Minerva Anestesiologica
EDIZIONI MINERVA MEDICA

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Minerva Anestesiologica 2019 May 21
DOI: 10.23736/S0375-9393.19.13490-6

Article type: Experts' opinion and Point of view

Article first published online: May 21, 2019
Manuscript accepted: May 10, 2019
Manuscript revised: April 11, 2019
Manuscript received: November 27, 2018

vvECMO in ARDS: should the EOLIA study results change our clinical approach?

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ABSTRACT

The original discouraging results of ExtraCorporeal Membrane Oxygenation (ECMO) application in acute respiratory failure caused the technique to be almost abandoned. Fortunately, ECMO survived thanks to the good results obtained in neonates. The interest on ECMO renewed after the publication of the CESAR trial in 2009. The ultimate rebirth of the technique, however, was due to its use as a rescue therapy in severely hypoxemic patients untreatable with conventional methods during H1N1 flu epidemics in Australia and New Zealand. In 2018 the group of investigators led by Alain Combes designed and implemented the EOLIA study to test the efficacy of veno-venous ECMO in patients with severe acute respiratory distress syndrome (ARDS). This article discusses the primary and secondary results of the trial and the considerations emerged in the medical community. We will also discuss how ECMO could evolve to maximize lung protection rather than just prevent hypoxic death.

KEYWORDS

extracorporeal membrane oxygenation - acute respiratory failure – randomized clinical trial

In 1979 Jama published what is considered the first randomized clinical trial (RCT) in Critical Care.[1] The study aimed at comparing ExtraCorporeal Membrane Oxygenation (ECMO) plus mechanical ventilation with conventional mechanical ventilation alone in patients with severe hypoxemic Acute Respiratory Failure. The results were dismal, being mortality the same in ECMO treated patients and in controls, reaching around 91% in both groups. ECMO almost completely disappeared from Adult Critical Care for three decades. Gille and Bagniewski had already hinted at the reasons of the unsuccess, having reviewed in 1976 a 10-year world wide experience in 233 ECMO patients with 15% survival.[2] They had concluded that attention should be paid to mechanical ventilation as a cause of progressive lung injury.

Kolobow, Gattinoni and others indicated high tidal volume and high airway pressure as the cause of the ECMO study failure.[3] They suggested that ECMO should be exploited to achieve a more protective lung management, aimed to foster lung healing, rather than simply warrant a viable oxygenation.

Fifteen years later, Alan Morris published a second RCT using low frequency positive pressure ventilation combined with intermediate extracorporeal blood flow (< 2.5 l/min) veno-venous bypass.[4] Though the study focused on carbon dioxide (CO_2) removal, the results were once again disappointing, showing no improvement in survival.

This series was unfortunately doomed by a very high rate of bleeding and possibly by other technical problems. Most of the ECMO survivors were indeed those who had been disconnected early due to major life threatening bleeding, and not because of a real improvement in lung function.

Luckily enough ECMO survived thanks to the good results obtained in neonates,[5] that made possible the conduct of a trial in UK devoted to neonatal acute distress syndrome.[6]

The positive results obtained in neonates led the UK ECMO Leicester group to design an RCT for Adults (CESAR trial), which basically compared a composite outcome (survival + quality of life) in severe acute respiratory distress syndrome (ARDS) patients transferred to an ECMO center with patients randomized to conventional care in non ECMO centers.[7]

The study, published in September 2009 in the Lancet, showed indeed a clear advantage for the “ECMO treatment” (ECMO was applied in the majority but not in all patients randomized to “ECMO”): despite this, it did not satisfy the skepticism of many in the scientific community, but it provided fuel for the activities of the ECMO enthusiasts. One month later the Australia and New Zealand Extracorporeal Membrane Oxygenation (ANZ

ECMO) Influenza Investigators published on JAMA a seminal study of the role of ECMO in acute, catastrophic respiratory distress syndrome caused by H1N1 influenza pandemic.[8] A great momentum was back for ECMO, and in many countries, ECMO regained a major role in the treatment of severe ARDS.

The time for a new, definitive RCT on ECMO had come. The group of investigators led by Alain Combes designed and implemented the EOLIA study.[9] The trial aimed at assessing whether the application of ECMO in early severe ARDS could provide an advantage over conventional protective mechanical ventilation. Ethical considerations required the possibility of a rescue crossover to ECMO for patients of the control group, when conventional treatment failed causing the patient to reach an extremely severe state. The crossover was applied in 28% of the patients of the control group.

Two major end-points were identified: mortality (primary end-point) and a composite end-point of death plus treatment failure (crossover to ECMO).

The actual mortality for ECMO was 35% versus 46% in the control, while with the composite outcome it was 35% versus 58% in the control. Hence, mortality was not significantly different ($p = 0.09$) between groups, while the composite outcome was highly significantly different ($p < 0.01$). The EOLIA investigators should therefore be congratulated, having done an excellent job in very difficult conditions.

