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Mechanical ventilation (MV) is a lifesaving treatment delivered to patients who suffer of a wide spectrum of respiratory failure. However, several concerns have emerged about its limits and iatrogenic potential. Extracorporeal life support (ECLS) techniques complement MV in several circumstances: (1) to correct life-threatening hypoxemia in patients with acute respiratory distress syndrome (ARDS) when all conventional therapies have failed; (2) to minimize the risk of ventilator-induced lung injury (VILI), allowing an “ultra-protective” ventilation strategy with very low tidal volume; and (3) to prevent the risk of endotracheal intubation when noninvasive mechanical ventilation is failing. To accomplish these putative indications, ECLS techniques range from the full-support devices called extracorporeal membrane oxygenation (ECMO, blood flow ≥ 3 L/min), which ensures full oxygenation and carbon dioxide (CO₂) clearance with minimal need of MV, to minimally invasive extracorporeal CO₂ removal systems (ECCO₂R, blood flow 0.4–1 L/min), which remove CO₂ without any effect on oxygenation. The objectives of this chapter are to review fundamental concepts of CO₂ handling during ECCO₂R and provide current evidences of its application in patients with ARDS, chronic obstructive pulmonary disease (COPD), and acute kidney injury (AKI) requiring renal replacement therapy.

OBJECTIVES
This chapter will:
1. Explain the physiology of CO₂ removal during extracorporeal support.
2. Describe potential clinical applications of extracorporeal CO₂ removal systems (ECCO₂R) support therapy in patients with acute respiratory distress syndrome (ARDS) and chronic obstructive pulmonary disease (COPD) as well as in those with acute kidney injury requiring renal replacement therapy.

FROM RENAL TO RESPIRATORY DIALYSIS
(HISTORICAL PERSPECTIVE)
Since the late 1970s, hypoxia and hypoventilation were described as usual respiratory adverse events that occurred during hemodialysis. The reduction in arterial partial pressure of CO₂ (PaCO₂) was considered the leading mechanism of these alterations, and the acetate buffer that was used conventionally at that time in dialysis circuits was identified as the primum movens of this physiologic disturbance. In fact, decrease of PaCO₂ resulted from the corresponding reduction of HCO₃⁻ in exchange for acetate. When bicarbonate dialysate was used, hypopnea and hypoxia were not detected. In those years, Kolobow andGattinoni attempted to take advantage of this adverse effect and
designed a modified venovenous ECMO circuit (blood flow of around 1 L/min) to reduce minute ventilation and consequently the risk of lung overdistension in patients with severe ARDS. Moreover, at that time full ECMO with high blood flow rates failed to demonstrate any improvement in survival of these patients because of ventilation strategy that did not prevent VILI and major bleeding complications.

CARBON DIOXIDE PHYSIOLOGY
Carbon dioxide is produced in mitochondria as the end product of the aerobic metabolism and in blood combines with free water (H₂O) to form carbonic acid (H₂CO₃); this reaction is catalyzed in red blood cells (RBC) and on pulmonary capillaries membranes by carbonic anhydrase, which is not present in plasma. At physiologic pH ranges, 96% of carbonic acid is dissociated in bicarbonate ion (HCO₃⁻) and hydrogen ion (H⁺).

CO₂ + H₂O ⇌ H₂CO₃ ⇌ HCO₃⁻ + H⁺

Five percent of the total CO₂ is conveyed in physical solution, following Henry’s solubility law, stating that the mass of a dissolved gas is proportional to its partial pressure. The remaining fraction of CO₂ binds to carboxymino compounds to their free amine group (R-NH₂). Among these, hemoglobin (Hb) is the most efficient CO₂ carrier, in particular in its reduced, nonoxygenated form.

In the healthy adult subject at rest, the amount of CO₂ production by systemic metabolism (VCO₂) is about 200 mL/min, which can increase to a value of 30% higher in pathologic conditions. The concentration of CO₂ in arterial blood is about 48 mL/dL (at a PaCO₂ of 40 mm Hg), and the same in mixed venous blood is 52 mL/dL (at a PvCO₂ of 46 mm Hg). Consequently, an ideal ECCO₂R device may be able theoretically to remove up to 250 mL/min of CO₂ with a low blood flow of 500 mL/min.

