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CHAPTER 124

Extracorporeal Carbon Dioxide Removal

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OBJECTIVES

This chapter will:

1. Explain the physiology of CO_2 removal during extracorporeal support.
2. Describe potential clinical applications of extracorporeal CO_2 removal systems ($ECCO_2R$) 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.

Mechanical ventilation (MV) is a lifesaving treatment delivered to patients who suffer of a wide spectrum of respiratory failure.[1] However, several concerns have emerged about its limits and iatrogenic potential.[2] 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 (CO_2) clearance with minimal need of MV, to minimally invasive extracorporeal CO_2 removal systems ($ECCO_2R$, blood flow 0.4–1 L/min), which remove CO_2 without any effect on oxygenation.[3] The objectives of this chapter are to review fundamental concepts of CO_2 handling during $ECCO_2R$ 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.

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.[4] The reduction in arterial partial pressure of CO_2 ($PaCO_2$) 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 $PaCO_2$ resulted from the corresponding reduction of HCO_3^- in exchange for acetate. When bicarbonate dialysate was used, hypopnea and hypoxia were not detected.[5] In those years, Kolobow and Gattinoni 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.[4,6–9]

CARBON DIOXIDE PHYSIOLOGY

Carbon dioxide is produced in mitochondria as the end product of the aerobic metabolism and in blood combines with free water (H_2O) to form carbonic acid (H_2CO_3); 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 (HCO_3^-) and hydrogen ion (H^+).

$$CO_2 + H_2O \leftrightarrow H_2CO_3 \leftrightarrow HCO_3^- + H^+$$

Five percent of the total CO_2 is conveyed in physical solution, following Henry's solubility law, stating that the mass of a dissolved gas is proportional to its partial pressure.[10] The remaining fraction of CO_2 binds to carbamino compounds to their free amine group ($R\text{-}NH_2$). Among these, hemoglobin (Hb) is the most efficient CO_2 carrier, in particular in its reduced, nonoxygenated form.

In the healthy adult subject at rest, the amount of CO_2 production by systemic metabolism (VCO_2) is about 200 mL/min, which can increase to a value of 30% higher in pathologic conditions. The concentration of CO_2 in arterial blood is about 48 mL/dL (at a $PaCO_2$ of 40 mm Hg), and the same in mixed venous blood is 52 mL/dL (at a $PvCO_2$ of 46 mm Hg). Consequently, an ideal $ECCO_2R$ device may be able theoretically to remove up to 250 mL/min of CO_2 with a low blood flow of 500 mL/min.

In fact, $ECCO_2R$ systems are able only to remove the amount of the dissolved CO_2 from blood, and in the membrane lung the input partial pressure of CO_2 is directly proportional to CO_2 removal.[11] However, as has been mentioned already, only a small amount of CO_2 is dissolved in blood. Finding a way to increase free CO_2 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 CO_2 removal capacity of a low-flow $ECCO_2R$ device, but the impact on ventilation was limited to a rise in energy expenditure resulting from lactic acid infusion.[12–14] In another animal model, Zanella et al. proposed an appealing approach to enhance the inlet CO_2 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 CO_2 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 $PaCO_2$ 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 HCO_3^- for Cl^-, and CO_2 extraction is increased about two times more compared with standard $ECCO_2R$ efficiency.[15]

TECHNICAL DESCRIPTION OF EXTRACORPOREAL CARBON DIOXIDE REMOVAL SYSTEMS

$ECCO_2R$ devices can be grouped in two main categories: the low-flow venovenous pump-driven $ECCO_2R$ devices ($VV\text{-}ECCO_2R$) and the arteriovenous pumpless systems ($AV\text{-}ECCO_2R$). In $VV\text{-}ECCO_2R$ 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 CO_2 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 $VV\text{-}ECCO_2R$. 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 anterograde 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 CO_2 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 CO_2 in excess from blood by diffusion passing through the oxygenator. The amount of sweep gas (expressed in L/min) is directly proportional to CO_2 clearance.

