Extracorporeal Carbon Dioxide Removal During Continuous Renal Replacement Therapy as Adjunctive Therapy

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Lung-protective ventilation targeting low tidal volumes and plateau pressures is the mainstay of therapy in patients with ARDS. This ventilation strategy limits pulmonary strain, inflammation, and injury, but it may be associated with profound hypercapnic acidosis. In such conditions, extracorporeal CO_2 removal can attenuate or normalize hypercapnia and may even facilitate ultraprotective ventilation. Almost half of patients with ARDS develop renal failure. Pathophysiological cross-talk between the injured lung and kidney may aggravate global organ failure and weighs negatively on outcomes. A substantial number of patients with ARDS require continuous renal replacement therapy. Systems adapted from conventional renal replacement platforms with blood flows < 500 mL/min can achieve significant CO_2 elimination. Therefore, incorporating low-flow extracorporeal CO_2 removal in a continuous renal replacement therapy circuit is an attractive therapeutic option. We reviewed the relevant literature on combining extracorporeal CO_2 removal with continuous renal replacement therapy. *Key words: ARDS; acute kidney injury; lung-protective ventilation; hypercapnia; extracorporeal carbon dioxide removal; continuous renal replacement therapy.* [Respir Care 2020;65(4):517–524. © 2020 Daedalus Enterprises]

Ventilating Patients With Acute Lung Injury

ARDS is a severe form of inflammatory lung injury characterized by decreased lung compliance, hypoxemia, and bilateral alveolar infiltrates on chest radiography.[1] The mortality rate is high, and invasive mechanical ventilation is required in almost all patients. Lung-protective ventilation is the current standard of mechanical ventilation for patients with ARDS. This ventilation strategy focuses on limiting tidal volume (6 mL/kg predicted body weight) and plateau pressure (< 30 cm H_2O) while recruiting collapsed alveoli and keeping them open throughout the ventilatory cycle.[2] Compared to conventional ventilation, lung-protective ventilation is associated with lower mortality. This survival benefit is significantly related to tidal volume reduction.[3] However, even ventilated accordingly, patients still remain exposed to forces that can induce lung injury.[4,5] Therefore, further reductions in tidal volume (4 mL/kg) and

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plateau pressure ($\leq$ 25 cm H_2O) have been proposed.[6] Reducing alveolar ventilation to minimum values inevitably will enhance CO_2 retention. Accumulation of CO_2 causes a drop in pH, leading to a state of respiratory acidosis, which may adversely affect cardiovascular, brain, and immune function.[7]

Extracorporeal Techniques at the Rescue

Venovenous extracorporeal membrane oxygenation (VV-ECMO) allows adequate oxygenation and ventilation while ventilator-generated pressures and volumes remain drastically reduced. However, results from the recent EOLIA trial suggest that VV-ECMO should be performed only in high-volume expert centers and in patients with ARDS who are severely hypoxemic ($P_{aCO_2}/F_{IO_2} < 80$ mm Hg).[8]

Over the last decade, extracorporeal CO_2 removal has been introduced as an artificial support to control CO_2 levels.[9,10] Unlike VV-ECMO, extracorporeal CO_2 removal refers to a low-flow (ie, 0.5–1 L/min) extracorporeal circuit that selectively extracts CO_2 from blood and minimally affects oxygenation. Extracorporeal CO_2 removal devices include a drainage cannula placed in a central vein (ie, venovenous systems) or artery (ie, arteriovenous systems), an artificial membrane lung, a pump in venovenous configurations, and a return cannula into the venous system.

