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Indications for extracorporeal support: why do we need the results of the EOLIA trial?

Introduction

Acute respiratory distress syndrome (ARDS) is a severe lung disease, the associated mortality rate of which remains high [1]. The most severe forms of the disease, of which hypoxemia resulting from pulmonary involvement is the most profound, have an even worse prognosis, with mortality exceeding 60% [2, 3], despite recourse to exceptional adjunctive therapies, such as inhaled NO [4], recruitment maneuvers [5], or prone positioning [6].

In these situations, some teams propose establishing an extracorporeal circuit, combining a centrifugal pump and a membrane oxygenator, assuring total pulmonary assistance (oxygenation and CO_2 removal from the blood), or extra-corporeal membrane oxygenation (ECMO) [7–12]. ECMO also permits ultraprotective mechanical ventilation to minimize the trauma caused by mechanical ventilation and to allow the lungs to rest [13]. Unfortunately, trials evaluating ECMO in this indication over the past few decades [14, 15] failed due to the interval between the onset of disease and the installation of extra-corporeal assistance, the poor oxygenation and CO_2-removal capacities of the devices used, and the high rate of complications linked to the apparatus (massive hemorrhage resulting from intense anticoagulation and the poor 'biocompatibility' of the circuits).

However, over the past few years, pivotal progress has been made in the conception and construction of ECMO circuits, rendering them more 'biocompatible', effective, and resistant [16]. Good outcomes were reported for patients that received ECMO as rescue therapy during the H1N1 influenza pandemic [17–19], and the CESAR trial [20] yielded promising results, although it was highly criticized for methodological limitations.

Thus, the international multicenter randomized controlled EOLIA (ECMO to rescue Lung Injury in severe ARDS) trial was designed to test the benefit of the early installation of the latest-generation ECMO in patients with the most severe forms of ARDS.

Randomized trials of ECMO in ARDS patients

The first multicenter, randomized trial to evaluate ECMO for ARDS was conducted by the NIH in the US in the 1970 s on 90 patients with severe ARDS refractory to conventional ventilation techniques [14]. The ECMO circuit had a venoarterial hook-up. Patient survival in that trial was extremely low (< 10%) and no improvement was demonstrated with ECMO. However, that study can now be considered, if not prehistoric, as least very old, and its protocol suffered from major methodological limitations. For example, since the ECMO group did not receive protective ventilation, severe barotraumatic complications occurred. In addition, when no improvement was observed after 5 days, ECMO was stopped, which prevented any possibility of late clinical improvement. Thirdly, the patients were included in the trial after prolonged mechanical ventilation and it was demonstrated that the deaths of patients who had received ECMO support was strongly associated with the number of days of mechanical ventilation before installation of the device [3]. Indeed, the benefit anticipated with that new technique was to rapidly ensure rest for the lungs due to the highly protective ventilation, before the disease could evolve towards destructive fibrosis. Fourthly, that trial enrolled a very high percentage of patients with hemorrhagic complications, probably attributable to excessive anticoagulation. Lastly, the centers enrolling patients in the trial had very limited experience with the technique. After that study, ECMO implantation to treat severe ARDS declined sharply.

The most recent trial (CESAR) was conducted in the UK from 2001 to 2006 [20]. The selection criteria for patients with severe ARDS included a Murray score ≥3 or non-compensated hypercapnia (pH < 7.20). The patients randomized to receive ECMO support were transferred to a single center (Glenfield, Leicester), while the patients randomized to the controls were treated conventionally in their center of origin. The primary evaluation criterion was mortal-

ity or severe disability (defined as being confined to bed or incapable of washing or dressing oneself) 6 months post randomization. Of the 180 patients randomized to 68 centers, 90 received conventional treatment and 90 ECMO support. At the end of the trial, 36.6% of ECMO patients and 52.8% of controls had died or were severely handicapped ($p = 0.03$; relative risk: 0.69, 95% confidence interval [CI] 0.05–0.97). An almost significant trend towards lower mortality was observed at 6 months for the ECMO group (36.6% vs. 46%; $p = 0.07$). Patients in the conventional treatment group died earlier than those receiving ECMO (5 vs. 15 days). However, that trial had two limitations that merit attention. Firstly, 22 patients randomized to the ECMO arm were not hooked-up to the device (died during transportation, arrived at the ECMO center either in an extremely further weakened condition or in a markedly improved condition). The other major methodological problem was the absence of mechanical ventilation standardization for the control group, for which it was merely recommended that the treating physicians adopt a strategy of protective ventilation without further specifications.

