
Extracorporeal CO₂ Removal

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Abstract

The extracorporeal carbon dioxide removal (ECCO₂R) concept, used as an integrated tool with conventional ventilation, plays a role in adjusting respiratory acidosis consequent to tidal volume (V_t) reduction in a protective ventilation setting. This concept arises from the extracorporeal membrane oxygenation (ECMO) experience. Kolobow and Gattinoni were the first to introduce extracorporeal support, with the intent to separate carbon dioxide removal from oxygen uptake; they hypothesized that to allow the lung to ‘rest’ oxygenation via mechanical ventilation could be dissociated from decarboxylation via extracorporeal carbon dioxide removal. Carbon dioxide is removed by a pump-driven modified ECMO machine with veno-venous bypass, while oxygenation is accomplished by high levels of positive end-expiratory pressure, with a respiratory rate of 3–5 breaths/min. The focus was that, in case of acute respiratory failure, CO₂ extraction facilitates a reduction in ventilatory support and oxygenation is maintained by simple diffusion across the patient’s alveoli, called ‘apneic oxygenation’. Concerns have been raised regarding the standard use of extracorporeal support because of the high incidence of serious complications: hemorrhage; hemolysis, and neurological impairments. Due to the negative results of a clinical trial, the extensive resources required and the high incidence of side effects, low frequency positive pressure ventilation ECCO₂R was restricted to a ‘rescue’ therapy for the most severe case of acute respiratory distress syndrome (ARDS). Technological improvement led to the implementation of two different CO₂ removal approaches: the iLA called ‘pumpless arteriovenous ECMO’ and the veno-venous ECCO₂R. They enable consideration of extracorporeal support as something more than mere rescue therapy; both of them are indicated in more protective ventilation settings in case of severe ARDS, and as a support to the spontaneous breathing/lung function in bridge to lung transplant. The future development of more and more efficient devices capable of removing a substantial amount of carbon dioxide production (30–100%) with blood flows of 250–500 ml/min is foreseeable. Moreover, in the future ARDS management should include a minimally invasive ECCO₂R circuit associated with noninvasive ventilation. This

would embody the modern mechanical ventilation philosophy: avoid tracheal tubes; minimize sedation, and prevent ventilator-induced acute lung injury and nosocomial infections.

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Introduction

Since 1979 it is possible to markedly hypoventilate the lung at a rate of 2–4 breaths/min or allow spontaneous but insufficient ventilation to maintain normal arterial blood gases, while the metabolically produced CO₂ is removed by an extracorporeal membrane lung and the oxygen is fed through a tracheal tube or a helmet with continuous positive airways pressure (CPAP) [1, 2].

In 2001 the NIH published a randomized controlled trial that recommended ventilating patients with acute respiratory distress syndrome (ARDS) with a tidal volume (V_t) of 6 ml/kg (predicted body weight) and a maximum end-inspiratory plateau pressure of 30 cm H₂O, in order to prevent ventilation lung damage [3]. Recently published studies show that despite these limitations, a tidal hyperinflation may occur in about the 30% of ARDS patients; furthermore they may benefit from V_t reduction even if they already have a plateau pressure of <30 cm H₂O [4, 5].

Those results support the concept of extracorporeal carbon dioxide removal (ECCO₂R) as integrated to conventional ventilation to adjust respiratory acidosis consequent to very low V_t, and therefore allowing more protective ventilator settings [6]. This approach might also reduce ventilator-induced lung injury that is one of the most important and actual problems in diseased lungs and may allow a wider clinical implementation of the new concept 'less ventilation, less injury' [7].

Extracorporeal CO₂ Removal: The Concept

The basic concepts of the CO₂ removal technique can be extracted from the original description of extracorporeal membrane oxygenation (ECMO) that appeared in the clinical setting more than 30 years ago. At that time, Hill et al. [8] were the first to report the successful use of extracorporeal circulation to treat acute hypoxemic respiratory failure in an adult patient, and Bartlett [9] demonstrated for the first time the successful use of ECMO in a neonate.

