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## Extracorporeal CO2 removal

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## **“Extracorporeal CO<sub>2</sub> removal”**

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### **KeyWords**

Extra-Corporeal Membrane Oxygenation (ECMO), Extra-Corporeal CO<sub>2</sub>Removal (ECCO<sub>2</sub>R), artificial lung, Acute Respiratory Distress Syndrome (ARDS),

## **Abstract**

*The extracorporeal carbon dioxide removal concept, used as an integrated tool with conventional ventilation, plays a role in adjusting respiratory acidosis consequent to Tidal Volume ( $V_t$ ) reduction in protective ventilation setting.*

*This concept arises from the ECMO experience and from this originates. Kolobow and Gattinoni were the first in introducing 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 with veno-venous bypass, while oxygenation is accomplished by high levels of positive end-expiratory pressure, with a respiratory rate of three to five sighs every minute. The focus was that, in case of acute respiratory failure,  $CO_2$  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 amount of required resources and the high incidence of side effects, LFPPV-ECCO<sub>2</sub>R was restricted to a “rescue” therapy for the most severe case of ARDS.*

*Technological improvement led to the implementation of two different  $CO_2$  removal approaches: the iLA called “pumpless arterio-venous ECMO” and the Veno-venous ECCO<sub>2</sub>R. They allow to considerate the extracorporeal support as something more than a 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.*

*Is foreseeable 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. Moreover the future ARDS management should include a minimally invasive extracorporeal carbon dioxide removal circuit associated with a 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.*

## **Introduction**

Since 1979 it is possible to markedly hypoventilate the lung at a rate of 2 to 4 breaths/minute or allow spontaneous but insufficient ventilation still maintaining normal arterial blood gases, while the metabolically produced CO<sub>2</sub> is removed by an extracorporeal membrane lung and the oxygen is fed through a tracheal tube or an helmet with a Continuous Positive Airways Pressure (CPAP). [1,2]

In 2001 the NIH published a randomized controlled trial that recommended to ventilate acute respiratory distress syndrome (ARDS) patients with a tidal volume (Vt) of 6 ml/kg (predicted body weight) and a maximum end-inspiratory plateau pressure (Pplat) of 30 cm H<sub>2</sub>O, in order to prevent a ventilation lung damage.[4] 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 Vt reduction even if they already have a Pplat < 30cm H<sub>2</sub>O.[5,6]

Those results support the concept of extracorporeal carbon dioxide removal concept as integrated to conventional ventilation to adjust respiratory acidosis consequent to very low Vt, and therefore allowing a more protective ventilator settings.[7] This approach might also reduce ventilator induce lung injury (VILI) that is one of the most important and actual problem in diseased lungs and allow a wider clinical implementation of the new concept “*less ventilation, less injury*”. [3]

## **Extracorporeal CO<sub>2</sub> removal: the concept**

The basic concepts of the CO<sub>2</sub> 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. In those years, Hill et al. reported for the first time the successful use of extracorporeal circulation to treat acute hypoxemic respiratory failure in an adult patient [8]; Barlett demonstrated for the first time the successful use of ECMO in a neonate [9].

In the same period, studies published by Kolobow and Gattinoni introduced extracorporeal support intended to separate carbon dioxide removal from oxygen uptake.[10] Extra-Corporeal CO<sub>2</sub>Removal (ECCO<sub>2</sub>R) refers to an extracorporeal support, focused on the removal of blood CO<sub>2</sub>, rather than on the improvement of the oxygenation. Extra-corporeal 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 Kolobow and Gattinoni for the acute respiratory failure. The blood flow levels required to obtain a carbon dioxide removal, are lower than the ones needed to achieve the oxygenation so Kolobow exploited the concept that, if CO<sub>2</sub> is removed by a membrane lung through a low flow high ventilation venovenous bypass, it is possible to reduce the ventilatory support in acute respiratory failure and severe ARDS, maintaining oxygenation simply with patient's alveoli diffusion, also called "apneic oxygenation"[10], allowing the lung rest. Originally the veno-venous bypass was set out via the cannulation of the common femoral and the 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 and 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's technique, we arrive to nowadays technique. The first membrane lungs consisted of microporous polypropylene fibers and were associated to constant plasma leakage, that determined a 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 sec).

