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RÉFÉRENTIEL / *GUIDELINES*

ECMO, $ECCO_2R$: From Origins to Date

ECMO et $ECCO_2R$: des origines à aujourd'hui

L. Gattinoni

Abstract This article reviews the history of extracorporeal membrane oxygenation (ECMO) from the first successful case reported at the beginning of the seventies till the recent extensive ECMO use in the intensive care unit to treat acute respiratory distress syndrome, especially following the 2011 H1N1 flu epidemics. ECMO development was contemporary with the improvements in ARDS ventilation and the development of various complementary techniques including extracorporeal CO_2 removal ($ECCO_2R$). However, despite the evidence already obtained, the definitive benefit and indications of ECMO to treat ARDS remain to be established. The history is still continuing.

Keywords Acute respiratory distress syndrome · ECMO · Extracorporeal CO_2 removal · History

Résumé Cet article présente une mise au point historique sur les développements de l'*extracorporeal membrane oxygenation* (ECMO) depuis le premier patient traité avec succès dans les années 1970 jusqu'à l'utilisation plus répandue de nos jours de la technique dans les services de réanimation pour traiter les patients en syndrome de détresse respiratoire aiguë (SDRA), notamment suite à l'épidémie de grippe H1N1 de 2011. L'histoire de l'ECMO est contemporaine des progrès de la ventilation mécanique du SDRA et du développement de techniques complémentaires dont l'*extracorporeal CO_2 removal* ($ECCO_2R$). Néanmoins, malgré les preuves d'intérêt déjà obtenues, le bénéfice définitif et les indications exactes de l'ECMO dans le SDRA restent encore à établir. C'est ainsi que l'histoire continue.

Mots clés Syndrome de détresse respiratoire aiguë · ECMO · Épuration extracorporelle de CO_2 · Histoire

Introduction

The enthusiasm risen by first successful extracorporeal membrane oxygenation (ECMO) at the beginning of the seventies by Hill et al. [1] led to the first large randomized trial launched in 1974 to compare veno-arterial (VA) ECMO versus conventional support with mechanical ventilation in patients with adult acute respiratory distress syndrome (ARDS) [2]. This trial was stopped for futility in 1975, before completion. Dr. Kolobow, at the National Institute of Health (NIH), was studying a new membrane lung with greater surface exchange and thinner membrane to optimize CO_2 removal, later called carbon dioxide membrane lung (CDML) [3]. The underlying hope was that an intermittent CO_2 dialysis could potentially improve the clinical scenario of chronic obstructive pulmonary diseases (COPD) patients. As a new fellow of Dr. Kolobow at the NIH, between 1975 and 1977, I was responsible for testing the performances of the CDML in awaken sheep, by measuring the CO_2 input and output across the membrane lung, as well as the CO_2 removed as gas from the exhalation port of the membrane lung. As I was curious to see the respiratory response of the spontaneously breathing awaken sheep during CO_2 removal, through a closed respiratory circuit, I measured the minute oxygen consumption and the CO_2 exhaled from the animal. The strong relationship between the CO_2 removed by the artificial lung and the CO_2 exhaled by the sheep was immediately evident. The metabolic CO_2 production of healthy sheep almost being constant, it became clear that the CO_2 exhaled by the sheep decreased proportionally to

L. Gattinoni (✉)
Dipartimento di Fisiopatologia Medico-Chirurgica e dei Trapianti, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico di Milano, Via Francesco Sforza, 35, 20122 Milano, Italy
Dipartimento di Anestesia, Rianimazione ed Emergenza Urgenza; Fondazione IRCCS Ca' Granda - Ospedale Maggiore Policlinico, Milan, Italy
Dipartimento di Fisiopatologia Medico-Chirurgica e dei Trapianti; Università degli Studi, Milano, Italy
e-mail : gattinon@policlinico.mi.it

the CO_2 removed by the membrane lung, up to complete apnea, when the CO_2 clearance of the artificial lung approached the metabolic production of CO_2. Oxygenation was provided by diffusion through the natural lung. The first set of experiments was published in *Anesthesiology,* and the title of the paper focused on the capability of the membrane lung to control the spontaneous breathing [4]. The idea of CO_2 dialysis in COPD patients was abandoned, and extracorporeal CO_2 removal ($ECCO_2R$) was extensively studied in experimental animals with the aim of applying it in ARDS patients in order to provide complete or partial lung rest. Therefore, between 1976 and 1980, a series of physiological studies explored the potential for CO_2 removal, its physiology, and the relationship between artificial and natural lungs. The best set we identified was the one providing complete CO_2 clearance associated to 2–3 breath/minute to maintain lung volumes, while oxygenation was primarily performed by 200–300 ml/minute of pure oxygen insufflated into the trachea. The technique was called low-frequency positive pressure ventilation with extracorporeal CO_2 removal (LFPPV-$ECCO_2$-R) [4–7]. The first patients were treated in Milan, and the first successful $ECCO_2R$ was presented in a poster session during an intensive care meeting in Paris in 1980. Curiously, this first successful CO_2 removal, presented as poster, had as neighbor poster the first report of Lachmann on inverse ratio ventilation (both posters were completely neglected).