In the same period, studies published by Gattinoni et al. [10] introduced extracorporeal support intended to separate carbon dioxide removal from oxygen uptake. Extracorporeal CO₂ removal (ECCO₂R) refers to extracorporeal support focused on the removal of blood CO₂ rather than on the improvement of the oxygenation. Extracorporeal oxygenation was initially designed as a heart-lung machine to render major cardiovascular surgery feasible and safe; this application was not that far from the one suggested by Gattinoni et al. [10]

for the acute respiratory failure. The blood flow levels required to obtain carbon dioxide removal are lower than the ones needed to achieve the oxygenation so Gattinoni et al. [10] exploited the concept that, if CO₂ is removed by a membrane lung through a low-flow veno-venous bypass, it is possible to reduce the ventilatory support in acute respiratory failure and severe ARDS, maintaining oxygenation simply with the patient's alveoli diffusion, also called 'apneic oxygenation', allowing the lung rest. Originally the veno-venous bypass was set out via the cannulation of the common femoral and jugular veins through a surgical cut; the larger lumen needed to be used for venous drainage, the smaller for blood return (toward the tricuspid valve minimizing the recirculation). Wounds and multiple cannulations determined continuous blood oozing, nursing care and patient mobility limitations, therefore the same authors developed a double-lumen femoral vein cannulation technique; with the introduction of newly designed percutaneous cannulas and the Seldinger technique, we arrive at the present technique. The first membrane lungs consisted of microporous polypropylene fibers and were associated with constant plasma leakage that determined the frequent need for membrane substitution and the circuit needed to be heparinized with 100 IU/kg at the cannula insertion. Heparin infusion was hence titrated on activated clotting time (150–200 s).

Gattinoni et al. [10], using this modified ECMO technique (using low frequency positive pressure LFPPV-ECCO₂R), reported ARDS survival of 49%, which was also attributed to patient selection, strict control of coagulation, and ventilator management directed to reach the 'lung rest' [11]. Anderson et al. in 1993, demonstrated 47% survival in adults with severe respiratory failure. In a retrospective review of 100 adult patients, Kolla et al. [12] reported a 54% overall survival. However, despite the later report by Brunet et al. [13] using LFPPV-ECCO₂R to improve oxygenation, reduce pulmonary barotrauma in ARDS and achieve a mortality rate of 50%, in 1994 Morris et al. [14] presented the results of a randomized clinical trial where they used 'conventional' pressure-controlled inverse ratio ventilation compared to ECCO₂R in ARDS patients. The study showed no significant difference in survival between the two interventions and reported several episodes of severe bleeding [14]. ECCO₂R was hence restricted to the sickest patients in whom all other treatments had failed and limited only to centers with large expertise [15].

At the present time, ECMO (fig. 1) with the new technologies (centrifugal blood pump and new polymethylpentene low-resistance diffusion membrane oxygenators) still performs very well in maintaining oxygenation and eucapnia in the most severe ARDS patients with refractory hypoxemia [16]. In this application, survival of >50% can be achieved, whereas sepsis and multiple organ failure are the leading causes of unsuccessful use. Only a minority of patients suffer major complications related to the technique itself, and these serious complications are almost exclusively related to bleeding (particularly intracranial bleeding) [17].



Fig. 1. Centrifugal pump (Rotaflow™, MAQUET Cardiopulmonary AG, Hechingen, Germany): (1) steering and control unit; (2) driveline; (3) pole for volume resuscitation; (4) membrane oxygenator, and (5) centrifugal pump.

Extracorporeal CO₂ Removal: The Clinical Data

The removal of ‘only a portion of carbon dioxide production’ was originally developed by Pesenti et al. [18], and has recently been implemented with new devices that may reduce side effects, complexity, and costs of ECCO₂R. In 1983, Ohtake et al. [19] described a simple method to remove carbon dioxide using arterial blood pressure in an arteriovenous setting including a hollow fiber oxygenator: the ‘pumpless arteriovenous ECMO’.

The system was characterized by a new membrane gas exchange system based on heparin-coated hollow fiber technology that optimized blood flow reducing the resistances and was connected to the patient via arterial and venous cannulas inserted with the Seldinger technique.

The device did not require extended technical and staff support: blood flow is determined by the driving force given by cardiac output, and the mean arterial pressure: 20–25% of the cardiac output passes as a left to right shunt (an ultrasound flow meter might indicate the amount of blood passing per minute). Furthermore, the system used a ‘low-dose’ heparin infusion that

did not exceed normal antithrombotic anticoagulation of the intensive care patient.