So how important and in which way will the EOLIA study affect the future of ECMO and the clinical practice of managing severe ARDS?

A first answer comes from the editorial of Harrington and Drazen,[10] which accompanied the publication of the study in the NEJM: ECMO probably has some benefit in severe ARDS. This statement is based on secondary analyses and on the circumstances of stopping the trial for "futility". Bartlett moreover, in another editorial, taking into consideration the total of the cases available at the time of stopping, concludes that "My thoughtful post hoc analysis is that the 11% difference in survival comparing early ECMO to conventional care with late rescue ECMO will probably ($p = 0.07$) be considered clinically significant by intensivists and payers for healthcare in severe ARDS".[11]

Hence, we are most probably correct in accepting the statement that ECMO has a positive effect on outcome when applied as a rescue procedure for severe ARDS.

Goligher et al analyzed the EOLIA results by a Bayesian analysis rather than by the classical statistical approach.[12] They calculated the distribution of probabilities related to a potential absolute risk reduction (ARR) of at least 2%, 4%, and up to 20% (the ARR tested originally

by the trial). Since they applied a Bayesian analysis Goligher et al needed a set of a priori information, that was in part descriptive (skeptical, neutral, or enthusiastic, with an appropriate mathematical conversion) or derived from previous trials on the topic, adjusted for their relevance. The conclusion of their analysis might possibly be summarized as follows:

1) the probability that ECMO has any benefit (Relative risk < 1) is relatively independent from the a priori information, and is very high (the probability that ECMO reduces mortality ranges from 88% to 99%).

2) the probability however that ECMO reduces mortality by 20% (the optimistic hypothesis tested by the trial) is low, ranging from 0% to 48%).

These sounds to us as much more attractive and informative conclusions than the one given from the classical analysis, which only tells us that we cannot exclude that the observed clinically relevant difference in mortality (11%) may be due to chance only (i.e. the difference in mortality does not reach the arbitrarily chosen conventional $p < 0.05$).

In summary, the EOLIA results strongly suggest a positive effect of ECMO when used as rescue procedure in very severe ARDS patients early in their disease course, and possibly also when applied late in almost desperate conditions (26% of crossover cases had cardiac arrest).

The Bayesian approach analysis reinforces this positive effect suggestion indicating a reduction of mortality of at least 2% with a 98% probability.

In general, an early application of the procedure seems to warrant better results than the late use, as somehow shown by the 57% mortality in the crossover late ECMO group compared with the 35% mortality of early ECMO.

Further indications are obtained from the additional on line material: some patients may be too sick to benefit from ECMO application as a rescue technique (Subgroup analysis: page 38 additional on line supplement): when the PaO_2/FiO_2 at enrollment is higher than 66 mmHg the mortality in treated and control group is 27.1% versus 48.4%, while it is 43.8 % versus 42.1% when PaO_2/FiO_2 is lower than 66 mmHg.

It is probably the first time that such an effect is suggested. However, the hypothesis that some patients might be too sick to respond positively to the ECMO procedure appears totally reasonable. ECMO is not indeed a magic bullet.

Last, but not less important, ECMO, proved to be a relatively safe procedure when applied with present day technology and in experienced centers. This is possible in spite of an

increased transfusion rate (46% versus 28%) and an increased incidence of thrombocytopenia (40% versus 32%). In fact these side effects may be compensated by a lower incidence of stroke (no patients vs. 5%) and a lower risk of need for renal replacement therapy (median days free from renal-replacement therapy at day 60: 50 versus 32 days).

In view of these results and considerations, we may raise the question of where to go and how to adjust the use of ECMO following the EOLIA trial.

First of all, we should take into account the opinion of the professional community about the use of ECMO in clinical practice: a recent NEJM poll between the readers of the journal concluded for an overwhelming 81% against 18% in favor of the application of ECMO in a case of severe hypoxemia in a patient with ARDS.[13]

Should we perhaps plan another ECMO RCT? The chances for a meaningful result from a RCT comparing ECMO as a rescue procedure versus conventional mechanical ventilation are very low, and the difficulties involved almost insurmountable, as discussed recently by Gattinoni et al.[14] This does not mean that such a study would not be desirable, but simply that it is almost impossible to perform. We strongly believe that for time being and as we do with other rescue procedures, we should be content with the evidence we have. RCTs are not the only and unique way to achieve knowledge, particularly when based upon frequentist statistics and linear models.

We should probably focus our efforts on preventing lung damage and foster lung healing rather than on substituting lung function once severely impaired. Besides warranting a viable oxygenation, extracorporeal gas exchange techniques should be directed to prevent Ventilator Induced Lung Injury (VILI).