During extracorporeal CO_2 removal, a flow of gas with little or no CO_2 (ie, sweep gas) favors CO_2 removal from the patient's blood by generating a diffusion gradient across the membrane.[11] Additional CO_2 removal depends on the blood flow to the membrane. An average adult produces about 200–250 mL/min CO_2 and 1 L of blood contains approximately 500 mL CO_2. Thus, a blood flow of 0.5 L/min would theoretically suffice to remove all of the CO_2 produced by the body. In practice, however, extracorporeal CO_2 removal removes up to 25% of CO_2 production because gas transfer is also influenced by premembranous blood CO_2 content, membrane characteristics, and hemoglobin concentration.[12]

Using an extracorporeal CO_2 removal system equipped with a silicone rubber membrane oxygenator, Kolobow et al[13] were the first to demonstrate that CO_2 transfer (35–65 mL/min) at a constant sweep gas flow of 2.5 L/min was dependent on blood flows (400–1,000 mL/min) and premembrane P_{CO_2} levels. Cardenas et al,[14] applying a polypropylene microporous hollow fiber membrane oxygenator, reported that CO_2 transfer was directly proportional to blood flow and gas flow, ranging from 31 mL/min (at 500 mL/min blood flow and 2 L/min gas flow) to 150 mL/min (at 1,000 mL/min blood flow and 15 L/min gas flow). In the clinical setting, extracorporeal CO_2 removal proved to be effective in 95 subjects with moderate ARDS, achieving ultraprotective settings in 82% by 24 h.[15]

Karagiannidis et al[16] highlighted the essential extracorporeal CO_2 removal requirements (ie, choice of cannula and optimal blood and sweep gas flow) for the successful treatment of severe respiratory acidosis. Extracorporeal CO_2 removal with a 0.98 m^2 surface oxygenator was performed in 6 acidotic (pH < 7.20) pigs using either a 14.5-French or a 19-French catheter and applying sweep gas flows of 8 and 16 L/min, respectively. During each experiment, blood flow was incrementally increased to a maximum of 400 mL/min (14.5 French catheter) and 1,000 mL/min (19 French catheter). Correction of acidosis was obtained only with the 19-French catheter at blood flows of 750–1,000 mL/min. Doubling sweep gas flow had less impact on extracorporeal CO_2 removal performance.

The same investigators studied the impact of different membrane lungs on CO_2 removal.[17] Extracorporeal CO_2 removal was performed in anesthetized and mechanically ventilated pigs that were subjected to severe respiratory acidosis (pH 7.0–7.1) using membrane lungs with surface areas of 0.4, 0.8, 1.0, and 1.3 m^2. A 20-French double-lumen catheter was inserted, and sweep gas flow was set at 8 L/min. During each experiment, blood flow was increased stepwise from 250 mL/min to 1,000 mL/min. Respiratory acidosis was attenuated only at blood flows of 750–1,000 mL/min over a membrane lung surface area of $\geq$ 0.8 m^2. Maximum CO_2 elimination with concomitant pH increase to 7.3 was obtained with the 1.3-m^2 membrane lung at a blood flow of 1,000 mL/min. The membrane lung with a surface of 0.4 m^2 allowed less than half of this CO_2 elimination rate and failed to normalize pH, even when blood flow was 1,000 mL/min.

Lung-Kidney Interaction in ARDS

ARDS and mechanical ventilation are independently associated with acute kidney injury (AKI).[18] Ventilated patients have a 3-fold increase in the odds ratio of AKI.[19] Conversely, presence of AKI prolongs ventilator dependence and increases mortality.[20] During ARDS, renal function is impeded by hemodynamic alterations, ischemic insults, toxic factors, and remote oxidative and neurohormonal stress.[21] In addition, the kidneys are exposed to injurious inflammation because mechanical ventilation-related overdistention or repetitive alveolar collapse can trigger the systemic release of proinflammatory cytokines and may increase expression of endothelial inflammatory mediators in the kidney.[22,23]

Renal replacement therapy is frequently initiated to treat AKI in patients with ARDS. Among other techniques, continuous renal replacement therapy (CRRT) is increasingly used in ICUs worldwide. CRRT allows constant blood purification, is hemodynamically well tolerated, permits safe fluid titration to achieve optimal hemodynamic and

nutritional goals, achieves metabolic control more rapidly, and swiftly removes excess fluid.[24]