Why a new trial now?

A critical review of the results of randomized trials and case reports published to date reveals the technological and methodological biases for some and absence of controls for the others. It must also be emphasized that the most recent studies reported mortality rates for patients with the most severe forms of ARDS, defined as hypoxemia or hypercapnia refractory to initial management and treated conventionally, exceeding 60% [1–3]. The results of the first randomized trial were disappointing, but it should be noted that it took place many years ago, when the technology was in its infancy. In particular, the poor biocompatibility of the materials used and the need for intense anticoagulation were responsible for numerous, often fatal, hemorrhagic complications. The latest trial (CESAR) has yielded encouraging data, despite the major methodological limitations raised [20].

Notably, the technological revolution in terms of the materials used in the last few years has been extremely rapid and extensive: the new ECMO circuits are more biocompatible, as they are less stimulatory of inflammatory and coagulation cascades and, hence, require lower anticoagulant doses [7, 13]. In addition, early ECMO implantation for severe ARDS not responding rapidly to adjunctive therapies allows earlier rest for the lungs, significantly minimizes mechanical ventilation-induced trauma, and thereby prevents disease progression towards destructive fibrosis [21]. In light of all these observations and the advances made in ECMO technology, it appeared necessary to undertake a new trial, optimizing the therapies to be administered in the ECMO arm as well as in the conventional treatment arm [22–24]. For the ECMO arm, it was essential to implant the system as rapidly as possible, once the patient met the trial's inclusion criteria, before inflammatory lesions, signs of ARDS progression towards fibrosis, are established and definitively destroy the pulmonary parenchyma. Indeed, the strategy of transporting the patient to a referral center without ECMO carries major risks and seriously compromises the outcome of the technique.

In contrast, it seemed more appropriate to send a highly trained mobile circulatory assistance team to the patient's bedside to implant the system and to subsequently transfer the patient to a more experienced center [25]. To minimize the complications linked to the technique, more restricted anticoagulation than that used in the past is now possible. Notably, the heparinization of cannula surfaces and the oxygenator membrane enabled a marked reduction in heparin anticoagulation.

Finally, ventilation of controls needed to be optimized, taking advantage of the experience obtained in randomized trials over the past few years: lower tidal volume (VT) to 6 ml/kg ideal body weight and adopt a maximum pulmonary-recruitment strategy while minimizing the trauma caused by mechanical ventilation.

Design of the EOLIA trial

Study design

EOLIA was designed as a multicenter, international, prospective, randomized, comparative open trial conducted on two parallel groups of patients that had developed severe ARDS: an experimental arm receiving early ECMO support and a control group managed with conventional ventilation (standard treatment). The trial was registered at Clinicaltrials.gov (identifier# NCT01470703) [23].

Study objectives

The main objective of the EOLIA trial was to evaluate the impact of early ECMO initiation on mortality reduction in a population of patients with severe ARDS progressing for < 7 days after initiation of mechanical ventilation, compared to a conventional treatment strategy.

Secondary objectives were to assess: the duration of mechanical ventilation; the duration of catecholamine support; the occurrence of ECMO-related adverse events; the occurrence of organ failure (assessed using the Sequential Organ Failure Assessment score); the duration of stay on an intensive care unit (ICU) and in hospital; as well as the long-term quality of life.

