



# Extracorporeal membrane oxygenation in acute respiratory distress syndrome: why is the EOLIA trial important?

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Severe acute respiratory distress syndrome (ARDS) is associated with mortality that can exceed 40%, despite the use of strategies such as low-volume ventilation, positive end-expiratory pressure (PEEP), prone positioning (PP) and early administration of muscle relaxants (1-4). Extracorporeal membrane oxygenation (ECMO), in which gas exchange occurs by means of an extracorporeal membrane perfused with venous blood, is considered as a therapeutic option in case of life-threatening hypoxemia or in case of severe respiratory acidosis preventing a protective mechanical ventilation. Indeed, since mechanical ventilation may contribute to perpetuate lung injury because of overdistention of ventilated lung units and repetitive opening and closing of other lung units (1), ECMO is considered not only to improve oxygenation but also to allow the application of a more protective mechanical ventilation. In the last decades, the technique has significantly progressed with a reduction of hemorrhagic and septic complications so that cohort studies have reported encouraging results with the use of ECMO in selected populations of severe ARDS patients (5-8). In 2009, in the CESAR trial (9), an ECMO-based management protocol for severe ARDS patients transferred to a referral center has shown to improve 6-month disability-free survival. However, this study suffered from several limitations.

Only two-thirds of patients in the ECMO group actually received ECMO. Moreover, protective low-volume low-pressure ventilation was significantly less applied in the control group than in the ECMO group. Thereafter, advances in the management of ARDS have been made leading to promote the use of early PP as well as neuromuscular blocking in severe ARDS patients (3-4). Since ECMO remains associated with an important risk of complications and is an expensive treatment relying on teams with maintained experience, the question of its impact on prognosis when compared with up to date care without ECMO required further investigation.

## The ECMO to Rescue Lung Injury in Severe ARDS (EOLIA) trial

Combes *et al.* designed this international (43 participating centers), randomized trial to determine the effect of early initiation of venovenous ECMO in patients with the most severe forms of ARDS (10). Patients were eligible for enrollment if they presented with ARDS and had at least one of the following criteria:

- (I) Partial pressure of oxygen ( $\text{PaO}_2$ ) to fraction of inspired oxygen ( $\text{FiO}_2$ ) ratio  $<50 \text{ mmHg}$  for  $>3$  hours or  $\text{PaO}_2$  to  $\text{FiO}_2 <80 \text{ mmHg}$  for  $>6$  hours despite optimization of mechanical

ventilation (tidal volume of 6 mL/kg and trial of PEEP  $\geq$ 10 cmH<sub>2</sub>O). Physicians were encouraged to use neuromuscular blocking agents and PP before considering for inclusion;

- (II) arterial blood pH <7.25 with a PaCO<sub>2</sub> >60 mmHg for >6 hours (with respiratory rate increased to 35/minute) resulting from mechanical ventilation settings adjusted to keep plateau pressure  $\leq$ 32 cmH<sub>2</sub>O (tidal volume reduction by 1 mL/kg decrements to 4 mL/kg, then PEEP reduction to a minimum of 8 cmH<sub>2</sub>O).

Main exclusion criteria were a mechanical ventilation for >7 days; a major obesity; a cardiac failure requiring venoarterial-ECMO; a simplified acute physiology score (SAPS) II >90; and a non-drug-induced coma following cardiac arrest.

Under ECMO, patients were ventilated in volume-assist control mode with a PEEP at least 10 cmH<sub>2</sub>O, a tidal volume lowered to obtain a plateau pressure 24 cmH<sub>2</sub>O or less, and a respiratory rate of 10 to 30 breathes per minute; or in airway pressure-release ventilation (APRV) mode, with a high-pressure level 24 cmH<sub>2</sub>O or less, PEEP at least 10 cmH<sub>2</sub>O, and a respiratory rate of 10 to 30 breathes per minute. In the control group, patients were ventilated in volume-assist control mode, with tidal volume set at 6 mL per kg of predicted body weight and PEEP set so as not to exceed a plateau pressure of 28–30 cmH<sub>2</sub>O. Neuromuscular blocking agents and prolonged periods of PP were strongly encouraged in the control group. Crossover to ECMO for patients in the control group was allowed in case of refractory hypoxemia [oxygen saturation (SaO<sub>2</sub>) <80% for >6 hours, despite the use of available and feasible adjunctive therapies]. ECMO weaning was also protocolized. The primary end point of the trial was mortality at 60 days. The key secondary end point was treatment failure, which was defined as crossover to ECMO or death in patients in the control group and as death in patients in the ECMO group. The maximum expected sample was 331 participants in order to show a 20% decrease in absolute mortality with ECMO.

Trial recruitment was stopped for futility after the inclusion of 249 patients in 67 months. Mean age of included patients was about 53 years, 22% were immunocompromised and 63% had pneumonia as the cause of ARDS. Before randomization, 59% of the patients had undergone PP, 94% had received neuromuscular blockers and 74% had received vasopressors. As expected, ventilator settings used after inclusion were different between groups.

In the ECMO group, minute ventilation was decreased from about 12 to 5 L/min, and tidal volume from about 400 to 230 mL. Whereas PEEP was not different between groups the day after ECMO initiation, plateau pressure was 3 cmH<sub>2</sub>O lower in the ECMO group. ECMO support lasted a mean of 15±13 days. Non-ECMO centers could enter patients if an ECMO retrieval team could establish ECMO within 2 hours after randomization and transfer the patient to the ECMO center. Thus, 48 of 124 patients (39%) were retrieved from non-ECMO centers by the mobile ECMO rescue team. Thirty-five patients (28%) in the control group received ECMO, in median 4 days after inclusion. These patients had signs of rapidly evolving respiratory and cardiovascular failure in the 24 hours before cross-over and 9 patients presented cardiac arrest. Venoarterial ECMO was applied in 7 patients of the control group, including 6 who received ECMO while undergoing cardiopulmonary resuscitation.