Extracorporeal CO_2 removal and CRRT circuits may be integrated into a global lung and renal support system. No additional vascular access other than the dialysis catheter is required. Any membrane oxygenator or gas exchanger can be implemented in the CRRT circuit. A typical example of combined extracorporeal CO_2 removal with CRRT is the DECAP (Hemodec, Salerno, Italy)/DECAPSMART (Medica, Medolla, Modena, Italy) system, which consists of a membrane lung placed in series with a polysulfone hemofilter (surface area of 0.3–1.35 m^2) (Fig. 1). A roller pump drives blood from the patient to the oxygenator and hemofilter, and CO_2 is eliminated by diffusion at a constant flow of air or oxygen through the oxygenator. A second roller pump returns the ultrafiltrate from the filter to the inflow of the oxygenator. The higher flow entering the membrane lung and the recirculation of CO_2 dissolved in the ultrafiltrate improve CO_2 removal. Additionally, the ultrafiltrate acts as predilution, reducing hematocrit and preventing blood packing. This allows lower flows (< 500 mL/min) than those used in CRRT but provides anticoagulation therapy similar to that of CRRT.[25]

CO_2 removal dramatically declines when blood flow decreases to 300–350 mL/min. De Bels et al[26] developed a novel approach to run extracorporeal CO_2 removal at a blood flow of 450 mL/min within a CRRT circuit. To achieve such blood flow, 2 double-lumen catheters (13 French) were inserted, one in the jugular vein and one in the femoral vein. The catheters were linked with a Y-adapter to create a single bloodline without loss of blood flow. Blood was extracted from the CRRT-extracorporeal CO_2 removal system via the femoral catheter and, after decarboxylation, reinfused through the cephalic catheter. Compared with to a single-catheter approach, blood flow increased by almost 40%, which permitted CRRT-extracorporeal CO_2 removal to run for up to 72 h in the majority of cases.

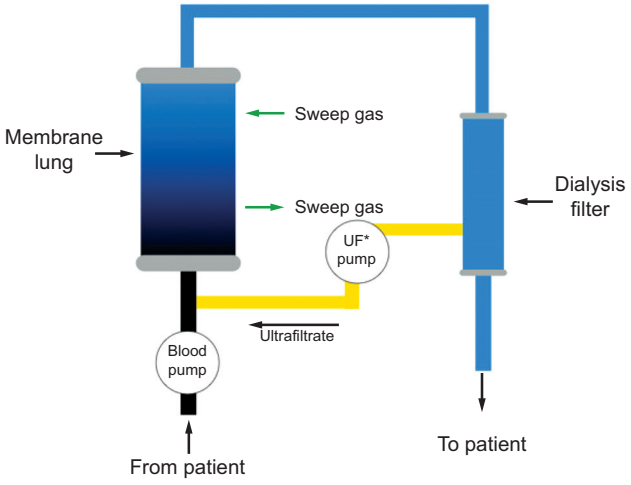

Fig. 1. Diagram showing the basic circuit design of the DECAP system.

Literature Review

We conducted a PubMed and MEDLINE literature search for studies investigating CRRT-extracorporeal CO_2 removal as a way to facilitate lung-protective ventilation. Only articles in English published in peer-reviewed journals were considered. We used the following search items: (carbon dioxide[MeSH Terms] OR (carbon[All Fields] AND dioxide[All Fields]) OR carbon dioxide[All Fields]) AND removal[All Fields] AND continuous[All Fields] AND (renal replacement therapy[MeSH Terms] OR (renal[All Fields] AND replacement[All Fields] AND therapy[All Fields]) OR renal replacement therapy[All Fields]). Related articles were used to broaden the search, and citations were scanned for relevance. The last search was performed on June 30, 2019. We initially identified 110 papers, of which 94 were discarded after screening the abstract or the article content. From the remaining 16 studies, 13 were used in our final analysis, including 4 preclinical studies, 3 case reports, 3 retrospective studies, and 3 prospective clinical trials.