These findings lead to the newly designed interventional lung assist (iLA) device. Bein et al. [20] recently reported a retrospective analysis of 90 patients with critical hypoxemia/hypercapnia treated with the iLA device, who, despite ventilation with low Vt (320–470 ml), showed physiologic PaCO₂ (31–42 mm Hg) and pH (7.38–7.50) values. However, the authors reported a complication rate of 24%, including limb ischemia, compartment syndrome, and intracranial hemorrhage. In addition, continuous intravenous norepinephrine infusion was needed to maintain an arteriovenous pressure gradient.

In 2008 Fisher et al. [21] described the new iLA concept of protective ventilation as a bridge to lung transplant: in the Hannover experience 12 patients who developed severe ventilation-refractory hypercapnia and acidosis despite maximal conventional ventilatory support received iLA implantation, obtaining a PaCO₂ level reduction and a significant improvement in pH values. In a recent study, Zimmermann et al. [22] implemented an iLA system in 51 ARDS patients suffering from persistent hypoxemia and/or hypercapnia who were unresponsive to conventional therapy, and achieved de-escalation of invasive ventilatory variables preventing ventilator-induced lung injury.

Although iLA is a simple device that can be established quickly, and has easy monitoring, arterial cannulation is always required which cannot be performed in patients with serious peripheral arterial disease and has the potential risk of inducing limb ischemia. Additionally, the only system driving force is the patient's heart and frequently a continuous intravenous norepinephrine infusion is necessary in order to maintain an arteriovenous pressure gradient.

In the last years, a new concept of CO₂ removal was experimented to reduce complexity, side effects and expenses of extracorporeal lung assistance. Livigni et al. [23] described in an animal model the efficacy and safety of a veno-venous device (ECCO₂R) with a low-flow CO₂-removal system. In 2009 Terragni et al. [6] studied the effects of further decreasing Vt in a group of ARDS patients who developed plateau pressures of 28–30 cm H₂O. The Vt was decreased to 4 ml/kg of predicted body weight, and the predictable consequence of an increase in PaCO₂ was corrected through an extracorporeal circuit. The intervention was safe and produced notable physiologic improvements [6].

This new generation ECCO₂R consists of a modified standard continuous veno-venous hemofiltration setup (Decap[®], Hemodec, Salerno, Italy) that includes an oxygenator in series with the hemofilter. This system is less invasive since the veno-venous circuit is accessed via a double-lumen catheter through a femoral vein, and the blood flow is driven through the circuit by a roller non-occlusive low-flow pump through a membrane lung that is connected to a fresh gas flow source delivering 100% oxygen. Exiting the membrane lung, blood is driven to an hemofilter. The resulting plasmatic water is re-circulated through the membrane lung by a peristaltic pump. The membrane lung and

the hemofilter are coupled in series in order to increase the pressure inside the membrane lung by adding the downstream resistance exerted by the hemofilter and therefore reducing the risk of air bubble formation, minimizing the need for heparin by diluting the blood entering the membrane lung by re-circulating the plasmatic water separated by the hemofilter, and enhancing the performance of the extracorporeal device extracting the carbon dioxide dissolved in the plasmatic water separated by the hemofilter and re-circulated through the membrane lung [6]. Ruberto et al. [24] described the use of this new generation ECCO₂R to assist a patient affected by primary graft dysfunction after a single lung transplantation. Although this system should not be considered a replacement for traditional ECMO because the performances are not comparable in terms of CO₂ removal and especially oxygenation improvement, available data suggest that this 'mini-ECMO' optimized pH values, reduced partial pressure of CO₂ allowing minimization of ventilatory support and therefore minimizing ventilatory-induced lung injury with no adverse events in terms of bleeding, circuit clotting, severe hemodynamic instability, or venous embolism [24].

Extracorporeal CO₂ Removal: The Technological Development

Extracorporeal circulation can be achieved using an oxygenator for the CO₂ removal from its dry form (dissolved CO₂) or a hemodialyzer for CO₂ removal from its wet form [6, 23, 25, 26].