The first experiences with LFPPV-$ECCO_2$-R performed in three patients with ARDS were published in *The Lancet* in 1980 [7], and 6 years later we reported the results obtained in a group of 43 patients in *JAMA*. We found that more than 70% (31) of the patients improved lung function and 21 patients eventually survived [8] without major technical accidents in more than 8,000 hours of perfusion. Therefore, we concluded that this technique could be a reliable alternative to conventional treatments. These results led to major investigations into the technological development of extracorporeal support devices [9]. In 1984, we reported a strict association between the need of LFPPV-$ECCO_2$-R and total static lung compliance (TSLC) in a group of 36 ARDS patients meeting mortality rate criteria (90%) as defined in the Zapol ECMO trial [2]. TSLC was the only predictive value of success or failure of the management of severe ARDS patients unresponsive to conventional treatment [10]. We found that patients with TSLC lower than 25 ml/cmH_2O did not tolerate pressure-controlled inverse ratio ventilation (PC-IRV) or continuous positive airway pressure (CPAP), patients with TSLC higher than 30 cmH_2O were successfully treated with CPAP, while the other patients (TSLC comprised between 25 and 30 cmH_2O) had to be treated with PC-IRV for more than 48 hours, or were then placed on LFPPV-$ECCO_2$-R if $PaCO_2$ rose prohibitively. The results of the study became clear after the introduction of quantitative computed tomography (CT)-scan analysis for the evaluation of respiratory failure. It was shown, in fact, that the TSLC is strictly related to the size of the injured lung that is still viable for ventilation, which, at TSLC around 25 cmH_2O has the size of the normal lung of 2–3-year child ("baby lung"). Therefore, we found that the ARDS lung is not stiff but just small [11]. In the nineties, as reported by the Extracorporeal Life Support Organization (ELSO) registry, ECMO was mainly dedicated to the treatment of neonates with respiratory failure unresponsive to conventional treatment.

The results of the second randomized clinical trial on extracorporeal support were published in 1994 by Morris et al. [12]. The authors compared the effects of pressure-controlled inverse ratio ventilation followed by LFPPV-$ECCO_2R$ to positive pressure ventilation in 40 ARDS patients (21 $ECCO_2$-R patients and 19 mechanically ventilated). The study was stopped for futility, and the survival rates were not significantly different in the two groups (33% vs 42% in the control group, $P = 0.8$), despite mortality was impressively improved compared to the seventies. The study rose a lot of criticism for little experience with the technique in humans, the use of high pressure [positive end-expiratory pressure (PEEP) and peak] ventilation, and the elevated number of bleeding complications. The research in the field stopped until the new century when another prospective randomized trial on the efficacy and economic assessment of ECMO versus conventional mechanical ventilation was conducted in the United Kingdom between 2001 and 2007 (CESAR trial) [13]. The results were published in 2009 in *The Lancet*. The treatment arm of the study was treated at Glenfeld Hospital, a single high volume center capable of treating patients with ECMO. The control group was treated at the hospital on admission or at the nearest one participating to the study. The primary endpoint of the study, the survival at 6 months free of disabilities, was 63% in the ECMO-referred patients (75% of them actually received ECMO) versus 47% in control group. The study was criticized for the randomization of the patients and for the lack of information on the ventilation settings in the control group; however, the most important result was that the treatment of patients affected by respiratory failure unresponsive to conventional treatment in an high volume center with ECMO capabilities can significantly improve survival.

The H1N1 flu pandemics of 2009 caused an impressive increase of the number of patients characterized by acute pneumonia with severe hypoxemia that were considered not safely ventilatable even with safe mechanical ventilation criteria. The experience of Australian and New Zealand investigators [14] led to renewed interest for extracorporeal support and hundreds of ARDS patients worldwide received ECMO. The authors reported that the proper rescue therapy for life-threatening hypoxemia was high flow veno-venous

(VV) bypass and the overall mortality rate was 21%. After this report, and also due to political support, several countries in Europe, United States, South America, Canada, and Asia faced the pandemic using ECMO as maneuver to buy time while waiting for the resolution of the underlying pathology [15–20]. Obviously, the use of ECMO without a scientific background was criticized as the only evidence for ECMO application was the presence of sever life-threatening hypoxemia in patients untreatable with conventional mechanical ventilation.