Gattinoni, using this modified ECMO technique (LFPPV- ECCO<sub>2</sub>R), reported an ARDS survival up to 49%. [10] that was also attributed to patient selection, strict control of coagulation, and ventilator management directed to reach the "lung rest".[10,11] Anderson *et al.* in 1993, demonstrated a 47% survival in adults with severe respiratory failure. In a retrospective review of 100 adult patients, Kolla *et al.* reported a 54% overall survival. [12] However, despite the later report from Brunet that used LFPPV- ECCO<sub>2</sub>R to improve oxygenation, reducing pulmonary barotrauma in ARDS and achieving a mortality rate of 50% [13], in 1994 Morris *et al.* presented the results of a randomized clinical trial where he use of "conventional" Pressure Controlled Inverse-Ratio ventilation was compared to ECCO<sub>2</sub>R in ARDS patients; the study showed no significant difference in survival between the two interventions and reported several episodes of severe bleeding. [14] Extracorporeal carbon dioxide removal was hence restricted to the sickest patients in whom all other treatments had failed and limited only to the centers with large expertise.[15]

At the present time, ECMO, (**Figure 1**) with the news technologies, (centrifugal blood pump and news 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, a higher than 50% survival can be achieved, whereas sepsis and multiple organ failure are the leading causes of unsuccessful use. Only a minority of the patients suffers major complications related to the technique itself, and that serious complications are almost exclusively related to bleeding (particularly intracranial bleeding)[17].

### **Extracorporeal CO<sub>2</sub> removal: the clinical data**

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

The system was characterized by a new membrane gas exchange system based on an heparin-coated hollow fiber technology, that optimized blood flow reducing the resistances and that was connected to the patient via arterial and venous cannulae inserted with Seldinger’s technique. The device did not required extended technical and staff support: blood flow is determined by the driving force given by the cardiac output, and the mean arterial pressure: twenty to twenty-five percent of the cardiac output pass as 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 conducted to the newly designed Interventional Lung Assist (iLA) device. Bein *et al.* recently reported a retrospective analysis of 90 patients with critical hypoxemia/hypercapnia treated with iLA device, who, despite ventilation with low VT (320–470ml), showed physiologic values of Pa CO<sub>2</sub> (31–42 mmHg) and pH (7.38 –7.50)[20]. 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 artero-venous pressure gradient.

In 2008 Fisher and coll. described the iLA new concept of protective ventilation as a bridge to lung transplant (LTx): in the Hannover experience twelve patients who developed severe ventilation-refractory hypercapnia and acidosis despite maximal conventional ventilatory support received iLA implantation, obtaining a Pa CO<sub>2</sub> levels reduction and a significant improvement in pH values. [21] In a recent study, Zimmermann implemented an iLA system in 51 ARDS patients suffering from persistent hypoxaemia and/or hypercapnia, unresponsive to conventional therapy

achieving a de-escalation of invasive ventilatory variables preventing ventilator induced lung injury [22].

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

In the last years, a new concept of CO<sub>2</sub> removal device was experimented to reduce complexity, side effects and expenses of extracorporeal lung assistance. Livigni and coworkers, described in animal model the efficacy and safety of a veno-venous device (ECCO<sub>2</sub>R) with a low-flow CO<sub>2</sub> removal system.[23] In 2009 Terragni et al. studied the effects of further Vt decreasing in a group of ARDS patients who developed plateau pressures of 28–30 cm H<sub>2</sub>O. The tidal volume was decreased to 4 ml/kg of predicted body weight (PBW), and the predictable consequence of increase in PaCO<sub>2</sub> was corrected through an extracorporeal circuit. The intervention was safe and produced notable physiologic improvements.[7]

This new generation ECCO<sub>2</sub>R consists of modified standard continuous veno-venous hemofiltration setup (Decap®, Hemodec, Salerno, Italy) that includes, in series with the hemofilter an oxygenator. 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. [7] *Pietropaoli* and coworkers described the use of this new generation ECCO<sub>2</sub>R 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 CO<sub>2</sub> removal and especially oxygenation improvement, available data



suggest that this “mini-ECMO” optimize pH values, reduce partial pressure of CO<sub>2</sub> allowing to minimize ventilatory support and therefore minimizing VILI with no adverse events in terms of bleeding, circuit clotting, severe hemodynamic instability, or venous embolism[24].

## **Extracorporeal CO<sub>2</sub> removal: the technological development**

Extracorporeal circulation can be achieved using an oxygenator for the CO<sub>2</sub> removal from its dry form (dissolved CO<sub>2</sub>) or an hemodialyser for CO<sub>2</sub> removal from its wet form [7,23, 25,26].

In the artificial lung, the real limiting factor of CO<sub>2</sub> elimination is physiological. The reaction speed of bicarbonates dehydration, and the consecutive rise in the CO<sub>2</sub> concentration in plasma, are very slow. This explains the need to bypass the 25% of the cardiac output in order to eliminate metabolic CO<sub>2</sub> production. Oxygenator associated acidification and hamodialyzer associated alkalinisation are methods that facilitate the shifting of the bicarbonate/dissolved CO<sub>2</sub> equilibrium in the sense respectively of dissociation (CO<sub>2</sub> partial pressure raised) or of hydration (bicarbonate raised). Even if the efficacy of CO<sub>2</sub> removal through hemodialysis (with or without NaOH dialysate alkalinisation) was higher than the CO<sub>2</sub> 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 ARF because of the reduction in the circuit complexity. At the present time, only preliminary data are available from the Pesenti and coworkers about the effects of blood acidification to enhance carbon dioxide removal of Membrane Lung (ML) in swine model. In this study, the authors demonstrates that blood acidification at the inlet of a ML can significantly increase the CO<sub>2</sub> removal by the ML by converting the blood bicarbonate into physically dissolved CO<sub>2</sub>. (29-30)

