Extracorporeal membrane oxygenation in adult patients with acute respiratory distress syndrome.

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EXTRACORPOREAL MEMBRANE OXYGENATION IN ADULT PATIENTS WITH ARDS

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ABSTRACT

Purpose of the review

Examine the role of ECMO as potential therapeutic option for severe cases of ARDS.

Recent findings

Use of ECMO to treat acute respiratory failure dramatically increased. Factors that may explain this increase in the use of ECMO are H1N1 pandemic influenza, results of recent clinical trials and not lastly the technological development and consequently the commercial pressure of the industry. Under these circumstances clinicians urgently need clinical trials and formal indication, contra-indication and rules for implementation to provide reproducible results.

Summary

Guidelines from the Extracorporeal Life Support Organization (ELSO) still indicate ECMO for acute severe pulmonary failure potentially reversible and unresponsive to conventional management. The new definition of ARDS (*Berlin definition*) addresses clinicians to the best treatment options in respect of the severity of illness and allocate ECMO as a potential therapeutic option for patients with severe ARDS and a P/F ration lower than 100 and proposed that the indication of ECMO may be shifted from the treatment of choice for refractory hypoxemia to the treatment of choice to minimize ventilator induced lung injury.

Keywords:

ECMO, ARDS, Berlin definition, rescue therapy, refractory hypoxemia.

INTRODUCTION

In the recent years, the use of extra-corporeal membrane oxygenation (ECMO) to treat acute respiratory failure has dramatically increased even if evidence of benefit on mortality from large randomized clinical trial is still lacking.[1] Hirshberg and coworkers showed that in the US from 1996 to 2006 the use of ECMO stably remained around 100 cases a year, but in 2009 it increased dramatically up to 400 patients per year.[2**] Factors that may explain this increase in the use of ECMO are (a) the H1N1 pandemic influenza [1]; (b) the publication of the results of a recent randomized clinical trial [3]; (c) the technological development of ECMO devices. [4, 5].

During the H1N1 pandemic, hundreds of ARDS patients worldwide received ECMO. The Australian and New Zealand network reported 68 patients with suspected H1N1-associated ARDS treated with ECMO with 71% of survival to ICU discharge.[6] The Italian ECMO network reported 60 patients with a survival of 77% in patients receiving ECMO within 7 days from the onset of mechanical ventilation.[7] Conventionally, patients with ARDS need ECMO for a short-term respiratory or respiratory-circulatory associated support as a therapeutic option that may restore oxygenation when "conventional" supportive therapy fails. A more extended use would indicate ECMO as a total or partial alternative to mechanical ventilation to minimize ventilator-induced lung injury (VILI).

In the present chapter we will (***a***) describe the basic technological and physiological principles of ECMO; (***b***) discuss the current "conventional" indication as supportive therapy for hypoxemia refractory to standard treatments; (***c***) examine

the possible “non-conventional” use of ECMO as partial or total alternative to mechanical ventilation.

What is ECMO?

Basic characteristics of extra-corporeal devices are described in details somewhere else. [8-10] ECMO-devices conventionally used in patients with ARDS require vascular catheters with high diameter and wire-reinforced thin walled to minimize flow resistances and reduces the incidence of kinking. The modern oxygenators are made with polymethylpentene fibers that present low resistance, lesser incidence of thrombocytopenia and lower consumption of blood products and are connected to an oxygen source. These new devices are capable of oxygen delivery (3ml/Kg/min) and CO_2 removal (3-6 ml/Kg/min) equal to the normal metabolism of the patient.[5] In general with ECMO, blood flow and FiO_2 are the main determinant of arterial oxygenation while CO_2 elimination depends on sweep gas flow through the oxygenator. Other factors that influence oxygen transfer are blood-oxygen saturation in the ECMO drainage cannula, haemoglobin concentration and intrinsic membrane-oxygenator properties, which depend on exchange-membrane surface and O_2 diffusibility through hollow microfibers. In this case total support devices are able to completely supply the physiological blood gas exchanges normally performed by the native lungs. Blood should be re-infused in the aorta (in case of arterial-venous bypass) or in the right atrium (for veno-venous bypass) to obtain respectively cardiac and respiratory or only lung function support. It is also necessary to use high heparin doses and elevated volumes of priming for the device for proper function. A ratio between ECMO flow and cardiac output > 60 % can be