Animal Studies

Of the 4 preclinical studies, 3 were performed in sheep and 1 was performed in pigs under conditions of normal physiology; in 2 of these studies, hypercapnia was induced (Table 1). Livigni et al[27] quantified CO_2 removal of an extracorporeal membrane gas exchanger placed in a veno-venous pump-driven bypass (DECAPSMART) in 7 adult sheep. CO_2 was continuously cleared from the circulation

Table 1. Animal Studies

Study	Animals, no.	Blood Flow, L/min	Gas Flow, L/min	Result	Adverse Events
Livigni et al[27]	7	300	Not reported	CO_2 reduced by 17–22%	No
Godet et al[28]	5	200, 300, 400	Not reported	CO_2 removal rates 35–75 mL/min	Not reported
Young et al[29]	9	470–600	10	CO_2 elimination 130–180 mL/min	Not reported
Scaravilli et al[30]	3	250	10	CO_2 removal not influenced by ultrafiltrate recirculation	No

Table 2. Case Reports

Study	Condition	Blood Flow, L/min	Gas Flow, L/min	Result	Outcome	Adverse Effects
Gramaticopolo et al[25]	Septic shock	350–380	10 (FF 20%)	Pressure support reduced from 12 to 10 cm H_2O Peak pressure reduced from 33 to 26 cm H_2O Renal function improved	Alive	Not reported
Grant et al[31]	Sepsis, ARDS	Not reported	Not reported	pH increased from 7.33 to 7.37 P_{aCO_2} reduced from 48 to 44 mm Hg	Alive	Not reported
	Sepsis, AKI, ARDS	Not reported	Not reported	pH increased from 7.1 to 7.4 P_{aCO_2} reduced from 56 to 34 mm Hg	Alive	Not reported
Morris et al[32]	Sepsis, AKI, ARDS	Not reported	Not reported	P_{aCO_2} reduced from 63 to 40–50 mm Hg	Died	No

FF = filtration fraction
AKI = acute kidney injury

and on average reduced from baseline by 17–22%. P_{aCO_2} returned to baseline after treatment discontinuation.

Godet et al[28] studied 5 hypercapnic pigs equipped with a low-flow CO_2 removal device (PrismaLung) integrated on a CRRT platform (PrismaFlex). A polymethylpentene infant hollow fiber gas exchanger (Medos Hilite 1 800 LT) with a surface area of 0.32 m^2 was used as the decarboxylation filter. Sweep gas was adjusted to flows of 2, 5, 10, and 50 L/min. Blood flows were randomly set at 200, 300, and 400 mL/min. Gas analysis before and after the gas exchanger showed a significant reduction in P_{aCO_2} of 40.2 ± 13.0 mm Hg and an increase in pH of 0.24 ± 0.06. After 10 min of treatment, P_{aCO_2} decreased from 81.2 mm Hg to 70.0 mm Hg and pH increased from 7.17 to 7.22. CO_2 removal rates ranged from 35 to 75 mL/min. At the lowest blood flow, CO_2 removal rates remained constant and independent from sweep gas flow rising from 2 L/min to 10 L/min. At 300 and 400 mL/min blood flow, CO_2 removal rates increased with sweep gas flows, reaching a plateau between 10 and 50 L/min.

Young et al[29] investigated 9 sheep, using a 5-m^2 hollow fiber membrane lung with countercurrent gas flow (Capiox 350) combined with an hemofiltration blood pump (Dialysatoren) to flow through femoral arterial and venous hemodialysis catheters. A blood flow of 470–600 mL/min and a gas flow of 10 L/min guaranteed satisfactory CO_2 elimination (130–180 mL/min).