The intention to treat analysis showed that mortality at 60 days was not significantly lower in the ECMO group than that in the control group. Indeed, 44 patients (35%) in the ECMO group and 57 (46%) in the control group had died [relative risk, 0.76; 95% confidence interval (CI), 0.55 to 1.04; P=0.09]. However, the relative risk of treatment failure in the ECMO group was 0.62 (95% CI, 0.47 to 0.82; P<0.001). Mortality at 60 days was 57% among patients in the control group who crossed over to ECMO versus 41% among the other patients in the control group (relative risk, 1.39; 95% CI, 0.95 to 2.03). Patients in the ECMO group had significantly a higher rate of severe thrombocytopenia (<20,000 platelets per cubic millimeter; 27% vs. 16%), a higher rate of bleeding events leading to packed red-cell transfusion (46% vs. 28%), a lower rate of ischemic stroke (0 vs. 5%), but the rates of hemorrhagic stroke, pneumothorax, ventilator-associated pneumonia, and of massive bleeding were similar in the two groups. One patient in each group died from complications related to ECMO cannulation.

### Strengths and limitations

The EOLIA trial has multiple strengths. First, the main limitations of previous trials (9,11,12) had been addressed in the design of the study. Notably, all but 3 patients randomized to ECMO group actually received ECMO. Additionally, the protocol was very strict and included up to date standards of care which have been globally followed.

This trial has also several limitations. First, the rate

of enrolment was low and only 24% of eligible patients were actually included, although it reflected the logistical difficulties of such a trial. Second, the trial was stopped per protocol after 75% of the maximum calculated sample size had been achieved. Therefore, the study may be considered as neither definitively positive nor negative since the evaluation of the effects of ECMO will not have the benefit of the larger sample size that was originally planned (13). Third, the 28% rate of crossover in the control group may have diluted the potential effect of ECMO toward the null hypothesis of no difference (13). However, such as emphasized by the authors of the trial, it would have been unethical not to allow ECMO in the control group. Moreover, this high rate of cross-over reflects that patients with the most severe forms of ARDS require close monitoring of therapeutic strategies since they have a high rate of evolution towards intractable hypoxemia and cardiac arrest. Although patients who crossed over had a very severe respiratory and cardiovascular failure (mean SpO<sub>2</sub> 77%, 9 cardiac arrest among 35 patients), it is to note that 15 patients survived after ECMO initiation. It is unlikely that such a 43% survival rate had been observed in the absence of ECMO (14). Another potential weakness of the study is linked to the absence of systematic PP in the ECMO group. PP is the intervention that has been associated with the largest impact on survival in severe ARDS (3). Before inclusion, 59% of all patients had been turned prone. This can be considered as a satisfying rate when compared with previous cohort studies on ECMO or with recent surveys on the use of PP in severe ARDS (15,16). However, much more patients have been turned prone in the control group after randomization. Improvement in oxygenation with ECMO as well as potential risk of turning patients under ECMO have probably contributed to this difference. Based on the PROSEVA trial protocol (3), PP should be indicated according to the severity of hypoxemia. Although PaO<sub>2</sub> levels are improved under ECMO, this early improvement is probably more linked to the blood oxygenation by ECMO than to early effects of the changes in ventilatory settings on lung aeration. Moreover, some studies have shown complementary effects of ECMO and PP on oxygenation (17-19). Therefore, it is possible that survival might have been further improved in the ECMO group if PP had been more extensively performed during the very first days. Nevertheless, 35% of the control group required ECMO despite the use of PP and a significant number of patients' present contra indications to PP in the real life (3).

### Implications for clinical practice and future research

The authors have concluded that early application of ECMO was not associated with a decrease of 60-day mortality as compared with standard cares including systematic PP and rescue ECMO. This conclusion can be mitigated by a quite impressive 11% lower mortality rate in the ECMO group, although it did not reach the statistical significance (14). Moreover, ECMO was associated with a relatively low rate of severe complications such as severe bleeding when provided by experienced teams. Even if the ability of conducting a new trial in this field may be considered as very low because a powerful enough trial would require at least 10 years to be performed, future investigations will help in further optimizing ECMO use in ARDS patients.

First, ventilation strategies during ECMO as well as weaning protocols remain often empirical and very different among ECMO centers (20-22). Future studies will help us better defining what a real optimal ventilation under ECMO is.

Second, indications of ECMO may be further evaluated. Refractory hypoxemia is usually considered as the key indication of ECMO and represented 82% of inclusions in the EOLIA trial (10). However, the group in which the prognosis appeared as the most improved by ECMO in the trial was the group of patients presenting with respiratory acidosis compromising protective ventilation (24% mortality in the ECMO group vs. 55% in the control group). This important result underlines the fact that ECMO benefit probably relies more on prevention of ventilator-induced lung injury than on PaO<sub>2</sub> increase. The results of ongoing trials on low flow carbon dioxide removal (23) will be important to define respective indications of this technique and of ECMO in ARDS patients.

In conclusion, the EOLIA trial failed to strictly demonstrate an improvement in 60 day-mortality of ECMO in very severe ARDS patients. Nevertheless, the results of this study are encouraging in considering ECMO as an early therapeutic option performed on a case by case basis if life-threatening hypoxemia or respiratory acidosis persist despite the use of protective ventilation associated with neuromuscular blocking and PP if feasible. The use of ECMO should be considered in referral centers thanks to the use of ECMO rescue teams allowing cannulation followed by transfer to the ECMO center (24).

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## Footnote

*Conflicts of Interest:* The authors have no conflicts of interest to declare.

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