In the artificial lung, the real limiting factor of CO₂ elimination is physiological. The reaction speed of bicarbonate dehydration, and the consecutive rise in the CO₂ concentration in plasma, are very slow. This explains the need to bypass 25% of the cardiac output in order to eliminate metabolic CO₂ production. Oxygenator-associated acidification and hemodialyzer-associated alkalization are methods that facilitate the shifting of the bicarbonate/dissolved CO₂ equilibrium in the respective senses of dissociation (CO₂ partial pressure raised) and hydration (bicarbonate raised). Even if the efficacy of CO₂ removal through hemodialysis (with or without NaOH dialysate alkalization) was higher than the CO₂ elimination obtained through an oxygenator (with or without inlet HCl blood acidification) [25], the latter (without blood acidification) is today the most followed by clinicians in severe acute respiratory failure because of the reduction in the circuit complexity. At the present time, only preliminary data are available from Cressoni et al. [27] and Zanella et al. [28] about the effects of blood acidification to enhance carbon dioxide removal of membrane lung in a swine model. In these studies, the authors demonstrate that blood acidification at the inlet of a membrane lung can significantly increase the CO₂ removal by the membrane lung by converting the blood bicarbonate into physically dissolved CO₂ [27, 28].

For most adult patients with unresponsive severe respiratory failure, veno-venous support is the method of choice, including both ECCO₂R and veno-venous ECMO. If the need of extracorporeal ventilatory support is partial, a new generation of ECCO₂R devices that use arteriovenous pumpless bypass or low-flow venous-venous bypass that can remove only 20–30% of the CO₂ production are available in clinical practice [6, 24, 26].

1. Veno-Venous ECMO

ECCO₂R refers to an extracorporeal support focused on the CO₂ leaching from blood rather than improving oxygenation [1, 29]. In cases of hypoxic/hypercapnic respiratory failure, but preserved cardiac function, a veno-venous ECMO support is preferred to carry over the pulmonary function.

Centrifugal pumps and surface-heparinized (bioline coating) hollow fiber membrane lungs both mounted on a specially designed multifunctional holder represent the state of the art. A flow meter and a bubble sensor are integrated into the pump unit. The tubing circuit consists of a pre-connected, heparin-coated closed-loop extracorporeal circulation system for rapid setup and priming. Total priming volume is 600 ml of normal saline. The centrifugal pump provides non-pulsatile flow rates of up to 4.5 liters/min (depending on the size of the cannula). The circuit needs to be heparinized with 100 IU/kg at the cannula insertion, heparin infusion is titrated on an activated clotting time of 150–200 s, but on a heparinized surface the circuit can work well without any systemic anticoagulation for at least 12–48 h [27]. Before cannulation, usually performed with a modified Seldinger technique, ultrasonic measurement of the femoral vessels is performed to assess the appropriate caliber of the cannula. Depending on the ultrasonic findings and the patient's biometric data, a 17- or 23-Fr cannula must be inserted for venous and a 15- or 17-Fr cannula for arterial vascular access. Outflow is achieved via the femoral vein, and inflow is gained by cannulation of the internal jugular vein or femoral vein and thereafter into the superior vena cava.

Pumpless Arteriovenous Interventional Lung Assist

The iLA (NovaLung® GmbH, Hechingen, Germany) is a single-use compact extrapulmonary gas exchange system perfused by a passive femoral artery-femoral vein shunt, generated by the arterial blood pressure (60–80 mm Hg femoral artery-femoral vein) through a lung-assist device; a blood flow rate of approximately 1.0–2.5 liters/min produces effective CO₂ extraction and an improvement in arterial oxygenation. Apart from an oxygen supply (10–12 liters/min), the system does not require additional energy or substrate sources [20] (fig. 2). A polymethylpentene diffusion membrane resistant to plasma leakage is used as a separation layer between phases (blood/gas). Due to the molecular structure of this layer, the passage of air bubbles from gas to the blood path in the event of negative pressure on the blood side is impossible.