Ultrafiltrate recirculation may mitigate hemostasis through the membrane oxygenator and abate circuit-related inflammation. Scaravilli et al[30] were the first to examine the effects of such recirculation on CO_2 removal capability. Three conscious spontaneously breathing sheep were connected to an extracorporeal CO_2 removal device (Hemolung) installed at a blood flow of 250 mL/min and a gas flow of 10 L/min. A hemofilter (NxStage) placed in series with the membrane lung generated ultrafiltrate that was recirculated upstream to the membrane lung. Increasing ultrafiltrate flow progressively lowered premembrane blood CO_2 concentrations. The corresponding observed reduction in membrane CO_2 removal efficiency was countered by the increased (blood + ultrafiltrate) flow passing through the membrane and finally resulted in constant CO_2 elimination (40.5 ± 4.0, 39.7 ± 4.2, 39.8 ± 4.2, and 39.2 ± 4.1 mL/min at ultrafiltrate flows of 0, 50, 100, and 150 mL/min, respectively). Thus, application of ultrafiltrate recirculation did not alter CO_2 removal compared with no recirculation and, as a direct result, did not affect the animals' ventilatory patterns or arterial blood gas values.

In summary, animal studies generally reported substantial reductions in CO_2 volume and P_{aCO_2}. The magnitude of CO_2 removal appeared to depend upon both dialysis blood flow and sweep gas flow. Effectiveness of CO_2 removal reached a plateau at sweep gas flows of 10–50 L/min and was not influenced by ultrafiltrate recirculation.

Case Reports

Three case reports described the application of combined CRRT-extracorporeal CO_2 removal in patients with septic shock complicated by respiratory and renal failure (Table 2). Gramaticopolo et al[25] observed a progressive decrease of ventilator support and stable pH in a moderately hypercapnic man with septic shock and multi-organ failure who underwent DECAP plus CRRT for 12 h. Blood flow was kept at 350–380 mL/min, and gas flow was maintained at 10 L/min. At the end of treatment, renal function recovered, and protective ventilation could be continued without extracorporeal support.

Grant et al[31] reported a female kidney transplant patient with pulmonary septic shock and ARDS and a male patient with postoperative sepsis, AKI, and respiratory failure. In both patients, lung-protective ventilation provided acceptable oxygenation at the cost of severe

Table 3. Retrospective Studies

Study	Subjects, *N*	Condition	Blood Flow, L/min	Gas Flow, L/min	Result	Outcome	Adverse Events
Quintard et al[33]	16	Respiratory acidosis, AKI	400–500	10	Mean P_{aCO_2} reduction of 31% and 39% at 6 h and 12 h, respectively, with concomitant pH increase	7 subjects died	No
Forster et al[34]	10	ARDS	250–500 (mean 378)	Not reported	28% mean P_{aCO_2} reduction 65% reduction of vasopressors	3 subjects died	2 filters clotted
Moerer et al[35]	11	Mixed population	300	10	Mean P_{aCO_2} reduction from 34.4 to 28.8 mm Hg at 1 h and to 31.6 mm Hg at 6 h	Not reported	No

AKI = acute kidney injury

hypercapnia. A low-flow membrane oxygenator (CapiOx RX05) placed in line with a continuous venovenous hemodialysis circuit (NxStage System One renal replacement device) resulted in an immediate and sustained drop in P_{aCO_2}, pH normalization, and subsequent hemodynamic stabilization.

Morris et al[32] reported improved CO_2 removal in a 6-y-old boy with postoperative anasarca, sepsis-induced hepatorenal syndrome, and ARDS after adding a membrane oxygenator (CB Minimax or Lilliput I) before the filter of a continuous venovenous hemodialysis circuit. In summary, these case studies reported that combined CRRT-extracorporeal CO_2 removal substantially curbed hypercapnia and facilitated lung-protective ventilation in critically ill patients.