In fact, ECCO₂R systems are able only to remove the amount of the dissolved CO₂ from blood, and in the membrane lung the input partial pressure of CO₂ is directly proportional to CO₂ removal. However, as has been mentioned already, only a small amount of CO₂ is dissolved in blood. Finding a way to increase free CO₂ entering the membrane lung is a hot topic for the actual research in the field. In animal models, the acidification of blood entering the membrane lung with lactic acid demonstrated to be effective in increasing the CO₂ removal capacity of a low-flow ECCO₂R device, but the impact on ventilation was limited to a rise in energy expenditure resulting from lactic acid infusion. In another animal model, Zanella et al. proposed an appealing approach to enhance the inlet CO₂ concentration by blood acidification using an electrodialysis cell and thus avoiding the undesired effects related to the addition of an acid solution to the blood. Bicarbonate ion and dissolved CO₂ are in equilibrium in blood, and changes
in acid-base status can promote the conversion of one form in the other one. Electrodialysis can enhance PaCO₂ in blood before entering the membrane lung through the application of an electrical current to solutions separated by ion-exchange membranes into an acid and a base chamber. In the acid chamber, Cl⁻ ions combine with H⁺ thus reducing pH; on the contrary, in the base chamber OH⁻ ions derived from hydrolysis compensate for Cl⁻ loss and create an alkaline milieu. Blood in the circuit therefore is acidified with this net exchange of HCO₃⁻ for Cl⁻, and CO₂ extraction is increased about two times more compared with standard ECCO₂R efficiency.¹⁵

**TECHNICAL DESCRIPTION OF EXTRACORPOREAL CARBON DIOXIDE REMOVAL SYSTEMS**

ECCO₂R devices can be grouped in two main categories: the low-flow venovenous pump-driven ECCO₂R devices (VV-ECCO₂R) and the arteriovenous pumpless systems (AV-ECCO₂R). In VV-ECCO₂R systems blood is driven from a large vein, such as femoral or jugular vein, it passes through an oxygenator called “membrane lung,” and it returns to central venous circulation (Fig. 124.1).

Two one-lumen or one dual-lumen cannulas can be used, depending on the available system. With the advent of dedicated CO₂ removal devices, technology improvement allowed reduction of the size of cannulas, whose diameter may vary from 14 to 18 French (Fr), depending on systems and settings. In fact, if we approximate the Hagen-Poiseuille equation, laminar blood flow is directly proportional to the fourth power of the radius of the cannula and inversely to its length. Therefore targeting a blood flow rate of 400 to 1000 mL/min, it is possible to reduce invasiveness through downsizing cannulas’ diameter. Percutaneous cannulation with the Seldinger technique is the first choice for VV-ECCO₂R. Ultrasound visualization of vessels is recommended to identify the target central veins and to control their size, compared with cannulas diameters. With ultrasound it is also possible to control the guidewire before dilatation and to limit adverse events such as accidental arterial cannulation.

Blood is conveyed through a nonocclusive roller or a centrifugal or diagonal flow magnetic rotary pump, which generates the pressure gradient needed to generate an antegrade blood flow through the circuit. Blood is driven to a specifically designed oxygenator, which is called membrane lung. Membranes are composed by a microporous hollow-fiber of polypropylene, or by a nonmicroporous hollow-fiber of polymethylpentene (PMP). To date, PMP represents the most used configuration because it allows to reduce plasma leakage ad to obtain gas transfer by diffusion avoiding direct blood-gas contact.¹⁶

Membrane lung total surface is directly proportional to blood flow and so to oxygenation capability. This implies that for selective CO₂ removal membrane lung with small areas is sufficient, in comparison with full ECMO needs. Membrane lung is connected to a gas source (which can be air or 100% oxygen), called the “sweep gas,” which allows it to wash out CO₂ in excess from blood by diffusion passing through the oxygenator. The amount of sweep gas (expressed in L/min) is directly proportional to CO₂ clearance.

In AV-ECCO₂R blood is driven from the femoral artery to an oxygenator, and then it returns to the contralateral femoral vein; blood flow is strictly dependent on the patient’s cardiac output, and this device also allows partial oxygenation. It is more invasive than VV-ECCO₂R, and blood flow cannot be regulated from the outside. In addition, several complications have been described, such as lower limb ischemia, compartmental syndrome, and need for surgical cannulation in some patients.¹⁷,¹⁸ Accurate description of the technical features and the clinical applications of these devices is beyond the scope of this chapter, which focuses only on low-flow ECCO₂R.