constantly associated with adequate blood oxygenation, oxygen transport and delivery.[11] The ECMO device can be "undersized" to remove CO_2 (partial extracorporeal support: $ECCO_2$-R). The ability to remove CO_2 correlates with the level of blood flow level, the characteristics of membrane lung, the sweep gas rate and the patient's basal carbon dioxide production [5, 12, 13]. $ECCO_2$-R may be considered as an intermediate level of technical complexity. Small (14-Fr), usually double-lumen catheters allow a blood flow of 0.3–0.5 l/min, which is constantly guaranteed by a roller non-occlusive pump designed to minimize haemolysis. Blood is driven through an oxygenator membrane, which is connected to an oxygen source of 6–8 l/min. Some devices also include hemofilter in series with the oxygenator, to allow the extraction of plasmatic water that is re-infused in the circuit, in order to lower haematocrit and to prevent blood clotting. A centrifugal pump, which creates a radial flow going through an annular fiber oxygenator, has also been used in other veno-venous $ECCO_2$-R systems. This design maximizes the exchange surface and, therefore, the device efficiency. Both technological implementations are able to remove up to 25% of carbon dioxide production and can transfer no more than 10 ml/min of oxygen. Low doses of heparin (4–18 IU/min) are necessary to avoid clotting occurrence.[12]

During the extracorporeal procedures, complications may arise from malfunction of the device or from patient-related adversities. Technical complications occur in 5% of the treated patients and are represented by pump and cannula malfunction. Regarding patient-related complications, the most frequent is bleeding, which occurs with a frequency of up to 30%, haematological changes during extracorporeal support as haemolysis, coagulation problems with clotting in

the circuit and trombocytopenia due to heparin use or to blood surface exposure.

ECMO as rescue therapy of ARDS

Acute respiratory distress syndrome (ARDS) is characterized by a heterogeneous lung damage with significant variations in severity and consequently in survival. Mortality from severe ARDS in the 1970s was as high as 85–90%, but from 2000 it decreased to 20-40%.[14] Refractory hypoxemia, i.e PaO_2 < 60 mm Hg for at least 1 hour while receiving an FIO_2 of 1.0 is rare and a non frequent cause of death (15 % of ARDS deaths). Use of ECMO to treat refractory hypoxemia was controversial for the last 40 years. In the past, the highly specialized equipment and knowledge required to provide ECMO made this technique available only in few medical centers. In the last decade, vast improvements in technology, made ECMO simpler, less invasive, more biocompatible, inherently safer and relatively cheaper. (Fig.1, 2)

All these technological advances increased the practice of inter-hospital transfer of patients required ECMO: recent reports suggest that the transfer of patients with severe hypoxia to specialized centers is becoming a standard practice.

The CESAR trial is the only published study in the last two decades that evaluated modern ECMO practice. The CESAR study shows that an ECMO-based management protocol significantly improves survival without severe disability, if compared with conventional mechanical ventilation. The absolute risk reduction for the primary outcome (death or severe disability) was 16%, which translates to a NNT of 6 patients.[17] Major bias of the study are represented by inter-site variations of mechanical ventilation strategy (the condition of patients in the conventional arm did

not get a standardized ventilatory treatment) and the "centre experience" led to an improved outcome in patients randomized in the ECMO arm.

Referral networks of selected intensive care units able to provide advanced respiratory care for patients with ARDS, up to extracorporeal membrane oxygenation, started with the emergency of H1N1 influenza.[8] In the Italian ECMO network experience, clinicians planned two complementary strategies to minimize risks associated with patient transport: a) indication to move patients towards specialized centers based on a risk anticipation principle: clinical criteria for the transfer were chosen to allow the mobilization in advance of the as large as possible proportion of patients potentially at risk of severe respiratory deterioration; b) identification of precise criteria to place the patients under the responsibility of expert teams, able to place ECMO and then provide safe transportation of the patient with ECMO towards the referral center. In the 2011 Noah et al. compared in a cohort of 80 patients with severe H1N1-related ARDS the hospital mortality of patients referred, accepted, and transferred for ECMO with matched patients who were not referred for ECMO in the United Kingdom during the H1N1 pandemic in winter 2009-2010. The hospital mortality rate was 23.7% for ECMO-referred patients vs 52.5% for non–ECMO-referred patients.[18] A subsequent study from the French Research Network identified new factors associated with survival in ECMO patients (age, lactate, and plateau pressure). Authors analyzed factors associated with in-ICU death in ECMO recipients and the potential benefit of ECMO using a propensity score–matched (1:1) cohort analysis. Mortality was not different between the two matched cohorts but authors signaled that 51 ECMO patients who could not be matched were younger, had lower PaO_2/FIO_2 ratio, had higher plateau pressure, but

also had a lower ICU mortality rate, than the 52 matched ECMO patients (22% vs. 50%).[19]

A special warning should be raised for patients with severe ARDS caused by sepsis or septic shock with an higher cardiac output and impaired peripheral oxygen extraction. In these situations, even ECMO flow up to 6 L/min might not achieve adequate blood oxygenation and O_2 delivery particularly if the pulmonary gas-exchange capacity is severely impaired. When blood oxygenation and SaO_2 and O_2 delivery remain low despite maximal ECMO flow, clinicians should consider to increase the threshold of blood transfusion to a value of haemoglobin of 10 g/dL.

