Editorial

Extracorporeal membrane oxygenation in acute respiratory distress syndrome: does it really help?

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The concept of extracorporeal life support had been credited to Dr. Gibbon (1903 to 1973) as he described in a patient that suffered from a massive pulmonary embolism "*… if it were possible to remove continuously some of the blue blood … put oxygen into that blood and allow carbon dioxide to escape from it, and then inject continuously the now-red blood into the patient's arteries, we might have saved her life*" (1).

In almost the last 40 years, four randomized controlled trials (RCT) have been conducted to address the effectiveness of extracorporeal membrane oxygenation (ECMO) on acute respiratory distress syndrome (ARDS). In 1979, the first of these RCTs was published by Zapol *et al.* and concluded that there was no survival benefit to ECMO, with a high complication rate (2). Morris *et al.* compared pressure control inverse ratio ventilation versus extracorporeal carbon dioxide removal in ARDS and demonstrated survival of less than 10% with no significance differences (3). These trials are now recognized to have rudimentary ECMO technology, no mechanical ventilation (MV) treatment protocols, poor ventilatory management, and high complication rates for infections and severe bleeding.

The new era began with the Conventional Ventilatory Support versus Extracorporeal Membrane Oxygenation for Severe Adult Respiratory Failure (CESAR) trial (4). In this RCT, Peek *et al.* studied patients during the H1N1 influenza epidemic with severe respiratory failure treated either with MV plus ECMO at a referral center in United Kingdom or with conventional MV in peripheral hospitals. The results showed a substantial decrease in mortality in patients assigned to the ECMO group. The CESAR trial was a landmark RCT that showed improved survival and increased quality of life with the use of ECMO. However, this trial raised several critiques with many methodological issues and major differences in the ARDS management. A major critique was the failure to define the proper use of ECMO in ARDS in which the mortality benefit could be attributed to referral to a specialty care center rather than the use of ECMO itself.

In order to address the weaknesses of the previous trial, the EOLIA (ECMO to Rescue Lung Injury in Severe ARDS) trial was conducted with the primary objective to investigate whether early use of veno-venous ECMO coupled with conventional MV decreases 60-day mortality (5). Their results are now available. This was a multicenter, international RCT that randomized patients with severe ARDS as defined by one of three criteria: P/F ratio <50 mmHg for >3 hours, P/F ratio <80 mmHg for >6 hours, or pH <7.25 combined with $PaCO_2$ ≥60 mmHg for >6 hours (with respiratory rate <35 breaths/min and

plateau pressure ≤32 cmH_2O). Physicians were encouraged to use paralysis and prone positioning before randomization. Crossover from the control arm to ECMO treatment was allowed if the patient had refractory hypoxemia defined as arterial oxygen desaturation to <80% despite the use of adjunctive therapies and if the treating physician thought that the patient had no irreversible multiorgan failure and that ECMO might change the outcome. One of the keys issues of this study was that patients in both groups had access to similar rescue therapies and received low-pressure, low volume ventilation according to current standard of care.

It used a group sequential type design that allowed early stopping either for evidence of effectiveness and for futility. In fact, the trial stopped early, for futility, after the fourth interim analysis (67 months), when 240 out of the planned maximum of 331 patients had been recruited.

The results for 60-day mortality was that 44/124 patients (35%) in the ECMO group died and 57/125 (46%) in the control group died (risk ratio 0.76; 95% CI, 0.55–1.04; P=0.09).

A total of 35 patients (28%) in the control group received rescue ECMO therapy for refractory hypoxemia. It is worth to say that these patients were sicker at the time of enrolment than other patients in the control group (median P/F ratio 51 mmHg, median SaO_2 77%, median lactate 3.2 mmol/L). Nine patients had cardiac arrest, seven had right heart failure, 11 received renal replacement therapy and six patients had extracorporeal cardiopulmonary resuscitation (ECPR). They had higher 60-day mortality than the rest of the controls (57% *vs.* 41% of the remaining control group).