For most adult patients with unresponsive severe respiratory failure, veno-venous support is the method of choice, including both extracorporeal CO<sub>2</sub> removal (ECCO<sub>2</sub>R) and veno-venous ECMO (VV ECMO). If the need of extracorporeal ventilatory support is partial, new generation of ECCO<sub>2</sub>R devices that uses arterial-venous pump-less bypass or low flow venous-venous bypass that can remove only the 20-30 % of CO<sub>2</sub> production are available in clinical practice. [7,24,26]

### **1. V-V ECMO**

Extra-Corporeal CO<sub>2</sub> Removal refers to an extracorporeal support focused on the CO<sub>2</sub> leaching from blood rather than improving oxygenation [1,28]. In cases of hypoxic/hypercapnic respiratory failure, but preserved cardiac function, a veno-venous extracorporeal membrane oxygenation (V-V 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. 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 L/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 Activated Clotting Time (ACT) of 150-200 sec but in surface-heparinized, the circuit can work well without any systemic anticoagulation for at least 12-48 hrs [29]. Before cannulation, usually performed with a modified Seldinger technique, ultrasonic measurement of the femoral vessels is performed to assess the appropriate calibre of 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.

## **2. Pumpless Arterio-Venous interventional Lung Assist (iLA)**

The interventional Lung Assist (iLA, NovaLung GmbH, Hechingen, Germany) is a single-use compact extrapulmonary gas exchange system perfused by passive femoral artery-femoral vein shunt, generated by the arterial blood pressure (60-80 mmHg femoral artery-femoral vein) through a lung assist device; a blood flow rate of approximately 1.0–2.5 L/min produces an effective CO<sub>2</sub> extraction and an improvement in arterial oxygenation. Apart from an oxygen supply (10–12 L/min), the system does not require additional energy or substrate sources.[20] (**Figure 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. The entire effective gas exchange surface area amounts to 1.3 m<sup>2</sup>, 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, Hechingen, Germany).

To connect the iLA to the patient, a special percutaneous cannulation system has to meet the following conditions: implantable with Seldinger technique, cannulae walls extremely thin to minimize resistance to flow and availability 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. The weaning from iLA is attempted by reduction in mechanical ventilation and gas supply to approximately 1 L/min performed for 30 mins.

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 cannulae were removed and normal perfusion of the limb was restored. Cannula thrombosis was only observed in the early period without specially designed cannulae before 2001. The main contraindication for the application of the system is a hemodynamic depression.[27] It is also reported the application of iLA as a bridge to Lung Transplant as presented by Fischer with the Hannover experience.[21]

### **3. Low flow ECCO<sub>2</sub>R technique**

The Decap® (Hemodec, Salerno, Italy) ECCO<sub>2</sub>R device is a modified renal replacement circuit incorporating a neonatal membrane lung coupled in series with a hemofilter.(**Figure 3**) Vascular access is granted by femoral vein and via a double lumen catheter 14 Fr diameter, inserted with 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 L/min. Exiting the membrane lung, blood is driven to an hemofilter and the resulting plasmatic water is made re-circulate 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 with 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 recirculating 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 recirculated through the membrane lung. [7,23,24,26]

### **Extracorporeal CO<sub>2</sub> removal: the future**

The NIH protocol represents the standard for mechanical ventilation of acute respiratory distress syndrome (ARDS) patients, recommending the use of low Vt of 6 ml/kg (predicted body

weight) and an end-inspiratory plateau pressure of a maximum of 30 cm H<sub>2</sub>O.[4] Despite these ventilatory limitations, tidal hyperinflation may occur in up to 30% of ARDS patients that could benefit from an additional V<sub>t</sub> reduction.[5] 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 Pesenti *et al.*, has been recently implemented in new devices that may reduce side effects, complexity, and costs of extracorporeal carbon dioxide removal.[30]

Terragni *et coll.* managed effectively and safely respiratory acidosis consequent to V<sub>t</sub> lower than 6 L/kg PBW and reestablished a normal arterial pH through extracorporeal carbon dioxide removal technique. The system, at 380 ml/min blood flow, could allow a PaCO<sub>2</sub> reduction of approximately 20% at constant ventilation. [7] 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 ECCO<sub>2</sub>R 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 tidal volume could be theoretically reduced to zero. From these preliminary clinical data (waiting 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 like 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 lung open and high FiO<sub>2</sub> to avoid hypoxemia, as a bridge to recovery from the pulmonary disease.

## **Conclusions**

With improved technology and experience, low extracorporeal blood flow with high performance ECCO<sub>2</sub>R may be the key to a new severe ARDS ventilator management, 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 CO<sub>2</sub>, might make clinicians rethink the role of extracorporeal lung support procedures in the treatment algorithm of ARDS.

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