In 1980 we published a small series of cases managed by low frequency positive pressure ventilation with extracorporeal CO_2 removal.[15] Tidal Volume (TV) and Airway pressure were limited to safe levels, and respiratory rate was kept between 2 to 4 breath per minute. CO_2 clearance was warranted by relatively low blood flows (1.5 to 2 l/min). We claimed that such technique was able to prevent barotrauma and the systemic side effects of high volume/high pressure mechanical ventilation. Ten years later we reported our first case of low blood flow (0.4-0.6 l/min) CO_2 removal in a patient with bilateral bronchopleural fistulas: extracorporeal CO_2 clearance allowed liberation from mechanical ventilation and low level CPAP with closure of the air leaks within a week.[16]

More recently the pioneer experiments of Terragni[17] and Bein[18] showed that TV can be decreased to superprotective levels down to 3 ml/kg, provided a sufficient amount of carbon

dioxide is removed by the membrane lung. The European Society of Intensive Care Medicine is sponsoring a multicenter international trial based on the use of low flow CO_2 removal in mild/severe ARDS to allow superprotective lung ventilation at TV lower than the standard 6 ml/kg. The results of the pilot phase of the study are expected shortly.

Gattinoni and others introduced the concept of mechanical "power" applied to the lungs as the major unifying hypothesis about the mechanism generating VILI,[19] and proposed an equation quantifying the amount of energy applied to the lungs by mechanical ventilation in the unit time. When this concept is applied to the EOLIA study, it is possible to show how ECMO allowed a 66% reduction of the power injuring the lung. Surprisingly, respiratory rate was only marginally different between ECMO and controls: at variance, a decrease in respiratory rate could allow an additional major decrease in the risk of VILI.

The future direction to go with ECMO, or better with Extracorporeal gas exchange, could then be its use not as a rescue procedure, to save patients from impending hypoxemic death, but rather as a procedure aimed at minimizing the risk of VILI at a less severe stage of ARDS. This goal, focused more on CO_2 removal rather than oxygenation, could be reached with off-the-shelf technology at intermediate blood flows (1 to 1.5 l/min) and low frequency ventilation (4-8 bpm) with ultraprotective tidal volumes, warranted by the decreased ventilatory needs.

The recent introduction of newer approaches to personalized medicine applied to ARDS treatment might allow a better selection of patients potentially more responsive to ECMO. New biological treatments as well as the subphenotyping approach introduced by Calfee and colleagues are very promising in this direction.[20,21]

In this way, having defined the role of Extracorporeal gas exchange in correcting even the extreme hypoxemia, we will be able to clarify whether its effect upon VILI, when applied in an earlier phase, could maximize lung protection and improve the outcome of our patients.

Many other aspects of the mechanisms of VILI, such as the effects of atelectrauma,[22] the role of PEEP, recruitment and prone position, of pulmonary hypertension and intrapulmonary blood flow distribution, from hypo- to hyper- perfusion, just to mention a few, remain to be explored when combined to extracorporeal gas exchange, but this topic is still beyond the horizon of the present state of the art.

KEY MESSAGES

1. The EOLIA, a randomized trial comparing early application of ECMO in very severe ARDS versus conventional protective mechanical ventilation, shows no statistically significant difference (P = 0.07 by log-rank test) in mortality at 60 days (35% versus 46% in ECMO and control group, respectively). However, the composite outcome, defined as crossover to ECMO or death in patients in the control group and as death in patients in the ECMO group, was highly significantly different ($p < 0.01$).
2. Sustained also by a Bayesian approach analysis of EOLIA trial, it is possible that ECMO has a positive effect on outcome when applied early as a rescue procedure in severe ARDS.
3. ECMO proved to be a relatively safe treatment with a safety profile comparable to conventional mechanical ventilation.
4. Extracorporeal gas exchange could play a key role in minimizing Ventilator Induced Lung Injury (VILI) if applied at an earlier less severe stage of ARDS.

Funding: this work was funded by Fondazione IRCCS Ca Granda Ospedale Maggiore Policlinico, Project Title: RC 2019 -insufficienza respiratoria

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NOTES

Conflicts of interest.— The authors certify that there is no conflict of interest with any financial organization regarding the material discussed in the manuscript.
Prof. Grasselli reports payment for lectures from Getinge, Draeger Medical, Pfizer and Fisher & Paykel and travel/accommodation/congress registration support from Biotest and Getinge outside the submitted work.
Prof. Pesenti reports personal fees from Maquet, Novalung/Xenios, Baxter and Boehringer Ingelheim, outside the submitted work.
Prof. Pesenti and Dr. Zanella are inventors of patents related to mechanical ventilators and extracorporeal gas exchange.

Authors' contributions.— all authors have contributed equally to the manuscript conception and writing.