Retrospective Studies

Three retrospective studies were conducted in mechanically ventilated subjects. Two studies included subjects with ARDS and refractory hypercapnia due to COPD exacerbation, and one study investigated a mixed patient population with AKI undergoing lung-protective ventilation (Table 3). Quintard et al[33] studied 16 mechanically ventilated subjects with persistent significant respiratory acidosis and AKI necessitating CRRT (either continuous venovenous hemodialysis or continuous venovenous hemofiltration). A, rheoparine-coated, polypropylene oxygenation membrane with a surface area of 0.65 m^2 (Hilite 2400 LT) was introduced into the CRRT circuit in serial manner and upstream from the hemofilter. Unfractionated heparin was used for anticoagulation (target activated partial thromboplastin time, 45–50 s). Blood flow and sweep gas flow were set at 400 mL/min and 10 L/min, respectively. The mean P_{aCO_2} level before treatment was 77.3 (range 59–112) mm Hg. Adequate blood flow was achieved either with one femoral 16-French dual-lumen catheter or with two 13.5-French double-lumen catheters in the jugular and femoral positions. Mean P_{aCO_2} reduction was 24.4 mm Hg (31%) after 6 h and 30 mm Hg after 12 h (39%). Mean pH increase was 0.16 at 6 h and 0.23 at 12 h. Lung-protective ventilation was maintained in all subjects. Treatment was safe and hemodynamically well tolerated.

Forster et al[34] evaluated 10 critically ill subjects with ARDS and AKI. CRRT was initiated with a continuous venovenous hemodialysis device (bm11/14) equipped with a high-flux polysulfone capillary hemofilter with a membrane surface area of 1.4 m^2 (Polyflux 140H). Extracorporeal CO_2 removal was provided by a hollow-fiber gas exchanger (D902 Liliput 2 ECMO) placed after the dialysis filter. Gas flow through the gas exchanger was set at 4 L/min with blood flows $<$ 300 mL/min or at 4–6 L/min when blood flows exceeded 300 mL/min. A 13.5-French double-lumen catheter was placed in the jugular vein. In 2 subjects, a second 13.5-French double-lumen catheter was inserted in the femoral vein to allow higher blood flows. The 2 lumina of one catheter were linked with a Y-adapter to form a single bloodline. Blood flows of 250–500 mL/min could be achieved in all subjects. After 4 h of treatment, a mean P_{aCO_2} reduction of 17.3 mm Hg (28.1%) was observed with a concomitant pH increase of 0.12. A 65% average reduction of vasopressor dose was obtained in 5 of 6 catecholamine-dependent subjects during the first 24 h.

Moerer et al[35] conducted a study in 11 ventilated subjects with AKI on either pre- or postdilution CRRT running in continuous venovenous hemodiafiltration mode. A minimum-flow extracorporeal CO_2 removal (EQUA-smart) device was added to the circuit for 6 h. This combined CRRT-extracorporeal CO_2 removal system safely and significantly decreased minute ventilation, tidal volume, and P_{aCO_2} during the first hours of therapy, but it was not able to improve or preserve this result throughout the trial. Average total CO_2 removal reached 20.7 mL/min, with comparable values between pre- and postdilution. The system failed to significantly reduce lung stress due to ventilator settings.

Table 4. Prospective Studies

Study	Subjects, *N*	Condition	Blood Flow, L/min	Gas Flow, L/Min	Result	Outcome	Adverse Events
Allardet-Servent et al[36]	11	ARDS	Downstream 410 ± 30 Upstream 432 ± 25	Not reported	CO_2 removal rate 83 ± 20 mL/min	8 subjects survived to extracorporeal CO_2 removal 9 subjects died in ICU	1 filter clotted
Nentwich et al[37]	20	Hypercapnic critically ill subjects with renal failure	Mean extracorporeal CO_2 removal 43.4 ± 14.1	8	Mean P_{aCO_2} reduction from 68.3 ± 11.8 to 61.8 ± 11.5 mm Hg Mean pH increased from 7.18 ± 0.09 to 7.22 ± 0.08	2 subjects died	5 filters clotted
Schmidt et al[38]	20	ARDS	Mean 421 ± 40	Mean 10 ± 0.3	Mean CO_2 removal 51 ± 26 mL/min	28-d mortality 15%	10 filters clotted, 2 instances of hemoptysis

Taken together, combining extracorporeal CO_2 removal with CRRT in hypercapnic subjects with ARDS or COPD caused a P_{aCO_2} reduction of up to 30% and significantly increased pH. In AKI subjects undergoing lung-protective ventilation, an initial decrease in P_{aCO_2} was not sustained, and ventilator-induced lung stress remained unchanged. The application of CRRT-extracorporeal CO_2 removal either in pre- or postdilution mode was safe and hemodynamically well tolerated.

