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EDITORIAL

# Do we need randomized clinical trials in extracorporeal respiratory support? Yes

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**Abstract**

Extracorporeal respiratory support, also known as extracorporeal gas exchange, may be used to rescue the most severe forms of acute hypoxemic respiratory failure with high blood flow venovenous extracorporeal membrane oxygenation. Alternatively, lower flow extracorporeal carbon dioxide removal might be applied to reduce the intensity of mechanical ventilation in patients with less severe forms of the disease. However, critical reading of the results of the randomized trials and case series published to date reveals major methodological biases. Older trials are not relevant anymore since the ECMO circuitry was not heparin-coated leading to severe hemorrhagic complications due to high levels of anticoagulation, and because extracorporeal membrane oxygenation (ECMO) and control group patients did not receive lung-protective ventilation. Alternatively, in the more recent CESAR trial, many patients randomized to the ECMO arm did not receive ECMO and no standardized protocol for lung-protective mechanical ventilation existed in the control group. Since these techniques are costly and associated with potentially serious adverse events, there is an urgent need for high-quality data, for which the cornerstone remains randomized controlled trials.

**Keywords:** Acute respiratory distress syndrome, Mechanical ventilation, Extracorporeal membrane oxygenation, Extracorporeal $CO_2$ removal, Editorial

## Introduction

Extracorporeal gas exchange is an old technique that has recently benefited from major technical improvements [1–3]. While venovenous extracorporeal membrane oxygenation (VV-ECMO) might be used for the most severe forms of respiratory failure, lower flow extracorporeal carbon dioxide removal ($ECCO_2R$) might be applied in patients with less severe forms of the acute respiratory distress syndrome (ARDS) to allow "ultra-protective" ventilation with lower airway pressures, tidal volume (VT) and respiratory rate [4], as well as in hypercapnic respiratory failure. However, critical reading of the results of previous randomized trials and case series published to date reveals major methodological biases, as well as technological issues related to the use of currently outmoded equipment in some of these studies. Since these techniques are costly and potentially associated with serious adverse events, there is an urgent need for high-quality evidence, for which the cornerstone remains randomized controlled trials (RCTs). In this paper, we will focus specifically on extracorporeal gas exchange for patients with ARDS.

## Trials and case series of extracorporeal gas exchange in ARDS patients

The first multicenter, randomized trial to evaluate ECMO for ARDS was conducted in the United States in the 1970s on 90 patients with severe hypoxic respiratory failure refractory to conventional ventilation [5]. Mortality was greater than 90% in that trial with no improvement with ECMO. However, that study suffered from major methodological limitations. For example, the mode of ECMO support was only veno-arterial and, when no

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improvement was observed after five 5 days, ECMO was removed, which precluded the possibility of late clinical improvement. Because the ECMO group did not receive lung-protective ventilation, severe complications related to barotrauma occurred and, since ECMO circuitry was not heparin-coated at that time, a very high percentage of patients had severe hemorrhagic complications due to high levels of anticoagulation (Table 1).

The CESAR trial of VV-ECMO for ARDS was conducted in the UK from 2001 to 2006 and evaluated a strategy of transfer to a single center that had ECMO capability while the patients randomized to the control group were treated conventionally at designated centers [6]. 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, this study suffered major limitations. First, 22 patients randomized to the ECMO group, by design did not receive ECMO. Second, no standardized protocol for lung-protective mechanical ventilation existed in the control group, and the time spent with lung-protective mechanical ventilation was significantly higher in the ECMO group. Third, five VV-ECMO group patients died before or during transportation before receiving ECMO, while no ECMO retrieval mobile team was available. Lastly, information on 6-month disability was missing for three control group patients. Had all three of these patients been severely disabled, the relative risk of the primary outcome would have been 0.72 (0.51–1.01, $p = 0.051$).

Low-flow venovenous carbon dioxide removal was first tested in a randomized controlled trial in the early 1990s by Morris et al. [7]. It was stopped for futility after the enrolment of only 40 patients, and mortality was 67% in the 21 patients randomized to $ECCO_2R$, who also had numerous hemorrhagic complications. $ECCO_2R$ has more recently been evaluated in the Xtravent trial [8], which randomized 79 patients either to conventional mechanical ventilation using the ARDSNet ARMA strategy or to tidal volume reduction to 3 mL/kg. The number of ventilator-free days at day 60 were not different between groups. However, a post hoc subgroup analysis revealed that patients with lower $PaO_2/FiO_2$ ($\leq$150 mmHg) at randomization had significantly more mechanical ventilator-free days at days 28 and 60, and were more rapidly weaned from mechanical ventilation. Lastly, a recent systematic review by the Cochrane collaborative groups pointed out the clinical heterogeneity across randomized extracorporeal gas exchange studies that prevented pooling of data in a meaningful meta-analysis [9].

Propensity-matched case-controlled retrospective series have demonstrated a robust survival benefit for severe respiratory failure patients who received the latest generation VV-ECMO devices. The UK collaborative cohort of influenza A(H1N1)-associated ARDS [10] demonstrated lower mortality for patients referred for consideration of ECMO compared to other ARDS patients. Similarly, H1N1 patients who received ECMO in French ICUs of the REVA network [11] had better outcomes than their matched controls. Two more recent series [12, 13], including patients suffering ARDS from various etiologies, also demonstrated better survival with ECMO after propensity-matching cases and controls. It should, however, be mentioned that the best propensity-matching technique will always be limited by residual confounding, that is, by unmatched selection and indication biases which lead clinicians to initiate ECMO in some patients and not in others.