The study also showed that the relative risk of treatment failure (death at day 60 on ECMO, crossover to ECMO, or death in the control group) was 0.62 (95% CI, 0.47–0.82; P=0.001). At 60 days, patients on ECMO required less prone positioning, experienced less ischemic stroke, and had less need for renal replacement therapy. However, patients receiving ECMO had a higher rate of bleeding requiring red blood cell transfusion (46% *vs.* 28%) and severe thrombocytopenia (27% *vs.* 16%), but only 2% of patients in the early ECMO group developed hemorrhagic stroke compared with 4% in the control group.

The interpretation of the results is difficult because of the early stop of the study and a significant crossover that could have diluted the treatment effect.

Moreover, the study was underpowered to answer the trial question. The initial power calculation was based on a 60% mortality in the control group, which became clear was not realistic compared to the actual mortality rate of 46%. The EOLIA trial was designed to find a 20% absolute risk reduction in the ECMO group, which sets a very large requirement for a single ICU intervention, increasing the risk of a falsely negative trial (CESAR, had an absolute reduction risk of 16%).

However, despite not reaching the statistical significance threshold, this does not mean that ECMO is useless, but the trial simply failed to rule out the null hypothesis. Furthermore, the study did demonstrate a trend toward mortality benefit with the use of ECMO, with an 11% absolute mortality reduction in patients receiving the allocated treatment. In fact, if solely examining treatment failure (as defined by the secondary objective), there was a statistically significant benefit in favor of ECMO use. All these results are quite impressive.

In fact, the use ECMO not only ameliorated ventilator-induced lung injury (VILI) through decreasing the mechanical power (6), or reducing the levels of CO_2, a potent biological agent that at high levels (hypercapnia) could exert deleterious effects on lung biology (such impaired alveolar wound repair, decreased rate of reabsorption of alveolar fluid, and inhibition of alveolar cell proliferation) (7,8), but also decreased sedation needs, that could have been reflected in more free days from MV, less vasopressor use and short ICU and hospital length of stay.

Since it will be complicated to repeat a new study, given the slow recruitment rate (0.058 patients/unit/month) (6), we think the results of the EOLIA trial showed that performing early ECMO in specialized referral centers, is safe and may be a relevant option in very severe ARDS patients as a rescue therapy who do not improve after optimizing MV, prone positioning, and who have potential years of good quality of life ahead.

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None.

Footnote

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

References

1. Bartlett RH. Extracorporeal Life Support: Gibbon Fulfilled. J Am Coll Surg 2014;218:317-27.

2. Zapol WM, Snider MT, Hill JD, et al. Extracorporeal membrane oxygenation in severe acute respiratory failure. A randomized prospective study. JAMA 1979;242:2193-6.
3. Morris AH, Wallace CJ, Menlove RL, et al. Randomized clinical trial of pressure-controlled inverse ratio ventilation and extracorporeal CO2 removal for adult respiratory distress syndrome. Am J Respir Crit Care Med 1994;149:295-305.
4. Peek GJ, Mugford M, Tiruvoipati R, et al. Efficacy and economic assessment of conventional ventilatory support versus extracorporeal membrane oxygenation of severe adult respiratory failure (CESAR): a multicentre randomised controlled trial. Lancet 2009;374:1351-63.
5. Combes A, Hajage D, Capellier G, et al. Extracorporeal membrane oxygenation for severe acute respiratory distress syndrome. N Engl J Med 2018;378:1965-75.
6. Gattinoni L, Vasques F, Quintel M. Use of ECMO in ARDS: does the EOLIA trial really help? Crit Care 2018;22:171.
7. Briva A, Vadász I, Lecuona E, et al. High CO2 levels impair alveolar epithelial function independently of pH. PLoS One 2007;2:e1238.
8. Doerr CH, Gajic O, Berrios JC, et al. Hypercapnic acidosis impairs plasma membrane wound resealing in ventilator-injured lungs. Am J Respir Crit Care Med 2005;171:1371-7.

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