tidal volume-induced hypercapnia may be a target population that best tolerates mobilization.

Conclusion

The use of ECMO for ARDS remains controversial, with conflicting data regarding its impact on survival compared with standard of care ventilatory management. An ongoing trial may help to resolve such discrepancies. Beyond its currently accepted role as salvage therapy in severe ARDS, ECMO may prove to be advantageous in facilitating and maximizing lung-protective ventilation in

ARDS independent of its severity. Further study is needed before such practices are adopted.

Conflicts of interest Dr. Brodie reports receiving research support from Maquet Cardiovascular including travel expenses for research meetings, research support for the present study as well as anticipated support for upcoming studies and compensation paid to Columbia University for research consulting. He receives no direct compensation from Maquet. Dr. Brodie is a member of the Medical Advisory Board for ALung Technologies. Compensation is paid to Columbia University. Dr. Brodie receives no direct compensation from ALung Technologies. Pr. Combes is the primary investigator of the EOLIA trial, NCT01470703, a randomized trial of VV-ECMO supported in part by Maquet. Pr. Combes has received honoraria for lectures from Maquet. Dr. Abrams has no conflicts of interest to report.

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