To date, several VV-ECCO₂R devices have been designed especially for this purpose (Table 124.1). PALP (Maquet) is based on the Cardiohelp console and can be switched from low-flow CO₂ removal to full ECMO. In the same way, iLA active (Novamura) consists of modular components that allow support of the lung from CO₂ removal to complete oxygenation. Decap (Hemotec) is focused specifically on CO₂ removal, but now it has a feature to allow contemporary renal replacement therapy with the same circuit when used in combination with B. Braun Avitum. Ablycap (Bellco) incorporates an optimized oxygenator within a multiorgan support device called Lynda for septic and anuric patients. Hemolung RAS (Alung) represents the first device specifically designed for CO₂ removal with all the components integrated in one system. Prolung (Estor) provides a similar alternative to the previously described systems.
Anticoagulation management still represents a challenge for ECCO₂R devices. Although the main components of the commercially available systems invariably are coated with heparin or other similar substances with antithrombotic capability, systemic anticoagulation is still a duty. It can be achieved with a continuous infusion of unfractionated heparin following specific activated clotting time (ACT) or activated partial thromboplastin time (aPTT) therapeutic targets to prevent circuit and/or membrane lung clot formation.

**CLINICAL APPLICATIONS OF EXTRACORPOREAL CARBON DIOXIDE REMOVAL**

**Acute Respiratory Distress Syndrome**

In patients with ARDS, stretch forces generated across lung parenchyma during mechanical ventilation play a pivotal role in promoting lung inflammation, alveolar edema, impairment of edema clearance, and cell death. Therefore ventilation strategy with tidal volume of 6 mL/kg of predicted body weight that limits end inspiratory lung stretch has been demonstrated to reduce lung injury and mortality of 10%. Current use of ECCO₂R aims to further minimize the risk of VILI, ensuring ultraprotective mechanical ventilation strategy to ensure ultraprotective mechanical ventilation parameters (tidal volume, PEEP) that is independently associated with the risk of death in ARDS patients was reduced significantly from 13.9 to 11.6 cm H₂O. New generation of a low-flow ECCO₂R system, Hemolung Respiratory Assist System (RAS, ALung Technologies, Inc, Pittsburgh, PA), was used in this study. Venous blood was circulated through a 15.5-Fr dual-lumen venous catheter (jugular or femoral) by a magnetically driven centrifugal pump at a flow rate of 350 to 550 mL/min. The pump was integrated within a cylindric bundle of hollow fiber membranes. Sweep gas (air or 100% O₂) was drawn through the hollow fibers under negative pressure by a vacuum pump, creating a gradient for CO₂ diffusion. Maintaining the sweep gas under negative pressure mitigates the risk of air embolism across the membrane and also allowed for automatic removal of plasmatic water condensation from the fiber lumens to preserve gas exchange efficiency.

Appropriate strategies to manage worsening hypoxemia during ECCO₂R treatment are a compelling issue. In fact, ventilation with very low tidal volume may promote atelectasis formation because of alveolar derecruitment; moreover, ARDS may progress from moderate to severe making worse oxygenation. For this reason, during treatment with ECCO₂R, PEEP levels are increased consequently, and prone position is considered when PaO₂/FiO₂ drops to 150. Prone positioning has been demonstrated to be effective not only in improving oxygenation but also in decreasing early and late mortality.²² In Fanelli’s cohort, 27% of patients required prone positioning without any interruption of ECCO₂R and showed improvement in arterial oxygenation. Only two patients required escalation from ECCO₂R to ECMO because of life-threatening hypoxemia. Mortality at 28 days was 47%, which was expected in a cohort of moderate and severe ARDS patients.

Moreover, feasibility, safety, and efficacy of ECCO₂R strategy to ensure ultraprotective mechanical ventilation in patients with moderate ARDS will be the end point of the upcoming SUPEROVA randomized clinical trial (NCT02282657) promoted by the European Society of Intensive Care Medicine.