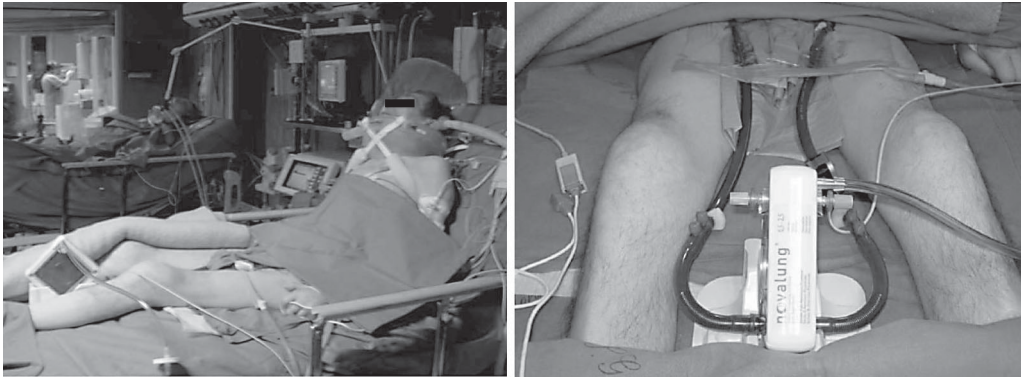


Fig. 2. Interventional lung assist device in place in a patient with CPAP.

The entire effective gas exchange surface area amounts to 1.3 m², integration of a heat exchanger is not necessary as temperature loss due to convection is negligible. To optimize hemocompatibility, the system is entirely (tip to tip) homogeneously treated with the coating method (Novalung Coating, NovaLung GmbH).

To connect the iLA to the patient, a special percutaneous cannulation system has to meet the following conditions: implantable with the Seldinger technique, cannula walls must be extremely thin to minimize resistance to flow and should be available in various diameters (13–21 Fr). In every individual case, the cannula size used is determined by the diameter of the vessel to be cannulated and the required shunt flow, diameter should be measured by ultrasound. Functional control is achieved through a monitoring Doppler device. Weaning from iLA is attempted by a reduction in mechanical ventilation and gas supply to approximately 1 liter/min performed for 30 min.

The frequency of complications reported is actually very high: about 25% serious complications were observed; episodes of ischemia of a lower limb after arterial cannulation were major problems; in other cases of ischemia, the cannulas were removed and normal perfusion of the limb was restored. Cannula thrombosis was only observed in the early period without specially designed cannulas before 2001. The main contraindication for the application of the system is hemodynamic depression. Fischer et al. [21] also reported the application of iLA as a bridge to lung transplant.

Low-Flow ECCO₂R Technique

The Decap® (Hemodec, Salerno, Italy) ECCO₂R device is a modified renal replacement circuit incorporating a neonatal membrane lung coupled in series with a hemofilter (fig. 3). Vascular access is granted by the femoral vein and via a