In $AV\text{-}ECCO_2R$ 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

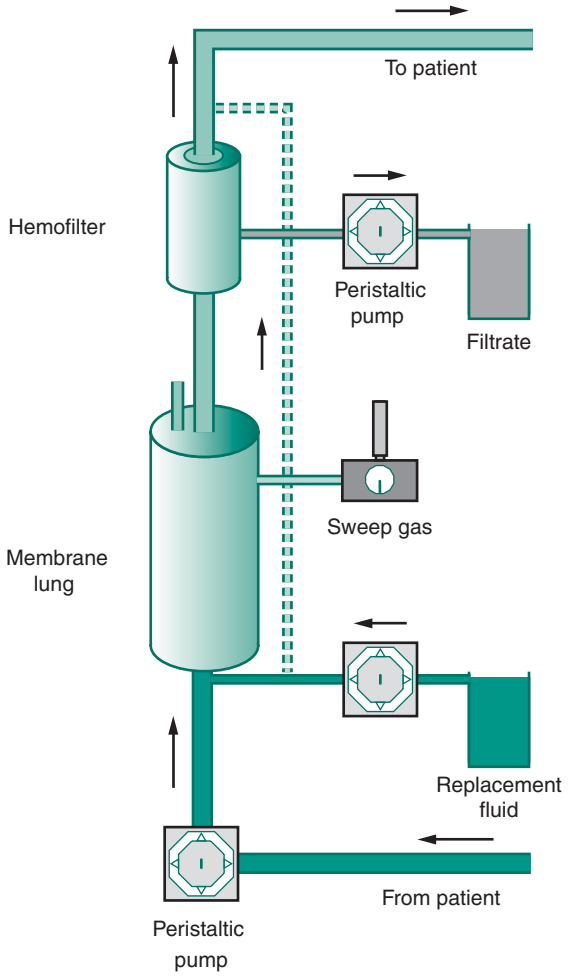

FIGURE 124.1 Schematic representation of an extracorporeal CO_2 removal ($ECCO_2R$) renal replacement therapy (RRT) integrated system. The hemofilter can be placed upstream or downstream (as shown in this figure) from the membrane lung. The replacement fluid can be delivered before or after the membrane lung and hemofilter.

partial oxygenation. It is more invasive than $VV\text{-}ECCO_2R$, 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 $ECCO_2R$.

To date, several $VV\text{-}ECCO_2R$ 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 CO_2 removal to full ECMO. In the same way, iLA active (Novalung) consists of modular components that allow support of the lung from CO_2 removal to complete oxygenation. Decap (Hemodec) is focused specifically on CO_2 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 CO_2 removal with all the components integrated in one system. Prolung (Estor) provides a similar alternative to the previously described systems.

TABLE 124.1

DEVICE	PUMP	MEMBRANE LUNG	BLOOD FLOW
PALP (Maquet)	Centrifugal	Polymethylpentene hollow fiber Surface area = 0.98 m^2	BF up to 2.8 L/min
iLA active (Novalung)	Rotary pump with diagonal flow and magnetic drive	Polymethylpentene Plasma-tight hollow fiber Surface area = 0.32 m^2	BF up to 800 mL/min (upgradable depending on cannulas and ML)
Ablycap (Bellco)	Roller pump	Polymethylpentene hollow fiber Surface area = 0.67 m^2	BF up to 450 mL/min
Hemolung RAS (Alung)	Centrifugal magnetically driven	Cylindric hollow fiber Surface area = 0.59 m^2	BF up to 550 mL/min
Prolung (Estor)	Roller pump	Polymethylpentene Surface area = 1.8 m^2	BF up to 450 mL/min
Decap SMART (B. Braun)	Roller pump	Polymethylpentene Surface area = 1.35 m^2	BF up to 450 mL/min

BF, Blood flow; *ML,* membrane lung.

Anticoagulation management still represents a challenge for $ECCO_2R$ 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 $ECCO_2R$ aims to further minimize the risk of VILI, ensuring ultraprotective mechanical ventilation that consists of very low tidal volume (around 4 mL/kg) to keep end inspiratory pressure at around 25 cm H_2O. In a proof of concept observational study, Terragni et al. demonstrated that minimally invasive $ECCO_2R$ system tempered VILI when used in combination with protective mechanical ventilation. In 10 patients with ARDS, in whom plateau pressure was between 28 and 30 cmH_2O, tidal volume was reduced to reach a plateau pressure of 25 to 28 cm H_2O. The following respiratory acidosis ($pH < 7.25$) was managed successfully with a modified continuous venovenous renal replacement circuit incorporating a neonatal membrane lung with a total membrane surface of 0.33 m^2 (Decap, Hemodec, Salerno, Italy) coupled in series with a hemofilter. This strategy was associated with less signs of alveolar overdistension at lung CT scan analysis and lower concentration of inflammatory cytokines in bronchoalveolar lavage fluid.[19]