**TABLE 124.1**

| DEVICE               | PUMP                  | MEMBRANE LUNG                | BLOOD FLOW          |
|----------------------|-----------------------|------------------------------|---------------------|
| PALP (Maquet)        | Centrifugal           | Polymethylpentene hollow fiber | BF up to 2.8 L/min  |
| iLA active (Novalung)| Rotary pump with diagonal flow and magnetic drive | Polymethylpentene | BF up to 800 mL/min (upgradable depending on cannulas and ML) |
| Ablycap (Bellco)     | Roller pump           | Plasma-tight hollow fiber    | BF up to 450 mL/min |
| Hemolung RAS (Alung) | Centrifugal magnetically driven | Cylindric hollow fiber    | BF up to 550 mL/min |
| Prolung (Estor)      | Roller pump           | Polymethylpentene            | BF up to 450 mL/min |
| Decap SMART (B. Braun)| Roller pump           | Polymethylpentene            | BF up to 450 mL/min |

BF, Blood flow; ML, membrane lung.
CHRONIC OBSTRUCTIVE PULMONARY DISEASE

Extracorporeal CO₂ removal with low-flow ECCO₂R devices has been applied in patients with exacerbation of COPD with the aim of avoiding intubation or facilitating weaning from invasive mechanical ventilation (IMV). In a pilot study Abrams et al. suggested that ECCO₂R devices may facilitate early extubation and ambulation of COPD patients requiring IMV. After 4 hours from the beginning of ECCO₂R, all five patients were extubated and after around 1 day patients were able to ambulate. The mean duration of ECCO₂R support was 8 days without any significant serious adverse effect except for minor bleeding at the site of cannula insertion. Noninvasive ventilation (NIV) is the mainstay of therapy for patients with acute exacerbation of COPD; however, NIV failure is associated with higher risk of hospital mortality. Toward this end, ECCO₂R removal has been proposed as a supportive therapy to avoid the risk of intubation with the assumption that CO₂ removal may reduce the request of minute ventilation and limit dynamic hyperinflation. In a matched cohort study, 25 patients who were at risk of failure NIV (defined by arterial pH < 7.3 with PaCO₂ ≥ 20% of baseline and respiratory rate ≥ 30 breaths/min use of accessory muscles/paradoxic abdominal movements) were treated with ECCO₂R. Compared with historic controls, these patients had 73% risk reduction of intubation, and this result may be attributable to reduction of respiratory rate after CO₂ removal.

The use of ECCO₂R also has been theorized in COPD patients who fail weaning from mechanical ventilation in absence of respiratory acidosis. In fact, CO₂ partial removal obtained with the use of ECCO₂R may reduce respiratory muscle effort, avoiding fatigue and pump failure. In four patients with COPD who have failed two consecutive trials of T-piece, ECCO₂R support was started during the following spontaneous breathing trials. All patients matched a priori defined criteria and were extubated successfully under ECCO₂R. Interestingly, all indices of respiratory muscles effort (pressure time integrals of the diaphragm and esophageal pressure per minute) and work of breathing were reduced significantly compared with those measured during the first attempts of spontaneous breathing.

PATIENTS WITH ACUTE KIDNEY INJURY WHO REQUIRE RENAL REPLACEMENT THERAPY

In critically ill patients with acute renal failure, concomitant respiratory failure that requires mechanical ventilation is one of the strongest risk factors for hospital mortality to levels similar to hematologic diseases and hepatoportal syndrome. Concomitant lung and kidney failures indicate higher severity of multiple organ dysfunctions and imply a lung-kidney cross-talk. In fact, a growing body of evidence indicates that AKI induces distant organ dysfunction. Lung failure–associated AKI is characterized by increased vascular permeability, impaired lung edema clearance, and overwheled leukocytes trafficking.

Animal models of AKI induced by bilateral nephrectomy or ischemia reperfusion injury showed cytokine mediated pulmonary injury and dysregulation of lung salt and water channels that are involved in alveolar edema clearance. Inflammatory cytokines are potential mediators of this effect. In fact, secondary data analysis from a multicenter randomized clinical trial on protective mechanical ventilation in patients with ARDS has identified higher plasma concentrations of PAI-1, interleukin 6 (IL-6), and soluble receptor of TNF (sTNFRs) as biologic predictors of AKI. ARDS patients often develop AKI, with potential need of renal replacement therapy (RRT) and ECCO₂R treatment. Technologic advances allow in a single minimally invasive treatment the combination of ECCO₂R and RRT; this strategy aims to support vital functions (i.e., respiratory and renal) modulating organ cross-talk, which is a signature of critical illness. In 16 patients with AKI requiring RRT and respiratory failure–associated respiratory acidosis, Quintard et al. showed that a pediatric membrane lung introduced into the circuit in a serial manner was able to correct acid base imbalance up to 24 hours.