## Why conduct new RCTs of extracorporeal gas exchange now?

Data from the aforementioned studies suggested that extracorporeal gas exchange might improve the outcomes of ICU patients suffering moderate to severe ARDS. Indeed, the newest generation devices are more

**Table 1 Randomized clinical trials of extracorporeal respiratory support**

| Completed RCTs | Study design | Year of publication |
|---|---|---|
| Zapol et al. | IMV vs. IMV with VA ECMO, acute hypoxemic respiratory failure | 1979 |
| Morris et al. | IRV IMV vs. IMV with VV $ECCO_2R$, acute hypoxemic respiratory failure | 1994 |
| CESAR, Peek et al. | IMV vs. consideration of IMV with ECMO, acute respiratory failure | 2009 |
| EXTRAVENT, Bein et al. | Low VT permitted by $ECCO_2R$ vs. conventional IMV, ARDS | 2013 |
| **Selected upcoming RCTs** | **Study design** | |
| EOLIA (NCT01470703) | IMV vs. IMV with VV ECMO | |
| REST (NCT02654327) | IMV vs. IMV with VV $ECCO_2R$, acute hypoxemic respiratory failure | |
| SUPERNOVA (NCT02282657) | IMV vs. IMV with VV $ECCO_2R$, ARDS | |

*RCT* randomized controlled trial, *IMV* invasive mechanical ventilation, *VA* venoarterial, *ECMO* extracorporeal membrane oxygenation, *IRV* inverse ratio ventilation, *VV* venovenous, *$ECCO_2R$* extracorporeal carbon dioxide removal, *VT* tidal volume, *ARDS* acute respiratory distress syndrome

efficient; more biocompatible, as they are less stimulatory of the inflammatory and coagulation cascades; and associated with fewer hemorrhagic complications since they require lower anticoagulant doses [2].

However, uncritical and large dissemination of this technology, which may sometimes be adapted on platforms that are available in most intensive care units, is premature and problematic without rigorous evaluation of associated risks and benefits. Risks associated with catheter insertion and extracorporeal blood circulation (catheter-related infections, bleeding, hemolysis, thrombosis, air embolism, pneumothoraces) must be balanced against potential benefits of reducing ventilator-induced lung injury, and providing adequate gas exchange. Furthermore, RCTs performed to date are either outdated, underpowered or flawed by major methodological limitations, and results of retrospective case-controlled cohort studies will always remain questionable because of inherent indication and selection biases. While RCTs cannot—and should not—be used to answer every clinical question, major questions of efficacy, for instance, are best scrutinized with RCTs. There are, of course, limitations to RCTs in this setting, especially where clinician equipoise is not easily ensured. However, when evaluating a technology that is high-risk and resource-intense, it is incumbent on us to seek the highest level of evidence justifying its use.

We therefore urgently need new high-quality data derived from adequately designed RCTs that will allow the least biased evaluation of the actual impact of extracorporeal gas exchange devices in ARDS patients [14]. The international multicenter randomized Extracorporeal Membrane Oxygenation for Severe Acute Respiratory Distress Syndrome (EOLIA) trial (ClinicalTrials. gov NCT01470703) tested the efficacy of early VV-ECMO in patients with severe ARDS with tight control of mechanical ventilation in the control group, initiation of ECMO prior to transportation to ECMO centers, and the use of ECMO in every patient randomly assigned to receive it. The trial was terminated in April 2017 and its results are expected in early 2018. $ECCO_2R$ to enable lower tidal volume ventilation is currently being evaluated in two international trials. The multicenter RCT comparing $ECCO_2R$ to enable lower tidal volume ventilation versus standard care (REST; ClinicalTrials. gov NCT02654327) is underway in the UK, and plans to include 1120 patients with acute respiratory failure and a $PaO_2/FiO_2$ $\leq$150 mmHg. The international multicenter pilot study SUPERNOVA trial (ClinicalTrials. gov NCT02282657) assesses the safety and feasibility of reducing VT to 4 mL/kg predicted body weight facilitated by $ECCO_2R$. Its results should be released later this year and set the stage for the large SUPERNOVA RCT, which will randomize over 1000 patients with moderate to severe ARDS. The feasibility of this trial might be enhanced by applying an adaptive design and using predictive enrichment strategies based on physiological response prediction frameworks, selectively enrolling patients most likely to benefit from the treatment, and therefore increasing treatment effect size and statistical power [15].

## Conclusion

The recourse to extracorporeal gas exchange for severe ARDS remains controversial, with conflicting data regarding its impact on survival compared with conventional ventilatory management. Randomized controlled trials will remain the cornerstone of clinical research to validate the utility of these techniques with the least possible biases. National and international organizations of ECMO centers such as the Extracorporeal Life Support Organization (ELSO, https://www.elso.org) and the International ECMO Network (ECMONet, http://www.internationalecmonetwork.org), will undoubtedly help in the design and conduct of these high quality trials and further advance our knowledge in the field.

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