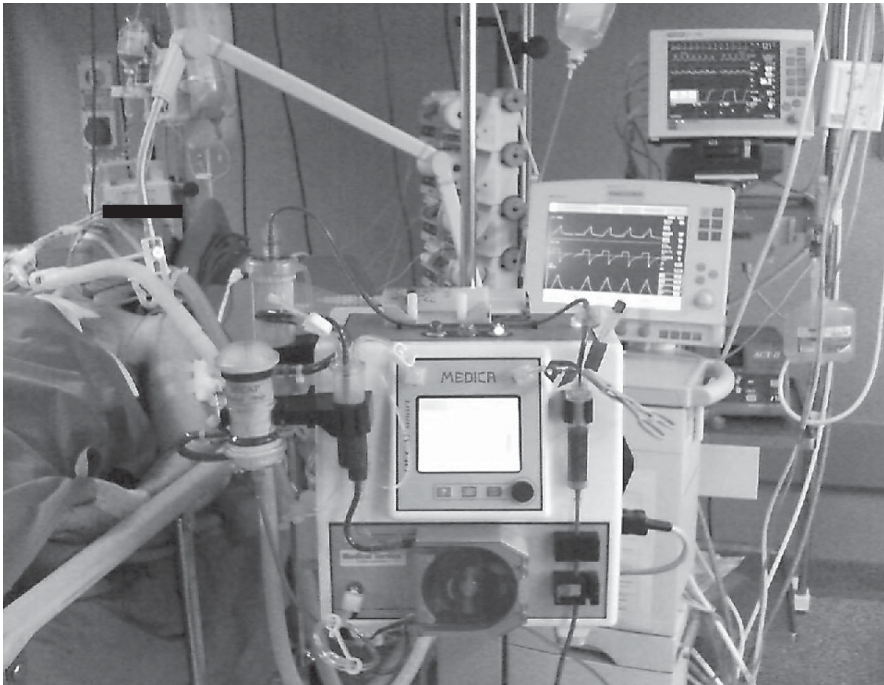


Fig. 3. Extracorporeal carbon dioxide-removal device (Decap® Hemodec, Salerno, Italy). The system consists of a standard continuous veno-venous hemofiltration system equipped with a membrane lung with a total membrane surface of 0.33 m².

double-lumen catheter with a 14-Fr diameter inserted using the Seldinger technique. Blood flow is driven by a roller non-occlusive low-flow pump (maximum flow 450 ml/min) through a membrane lung connected to a fresh gas flow source delivering 100% oxygen at a constant rate of 6 liters/min. Exiting the membrane lung, blood is driven to an hemofilter and the resulting plasmatic water is re-circulated through the membrane lung by a peristaltic pump (0–155 ml/min). Detectors of leaks and bubbles are inserted within the circuit. The circuit, including the membrane lung, is primed with saline at a volume that ranges between 140 and 160 ml. The new concept introduced by this newly designed technique is that the membrane lung and the hemofilter are coupled in series. This characteristic of the circuit increases the pressure inside the membrane lung by adding the downstream resistance exerted by the hemofilter and therefore reduces the risk of air bubble formation; minimizes the need for heparin by diluting the blood entering the membrane lung by re-circulating the plasmatic water separated by the hemofilter; produces a performance enhancement of the extracorporeal device extracting the carbon dioxide dissolved in the plasmatic water separated by the hemofilter and re-circulated through the membrane lung [6, 23, 24, 26].

Extracorporeal CO₂ Removal: The Future

The NIH protocol represents the standard for mechanical ventilation of ARDS patients, recommending the use of a low Vt of 6 ml/kg (predicted body weight) and an end-inspiratory plateau pressure of a maximum of 30 cm H₂O [3]. Despite these ventilatory limitations, tidal hyperinflation may occur in up to 30% of ARDS patients who could benefit from an additional Vt reduction [4]. In this scenario, extracorporeal lung support may play a role integrating conventional care and allowing the use of more protective ventilator settings. The concept of removing 'only a portion of carbon dioxide production', originally developed by Kolobow et al. [29], has recently been implemented in new devices that may reduce side effects, complexity, and costs of ECCO₂R.

Terragni et al. [6] effectively and safely managed respiratory acidosis consequent to a Vt of <6 liters/kg predicted body weight and reestablished normal arterial pH through an ECCO₂R technique. The system, at 380 ml/min blood flow, could allow a PaCO₂ reduction of approximately 20% at constant ventilation [6]. Therefore, the key for a revolutionary approach to ARDS ventilatory management, is shifting from invasive mechanical ventilation to the application of low extracorporeal blood flow combined with high efficiency ECCO₂R as lung support.

Venous blood contains large amounts of carbon dioxide, most carried as bicarbonate ion (approximately 500 ml/l of carbon dioxide under normocapnic conditions) and with a blood flow through the extracorporeal circuit of 500 ml/min, the Vt could theoretically be reduced to zero. From these preliminary clinical data (waiting for additional studies to further confirm these results), with the development of very efficient devices capable of removing a substantial amount of carbon dioxide production (30–100%) with blood flows of 250–500 ml/min we could assume the possibility of avoiding endotracheal intubation, with related complications such as pulmonary infections and need of sedation. In this way, severe ARDS patients could be managed without any form of mechanical ventilation, simply providing enough positive airway pressure to keep the lung open and high FiO₂ to avoid hypoxemia, as a bridge to recovery from pulmonary disease.

Conclusions

With improved technology and experience, low extracorporeal blood flow with high performance ECCO₂R may be the key to management of severe ARDS with a new respiratory support, shifting from invasive mechanical ventilation to the application of extracorporeal lung support, similar to renal support. Lung-protective ventilatory strategies with new solutions to remove CO₂, might make clinicians rethink the role of extracorporeal lung support procedures in the treatment algorithm of ARDS.

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