Feasibility and safety of an ultraprotective ventilation strategy facilitated by low-flow venovenous $ECCO_2R$ has been assessed more recently by Fanelli et al.[20] In 15 patients with moderate ARDS enrolled in four European intensive care units, V_T was reduced from baseline (6.2 mL/kg PBW) to 4 mL/kg PBW, while PEEP was adjusted to target plateau pressure: $P_{plat} \leq 25$ cm H_2O. In all patients, a significant respiratory acidosis developed, and $ECCO_2R$ with a blood flow of around 400 mL/min and sweep gas of 10 L/min was able to correct pH and $PaCO_2$ to within 10% of baseline values. Driving pressure (difference between plateau pressure and PEEP)[21] that is independently associated with the risk of death in ARDS patients was reduced significantly from 13.9 to 11.6 cm H_2O. New generation of a low-flow $ECCO_2R$ 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% O_2) was drawn through the hollow fibers under negative pressure by a vacuum pump, creating a gradient for CO_2 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 $ECCO_2R$ 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 $ECCO_2R$, PEEP levels are increased consequently, and prone position is considered when PaO_2/FiO_2 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 $ECCO_2R$ and showed improvement in arterial oxygenation. Only two patients required escalation from $ECCO_2R$ 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 $ECCO_2R$ strategy to ensure ultraprotective mechanical ventilation in patients with moderate ARDS will be the end point of the upcoming SUPERNOVA randomized clinical trial (NCT02282657) promoted by the European Society of Intensive Care Medicine.

CHRONIC OBSTRUCTIVE PULMONARY DISEASE

Extracorporeal CO_2 removal with low-flow $ECCO_2R$ 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 $ECCO_2R$ devices may facilitate early extubation and ambulation of COPD patients requiring IMV.[23] After 4 hours from the beginning of $ECCO_2R$, all five patients were extubated and after around 1 day patients were able to ambulate. The mean duration of $ECCO_2R$ support was 8 days without any significant serious adverse effect except for minor bleeding at the site of cannula insertion.[23] 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, $ECCO_2R$ removal has been proposed as a supportive therapy to avoid the risk of intubation with the assumption that CO_2 removal may reduce the request of minute ventilation and limit dynamic hyperinflation.[24] In a matched cohort study, 25 patients who were at risk of failure NIV (defined by arterial pH ≤ 7.3 with $PaCO_2$ > 20% of baseline and respiratory rate ≥ 30 breaths/minor use of accessory muscles/paradoxic abdominal movements) were treated with $ECCO_2R$. Compared with historic controls, these patients had 73% risk reduction of intubation, and this result may be attributable to reduction of respiratory rate after CO_2 removal.[25]

The use of $ECCO_2R$ also has been theorized in COPD patients who fail weaning from mechanical ventilation in absence of respiratory acidosis. In fact, CO_2 partial removal obtained with the use of $ECCO_2R$ may reduce respiratory muscle effort, avoiding fatigue and pump failure. In four patients with COPD who have failed two consecutive trials of T-piece, $ECCO_2R$ support was started during the following spontaneous breathing trials. All patients matched a priori defined criteria and were extubated successfully under $ECCO_2R$. 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.[26]

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 hepatorenal syndrome.[27] 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.[28] Lung failure–associated AKI is characterized by increased vascular permeability, impaired lung edema clearance, and overwhelmed leukocytes trafficking.[28]

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.[29–31] 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.[32] ARDS patients often develop AKI, with potential need of renal replacement therapy (RRT) and $ECCO_2R$ treatment. Technologic advances allow in a single minimally invasive treatment the combination of $ECCO_2R$ 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.[33]

In 2013 Forster et al. treated patients with AKI combining $ECCO_2R$ and continuous venovenous hemodialysis (CVVHD). In 10 patients, application of a hollow-fiber gas exchanger with a surface area of 0.67 m^2 in series with the hemofilter in the CVVHD circuit allowed 28% reduction of $PaCO_2$ 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.[34] Allardet-Servent et al. expanded these findings, demonstrating that a combined strategy of $ECCO_2R$ 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 0.65^2) upstream or downstream of hemofilter was able to remove CO_2 at a rate of 83 ± 20 mL/min (corresponding to 20% of $PaCO_2$ baseline value) with a blood flow of around 400 mL/min. Importantly, plateau pressure decreased from 25 to 21 cm H_2O after VT reduction to 4 mL/kg.[35]

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 $ECCO_2R$ would allow reduction of tidal volume, plateau pressure, and release of inflammatory and apoptotic mediators in plasma (NCT02595619).

COMPLICATIONS OF EXTRACORPOREAL CARBON DIOXIDE REMOVAL

Compared with VV-ECMO, a fewer number of complications have been described with new $ECCO_2R$ 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 CO_2 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 PTTr of 1.5 to 2. In a prospective trial involving 10 ARDS patients treated with $ECCO_2R$, 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.[19]

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 $ECCO_2R$ 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.[20]

CONCLUSION

$ECCO_2R$ 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 CO_2 can be removed effectively with a low-flow extracorporeal device (blood flow from 400 to 1000 mL/min). Extracorporeal CO_2 removal ($ECCO_2R$) systems do not improve oxygenation.
2. $ECCO_2R$ 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 $ECCO_2R$ 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 $ECCO_2R$ systems.

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