Prospective Trials

The 3 prospective studies identified in the literature search primarily enrolled subjects with ARDS (Table 4). Allardet-Servent studied 11 subjects with ARDS and AKI requiring CRRT.[36] CRRT was provided as continuous venovenous hemofiltration and delivered with a PrismaFlex 6.0 CRRT platform titrated to maintain a maximum blood flow and an effluent flow of 45 mL/kg/h with a 33% predilution rate. A 0.65-m^2 polymethylpentene heparin-coated hollow fiber membrane oxygenator (Hilite 2400 LT) was inserted either upstream or downstream of the hemofilter. Twelve combined therapies were conducted, of which 7 lasted 72 h. At tidal volumes of 6 mL/kg, P_{aCO_2} decreased by 21% (from 47 ± 11 to 37 ± 8 mm Hg). Lowering tidal volume to 4 mL/kg raised P_{aCO_2} from 37 ± 8 to 48 ± 10 mm Hg. pH behavior was inversely correlated with changes in P_{aCO_2}. Blood flow and CO_2 removal rates tended to be higher when the membrane oxygenator was placed upstream of the filter.

Nentwich et al[37] enrolled 20 hypercapnic critically ill subjects in a multicenter observational pilot study for combination treatment incorporating a 0.32-m^2 membrane oxygenator (Prismalung) in a conventional CRRT circuit in continuous venovenous hemofiltration F mode (Prismaflex system). The membrane oxygenator was serially inserted in the CRRT circuit downstream of the hemofilter. Implementation of this extracorporeal CO_2 removal system significantly decreased P_{aCO_2} (from 68.3 ± 11.8 to 61.8 ± 11.5 mm Hg and attenuated acidosis (pH increase from 7.18 to 7.22). Tidal volumes, plateau pressures, and pulmonary strain all significantly decreased.

Schmidt et al[38] conducted a pilot trial in 5 medical and surgical ICUs, which included 20 subjects with mild or moderate ARDS. Extracorporeal CO_2 removal was performed with a low-flow CO_2 removal device (Prismalung) integrated into the Prismaflex platform. Standalone extracorporeal CO_2 removal with no hemofilter associated within the CRRT platform was initiated when P_{aCO_2} increased > 20% from baseline. This system easily and safely enabled very low tidal volume ventilation at higher PEEP levels and significantly decreased plateau and driving pressures.

Taken together, these prospective trials confirm that CRRT-extracorporeal CO_2 removal systems can perform safe and adequate CO_2 removal, thereby facilitating or enhancing lung-protective ventilation at lower pulmonary strain.

Summary

Ventilation-induced respiratory acidosis and AKI during the course of acute respiratory failure can be managed simultaneously by integrating extracorporeal CO_2 removal into a standard CRRT platform. Results of animal studies, patient case studies, and retrospective clinical trials indicate that implementation of this technique is feasible, safe, and effective. Current evidence from prospective clinical pilot studies is still limited but highlights that substantial CO_2 clearance is achieved when blood flows of 400–450 mL/min and a sweep gas flow of 10 L/min are applied. To date, the best studied setup

that allows or facilitates adequate protective and even ultraprotective ventilation with the least pulmonary compromise uses a 0.32-m^2 membrane oxygenator integrated in the Prismaflex platform. Technical considerations and progress may contribute to a more patient-tailored approach or improve system performance and safety. CO_2 removal is enhanced by using a larger membrane surface or by positioning the membrane upstream from the hemofilter. Regional circuit anticoagulation may improve filter life span and decrease the incidence of membrane clotting. A double-catheter approach to run extracorporeal CO_2 removal at higher blood flow within a CRRT circuit has been proposed. Large, prospective, and controlled studies are needed to assess the real impact of combined lung-renal support on patient outcome.

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