Study population

To be eligible for enrolment, the patients had to fulfil the ARDS criteria defined according to the American-European Consensus Conference on ARDS [19] and to be intubated and on mechanical ventilation for < 7 days. Additionally, one of the three following criteria of disease severity was required:

- PaO_2/FiO_2 < 50 mm Hg with $FiO_2 \geq$ 80% for > 3 h, despite optimization of mechanical ventilation (Vt set at 6 ml/kg and trial of PEEP ≥ 10 cm H_2O) and despite possible recourse to usual adjunctive therapies (NO, recruitment maneuvers, prone position, HFO ventilation, almitrine infusion) *OR*
- PaO_2/FiO_2 < 80 mm Hg with $FiO_2 \geq$ 80% for > 6 h, despite optimization

of mechanical ventilation (Vt set at 6 ml/kg and trial of PEEP ≥ 10 cm H_2O) and despite possible recourse to usual adjunctive therapies (NO, recruitment maneuvers, prone position, HFO ventilation, almitrine infusion) *OR*

- pH < 7.25 (with $PaCO_2$ ≥ 60 mm Hg) for > 6 h (with respiratory rate increased to 35/min) resulting from MV settings adjusted to keep Pplat ≤ 32 cm H_2O (first, tidal volume reduction by steps of 1 mL/kg to 4 mL/kg then PEEP reduction to a minimum of 8 cm H_2O).

Study intervention

For patients randomized to the experimental treatment arm, ECMO was initiated as rapidly as possible by venovenous (VV) access. To minimize the trauma induced by mechanical ventilation, the following ventilator settings were used: volume-assist control mode, FiO_2 30–60%, PEEP ≥ 10 cm H_2O, VT lowered to obtain a plateau pressure ≤ 24 cm H_2O, respiration rate (RR) 10–30/min or airway pressure release ventilation (APRV) mode with a high pressure level ≤ 24 cm H_2O and a low pressure level ≥ 10 cm H_2O [26].

Standard management of ARDS, according to the modalities applied by the 'maximal pulmonary recruitment' group of the EXPRESS trial [27] was applied to patients randomized to the control arm. Mechanical ventilator settings were as follows: assist–controlled ventilatory mode, VT set at 6 ml/kg of ideal body weight and positive end-expiratory pressure (PEEP) set so as not to exceed a plateau pressure of 28–30 cm H_2O. In the case of refractory hypoxemia, the usual adjunctive therapeutics were used: NO, prone position, high-frequency oscillatory (HFO) ventilation, and almitrine infusion. A crossover option to ECMO was possible in the case of refractory hypoxemia defined as blood arterial saturation SaO_2 < 80% for > 6 h, despite the mandatory use of recruitment maneuvers, and inhaled NO/prostacyclin and, if technically possible, a test in prone position—and this only if the patient had no irreversible multiple

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Indications for extracorporeal support: why do we need the results of the EOLIA trial?

Abstract

Acute respiratory distress syndrome (ARDS) is a severe lung disease, with an associated mortality rate exceeding 60% for the most severe forms of the disease. In these situations, establishing an extracorporeal circuit, combining a centrifugal pump and a membrane oxygenator (extra-corporeal membrane oxygenation, ECMO), can ensure total pulmonary assistance and allow the lungs to rest under ultraprotective mechanical ventilation. Unfortunately, former trials of ECMO in ARDS were negative or highly criticized due to many technical and methodological shortcomings. Prior to the widespread use of venovenous ECMO for severe ARDS, new trials are needed to test the efficacy of early initiation of the technique 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 all patients randomly assigned to receive this treatment. Therefore, the international multicenter randomized EOLIA (ECMO to rescue Lung Injury in severe ARDS) trial was designed to test the benefit of systematic and early installation of the latest-generation ECMO circuits in patients with very severe ARDS. Patients randomized to the control group were managed with tight control of mechanical ventilation and recourse to paralyzing agents and prone positioning, while an ethical crossover option to ECMO was permitted only if refractory hypoxemia (SaO_2 < 80%) lasted for > 6 h despite all possible conventional emergency interventions. The primary endpoint of the study was the 60-day mortality rate, with an expected 20% absolute mortality reduction with ECMO.

Keywords

Acute respiratory distress syndrome · Mechanical ventilation · Extracorporeal membrane oxygenation · Randomized trial · Absolute mortality

Indikationen für die extrakorporale Unterstützung: Warum brauchen wir die Ergebnisse der EOLIA-Studie?