ECMO TO PREVENT VENTILATOR INDUCED LUNG INJURY

Mechanical ventilation (MV) is a lifesaving treatment delivered in various settings. The thought of artificially inflate the lung with air has been considered and mentioned since the ancient Egyptians and in the Bible, as nicely described by Baker in his "Artificial respiration, the history of an idea" [20]. Interestingly, the paper that provided the first formal description of MV as a clinical tool, anticipated the possibility of replacing the function of the lung by extracorporeal means by trying "*whether the suffering the Blood to circulate through a vessel, so as it may be openly exposed to the fresh Air, will not suffice for the life of an animal*" [21].

V_T of 6 ml/kg predicted body weight (PBW) and end-inspiratory plateau pressure (P_{PLAT}) of a maximum of 30 cm H_2O represent the gold standard of mechanical ventilation in ARDS patients [14]. However, it is still unclear whether tidal volume as low as 6 mL/kg and plateau pressures <30 cmH_2O are safe enough or an additional reduction of these threshold would further reduce VILI and improve the

survival rate. Along this line of research, Terragni and colleagues demonstrated with CT scan of the chest that about one third of patients with severe ARDS, although ventilated with tidal volumes of 6 mL/kg of predicted body weight, had evidence of alveolar overdistension. [22] Accordingly, Hager and colleagues showed that a plateau pressure of 30 cmH_2O in some patients may not be safe and suggested that the lower the plateau pressure the lower the mortality rate [23]. This further reduction in VT and Pplat may theoretically be managed by two different kinds of extracorporeal support: (a) Extra-Corporeal CO_2 Removal ($ECCO_2$-R or partial ECMO support) [4, 5]; (b) total ECMO support in which clinician can select the right ventilatory setting increasing the blood flow from two liters (to remove total CO_2) to 5-6 liters in cases of severe hypoxemia. [7-10]

The use of ECMO to "rest the lung" was first tested by Gattinoni and coworkers who showed that ECMO was associated to an observed mortality rate of 51%, significantly lower than what predicted in these patients [24]. Unfortunately, the study did not have a control group. Moreover, the authors reported a significant incidence of adverse effects, such as blood loss in the circuit, need of blood transfusion (~1800 ml per day) and bleeding from the insertion site of the catheters of the extracorporeal circuit. Morris et al. published a randomized clinical trial comparing pressure controlled inverse-ratio ventilation with an extracorporeal CO_2 removal technique in patients with ARDS. However, no significant difference in survival was found between the mechanical ventilated patients and those treated with the extracorporeal CO_2 removal strategy [25].

More recently, a pumpless extracorporeal technique (interventional Lung Assist: iLA NovaLung GmbH, Hechingen, Germany), has been proposed for the

treatment of patients with critical hypoxia/hypercapnia [26]. A membrane with high efficiency in CO_2 removal is placed in an artero-venous extracorporeal circuit (usually between the femoral artery and the femoral vein). Blood flow is driven by the artero-venous pressure gradient through a very low-resistance heparin coated circuit and, therefore, it cannot be controlled, but depends only on the hemodynamic features of the patient. Moreover, similarly to the ECMO technique, the arterial cannulation can induce lower limb ischemia if the use of this device is required for prolonged period of time. These limitations may reduce the clinical indication for this very promising strategy. The efficacy of a new minimally invasive CO_2 removal technique using an extracorporeal membrane gas exchanger placed into a veno-venous pump-driven bypass has been evaluated in severe ARDS patients [27]. The main features of this system are a lower blood flow (191–422 ml/min - 5–10% of cardiac output), a small neonatal membrane lung (0.33 m^2) instead of two large adult membrane lung (3 - 4.5 m^2 each), the use of smaller (14-French) double-lumen catheters, and a relatively small infusion rate of heparin (3–19 IU/kg). This minimally invasive CO_2 removal technique efficiently and safely contributed to the correction of the respiratory acidosis consequent to the significant reduction of tidal volume in subjects with severe ARDS, allowing a more protective ventilation strategy.