In Italy, the Italian Health Authorities set up a national referral network (ECMOnet) of 14 selected intensive care units able to provide ECMO to face the H1N1 flu pandemic [21]. Two clinical experts coordinated the communication between the authorities and the net and organized the operations. A call center service was set up to grant the communication between hospitals and the referral centers and a series of training courses were performed. A list of recommended national clinical criteria for early patient centralization and for ECMO eligibility was written up. Between August 2009 and March 2010, 153 patients were admitted to the 14 centers with suspected H1N1. Sixty patients were treated with ECMO; among them 49 patients had ARDS caused by H1N1, while 11 patients had ARDS because of other causes. Overall survival at hospital discharge was 41/60 (68.3%), while survival for confirmed H1N1 was 35/49 (72%) versus 6/11 (54%) for non-confirmed H1N1. One patient died of cerebral hemorrhage, 16 patients had hemorrhagic complications, and 10 of them had major bleeding events but none of them stopped the treatment. Concerning the ventilatory strategy, the setting was left to the referral center. In several centers in Italy, ventilatory support was characterized by very low tidal volume and respiratory rate limited to 7–8 breath/min with high mean airway pressure due to high PEEP. In Milan, patients are initially treated with high PEEP (above 15 cmH_2O) and low frequency ventilation. In 2011, a study published in *JAMA* by Noah et al. compared the hospital mortality of patients affected by H1N1-related ARDS treated with ECMO in one of the four adult ECMO centers in the United Kingdom during the pandemic with matched patients who were not referred for ECMO from the Swine Flu Triage study [22]. The hospital mortality rate was significantly lower in ECMO-referred patients compared to non-ECMO-referred patients. This study further reinforced the result that new generation devices and the promotion of support from experienced centers seems relevant for a successful ECMO treatment and to reduce hospital mortality.

It must be pointed out, however, that under the umbrella of ECMO, different techniques are included, from the vascular approach, VV vs. veno-arterial (VA), to the blood flow available (low or high, depending primarily on the diameter of the catheters). The classical ECMO to provide sufficient oxygenation requires very high flow (greater than 3 liters). A strict removal of CO_2 requires lower flow (below 1.5 liters). The choice depends only on the goals that one desires to reach. We prefer to use larger catheters even for CO_2 removal to be prepared for possible deterioration of oxygenation, and we reserve VA cannulation only to patients with heart failure.

At the time we are writing, the "Extracorporeal Membrane Oxygenation for Severe Acute Respiratory Distress Syndrome (EOLIA)" (NCT01470703) is currently recruiting participants. The goal of the study is to evaluate the impact on morbidity and mortality of VV-ECMO instituted early after the diagnosis of ARDS not evolving favorably after 3–6 hours of optimal treatment.

It is interesting to note the evolution of the technique since the first ECMO trial. After its failure, only few centers continued to use the membrane lung support, shifting its focus from oxygenation to the control of ventilation to decrease/abolish lung injury. It is worth noting that the entire approach was physiology-based as the evidence was lacking. We cannot ignore, however, the difficulties to provide this evidence through a formal randomized trial. If we consider, as an example, an exceptional absolute survival rate improvement of 20% in severe ARDS (the only indication for membrane lung in this syndrome) the number of patients required should be roughly of 390/arm, considering a baseline mortality of 50%. Note that the enrollment rate in the ARDS trials is about 0.3/unit/month, being lower if we limit to severe ARDS, which is 20–30% of the total ARDS population. That is, the time required for such a study, including 20 ECMO centers enrolling severe ARDS, would last 17 years. In this scenario (the CESAR trial lasted about 10 years), the H1N1 influence occurred. As Dr. Bartlett wrote to me, "the pigs did for ECMO more than whatever randomized trial." Although the Australian colleagues used ECMO primarily as rescue therapy for hypoxemia, the pandemic led to a worldwide renaissance of the technique, with the same "evidence" of benefit available 30 years ago, that is, nil. However, this ECMO explosion was due to combination of emotions, political interventions, for which several countries including Italy provided money for the ECMO program. After the pandemic, the ECMO story continued, as the people who used this technique realized how powerful it is, in ARDS and in other clinical situations, as COPD re-exacerbation and lung transplant programs, even introducing the use of spontaneous breathing. It is also interesting to realize how different countries reacted to ECMO renaissance. Only four centers were established in the United Kingdom, 14 were introduced in Italy based on previous experience and/or geographical location to cover the territory and were confirmed after the H1N1 pandemic. In Germany, no official rules were established introducing ECMO centers and 90 hospitals are equipped to provide such a support (personal communication of prof. Quintel). This indicates a certain level of

uncertainty on when, how, and where to use this technique. Time will answer and the story continues.

Conflict of interest: Dr L. Gattinoni don't have any conflict of interest to declare.

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