Zusammenfassung

Das akute Lungenversagen („acute respiratory distress syndrome" [ARDS]) ist eine lebensbedrohliche Lungenerkrankung, schwere Verlaufsformen sind mit einer Mortalitätsrate von über 60 % assoziiert. In diesen Fällen kann durch die Anlage eines extrakorporalen Kreislaufs (extrakorporale Membranoxygenierung [ECMO]) die weitreichende Unterstützung der Lungenfunktion sichergestellt werden, gleichzeitig wird eine Erholung der Lunge durch ultraprotektive Beatmung ermöglicht. Frühere Studien zur ECMO bei ARDS fielen leider negativ aus oder wurden heftig kritisiert, weil sie zahlreiche technische und methodische Mängel aufwiesen. Vor einer breiten Anwendung der venovenösen ECMO bei schwerem ARDS müssen weitere Studien durchgeführt werden, um die Wirksamkeit eines frühen Einsatzes zu prüfen – mit strikter Kontrolle der Beatmung in der Kontrollgruppe, Beginn der ECMO vor dem Transport ins ECMO-Zentrum und Anwendung der ECMO bei allen Patienten, die dieser Behandlung randomisiert zugewiesen wurden. Vor diesem Hintergrund wurde die internationale randomisierte Multicenterstudie „ECMO to rescue Lung Injury in severe ARDS" (EOLIA) konzipiert, die den Nutzen einer systematischen, frühen Anlage von ECMO-Kreislaufsystemen der neuesten Generation bei Patienten mit schwerem ARDS untersucht. Die in die Kontrollgruppe randomisierten Patienten erhielten eine streng kontrollierte Beatmung, mit Muskelrelaxierung und Anwendung der Bauchlage. Ein ethisch begründeter Wechsel zur ECMO war dann möglich, wenn für > 6 h – trotz Anwendung aller möglichen konventionellen Notfallinterventionen – eine refraktäre Hypoxämie (SaO_2 < 80 %) bestand. Primärer Endpunkt der Studie war die 60-Tages-Mortalitätsrate bei einer erwarteten absoluten Reduktion der Mortalität unter ECMO von 20 %.

Schlüsselwörter

Akutes Lungenversagen · Beatmung · Extrakorporale Membranoxygenierung · Randomisierte Studie · Absolute Mortalität

organ failure and if the physician in charge of the patient believed that this could actually change the outcome.

Study endpoints

The primary endpoint was the mortality rate on Day 60, with D1 being the day of randomization. Main secondary endpoints included: mortality on days 30 and 90; in-ICU and in-hospital mortality: probability of survival until D60; mortality on days 30, 60, and 90 and in-hospital mortality considering patients in the control group that received rescue ECMO as treatment failure (i. e. deceased on the day they received ECMO); mortality on days 30, 60, and 90 and in-hospital mortality using a per-protocol analysis, comparing patients who received ECMO vs. others.

Sample size

The expected D60 mortality rate was 60% for the control group receiving conventional mechanical ventilation and 40% for those receiving early ECMO support. For 80% power, a 5% α-risk and group sequential analysis every 60 subjects, the maximal sample size to be included, calculated with the two-sided single triangular test, was 331 subjects.

Trial status

Patient inclusion started in December 2011. The DSMB met four times after the inclusion of 60, 120, 180, and 240 subjects, following which it recommended in April 2017 stopping recruitment once 249 patients had been randomized.

Conclusion

Publication of the results of the CESAR trial and favorable outcomes of patients with severe H1N1-associated ARDS reignited interest in VV-ECMO in severe respiratory failure. However, since the CESAR study was criticized for methodological limitations and due to the fact that results of non-randomized case series of ECMO are prone to selection biases, indications for ECMO use remain highly controversial [28–30]. Before widespread application of this technique, more data are needed to evaluate the true impact of ECMO in this setting. This was the main objective of the international multicenter randomized Extracorporeal Membrane Oxygenation for Severe Acute Respiratory Distress Syndrome (EOLIA) trial, which 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 all patients randomly assigned to receive this treatment. Results of the EOLIA trial are eagerly awaited in the first quarter of 2018.

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Compliance with ethical guidelines

Conflict of interest. A. Combes has received lecture fees from Baxter and Maquet Getinge. A. Combes is the primary investigator of the EOLIA trial (NCT01470703), partly supported by Maquet Getinge. N. Bréchot, C.-E. Luyt, and M. Schmidt declare that they have no competing interests.

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