A recent trial from Bein and coworkers demonstrated the efficacy of ventilation with very low tidal volume (<3 ml/kg PBW) combined with a pumpless arterial-venous extracorporeal technique device in improving clinical outcome in ARDS patients with a PaO2/FIO2 <150. [28*] This trial confirms the feasibility and the potential efficacy of a "super protettive" ventilatory strategy that combines very

low tidal volume with extracorporeal elimination of carbon dioxide as previously reported by Terragni and colleagues in 2009.[12]

CONCLUSIONS

Successful clinical trials with statistical significance are difficult to perform in intensive care patient populations. Involving highly specialized treatments, studies on critical care lack of clear definitions and classification of their critical clinical conditions.

Identification of patients with more severe respiratory diseases could be crucial to evaluate treatment in more homogeneous populations. For this reason, a revised definition of clinical criteria for ARDS, the "*Berlin definition*", was recently established to classify patients according to their disease severity. [29, 30**] ARDS was classified depending on oxygenation as mild, moderate, or severe if PaO2/FiO2 was, respectively, between 201 and 300 mm Hg, 101 and 200 mm Hg, or 100 mm Hg or less, using a minimal PEEP level of 5 cm H2O. Oxygenation criteria were well correlated to severity, with a mortality corresponding to 27, 32, and 45% in mild, moderate, and severe ARDS. These news P/F thresholds chosen for the different levels of ARDS severity could be helpful in categorizing patients with respect to different therapeutic approaches identifying a P/F ratio ≤ 100 mm as main entry criteria for trials testing ECMO in severe ARDS.[29]

The "EOLIA" trial (ECMO to rescue Lung Injury in severe ARDS; ClinicalTrials.gov NCT01470703) and the SUPERNOVA trial (A **S**trategy of **U**ltra**P**rotective lung ventilation with **E**xtracorporeal CO_2 **R**emoval for **N**ew-**O**nset moderate to se**V**ere **A**RDS; ESICM trial group-registration on going) have been

designed according to these principles. The former will evaluate the impact of ECMO, instituted early after the diagnosis of ARDS not evolving favorably after 3-6 hours under optimal ventilatory management and maximum medical treatment, on the morbidity and mortality associated with this disease, the latter will evaluate whether a strategy of enhanced lung-protective (lower tidal volume, lower pressure) ventilation, along with control of the ensuing hypercapnia using the latest generation $ECCO_2R$ devices, will improve clinical outcomes compared with standard-of-care lung-protective ventilation in patients with moderate ARDS.

Conflicts of interest

The authors do not have any financial relationship with a commercial entity that has an interest in the subject of this article and did not receive any grant for writing it.

Fig.1

Use of ECMO to treat refractory hypoxemia.

Patient on V-V ECMO (A) for primary graft failure (PGF) and severe associated ARDS, following one-lung transplantation.

PGF represents a severe form of ischemia-reperfusion lung injury to the lung allograft occurring in the early post-transplant period characterized by diffuse alveolar opacities (developing within 72 h of transplantation) and an arterial partial pressure of oxygen/fraction of inspired oxygen (PaO2/FIO2) ratio of < 100 (beyond 48 h postoperatively). [15]

Different value of compliance between the right (transplanted) and the left (native) lung needed independent lung ventilation (ILV) with two different ventilatory

strategies: High-Frequency Oscillatory Ventilation (HFOV) (B) in the transplanted lung to recruit the lung and protective low volume ventilation (C) in the native lung.[16]

Fig.2

Radiographic feature of primary graft failure in severe ARDS patient following one-lung transplantation.

A case of Independent High-Frequency Oscillatory Ventilation in the management of asymmetric ARDS: right transplanted (T) and the left native lung (N).

ILV is often applied in asymmetric lung injury because application of tidal inflation and PEEP to the heterogeneous lung may overdistend the uninvolved lung and divert pulmonary blood flow to the injured lung area, thus worsening ventilation/perfusion mismatch.[16]

KEY POINTS

1. In the last decade, vast technical improvements in technology have made ECMO practice much simpler, less invasive, more biocompatible, inherently safer and relatively cheaper.
2. The advances in technology and clinical practice, especially after the H1N1 pandemic influenza experience, have convinced clinicians to extend ECMO support to others fields such as severe bridge to lung transplant, COPD, ARDS combined with intracranial bleeding, asthma, and also to facilitate the use of **"***ultra-protective"* MV in severe ARDS (employing V_T <6 ml/kg PBW and lowering airway pressures) minimizing the risk of VILI.
3. To date, a standardized selection criteria for patients who will benefit from ECMO therapy does not yet exist, a future trial aimed to test a defined protocol with clear patient selection criteria and no crossover treatments would clarify the validity of ECMO support in ARDS patients.

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