In 2013 Forster et al. treated patients with AKI combining ECCO₂R and continuous venovenous hemodialysis (CVVHD). In 10 patients, application of a hollow-fiber gas exchanger with a surface area of 0.67 m² in series with the hemofilter in the CVVHD circuit allowed 28% reduction of PaCO₂ values. This strategy was associated with improvement in pH (from 7.18 to 7.3) and with lower need of norepinephrine (from 0.22 to 0.16 mcg/kg/min). Tidal volume was reduced after 24 hours of treatment (from 8.4 mL/kg to 7.3 mL/kg); unfortunately, values of plateau pressure were not provided.

Allardet-Servent et al. expanded these findings, demonstrating that a combined strategy of ECCO₂R and RRT in patients with AKI-associated moderate ARDS (P/F 134) was safe and effective in counterbalancing respiratory acidosis associated to tidal volume reduction to 4 mL/kg. In 11 patients, the authors showed that a membrane lung (surface 0.65 m² upstream) upstream of hemofilter was able to remove CO₂ at a rate of 83 ± 20 mL/min (corresponding to 20% of PaCO₂ baseline value) with a blood flow of around 400 mL/min. Importantly, plateau pressure decreased from 25 to 21 cm H₂O after VT reduction to 4 mL/kg.

An ongoing clinical trial promoted by the University of Turin-Italy aims to assess whether, in AKI patients requiring mechanical ventilation, a strategy that combines RRT and ECCO₂R would allow reduction of tidal volume, plateau pressure, and release of inflammatory and apoptotic mediators in plasma (NCT02595619).

COMPPLICATIONS OF EXTRACORPOREAL CARBON DIOXIDE REMOVAL

Compared with VV-ECMO, a fewer number of complications have been described with new ECCO₂R systems because of less invasiveness and technologic advances. In fact, blood flow of up to 0.4 to 1 L/min that is required for CO₂ clearance is reached with a size cannula ranging between 14 and 18 Fr. Despite less mechanical complication related to vessel cannulation, the risk of bleeding associated with systemic anticoagulation is still a concern. In our center, a heparin bolus of 50 UI/kg at the moment of cannulation is followed by a continuous infusion dose of 18 UI/kg/hr to reach a target PTr of 1.5 to 2. In a prospective trial involving 10 ARDS patients treated with ECCO₂R, patient-related complications were not reported. The authors described only few mechanical complications, namely three cases of membrane clotting that did not require additional transfusions, one case of cannula displacement, the need for cannula replacement for three patients, and one case of pump malfunction.
In 20 COPD patients, Burki et al. recorded one fatal case of retroperitoneal bleed after catheterization and perforation of the left iliac vein and one case of pneumothorax; both complications were related to venous cannulation and not specifically to the ECCO₂R device. Thrombocytopenia requiring transfusion, deep venous thrombosis of cannulated vessel and one significant bleeding event resulting from inadvertent excessive anticoagulation were reported.³⁶ In a matched cohort study of 25 COPD patients, Del Sorbo et al. reported six cases of circuit clotting, two of pump malfunction, and one of membrane lung failure. In addition, three patients experienced significant bleeding and in one case vein perforation at cannula insertion occurred.²⁵ Recently, Fanelli et al., in a multicenter trial of 15 patients with moderate ARDS, only one case of low flow rate resulting from catheter kinking and one of hemolysis that required transfusion were described.³⁶

CONCLUSION

ECCO₂R is an effective support therapy to add to the mechanical ventilation to limit its invasiveness and side effects in patients with ARDS, with acute exacerbation of COPD, and with AKI requiring RRT. However, its efficacy and safety must be proven in well-designed future clinical trials.

Key Points

1. Dissolved CO₂ can be removed effectively with a low-flow extracorporeal device (blood flow from 400 to 1000 mL/min). Extracorporeal CO₂ removal (ECCO₂R) systems do not improve oxygenation.

2. ECCO₂R can be used to minimize the risk ventilator induced lung injury (VILI) in ARDS patients and to reduce the need of invasive mechanical ventilation in patients with chronic obstructive pulmonary disease.

3. Veno-venous ECCO₂R devices can be incorporated within renal replacement therapy systems to allow simultaneous renal and pulmonary extracorporeal support.

4. The need for systemic anticoagulation may be still a concern that limits a wider application of ECCO₂R systems.

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