Extracorporeal CO₂ Removal Integrated within a Continuous Renal Replacement Circuit Offers Multiple Advantages

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Abstract

Extracorporeal CO₂ removal within a continuous renal replacement therapy circuit offers multiple advantages for the regulation of the CO₂ extraction. The authors review the impact of the dialysate solution, the buffer, and the anticoagulation on CO₂ removal. They propose a theoretical model of the ideal circuit for the optimization of CO₂ extraction.

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Introduction

The multiple organ dysfunction syndrome also called multiple organ failure (MOF) is defined by the “presence of altered organ function in an acutely ill patients such that homeostasis cannot be maintained without intervention” [1]. As part of this syndrome, it has been shown that in patients with MOF with respiratory support, 60% of them also require renal replacement therapy [2]. There is

an interaction between the mechanical ventilatory support and the renal function (Fig. 1). During mechanical ventilation, there is a production of pro-inflammatory mediators which can exert an effect on other organs, thus constituting the MOF. Ranieri et al. [3] randomized 37 patients with ARDS either in a protective ventilation arm or in a conventional control arm. They measured in the control arm a significantly higher rate of interleukin-6, tumor necrosis factor α , and tumor necrosis factor α receptor in plasma and in bronchoalveolar lavage [3]. Similarly, patients in the control group have a higher rate of renal failure and a degree of MOF correlated with the level of interleukin-6 [4].

All these observations have defined protective ventilation (tidal volume 6–8 mL/kg, limited airway pressure <25–30 cm H₂O) as the ventilation standard. This low-volume ventilation is done at the cost of permissive hypercapnia. Although it offers advantages, this permissive hypercapnia can have negative effects such as a harmful cerebral vasodilation in case of intracranial hypertension [5], hinder the lung epithelial and cellular repair after stretch-induced injury [6], and impact the response of the host to microbial attack [7]. A recent study showed that acute hypercapnia (>50 mm Hg) in ARDS was associated

Fig. 1. Interaction between mechanical ventilation and acute kidney injury.

with increased mortality (OR 1.93, 1.32–2.81, $p = 0.001$). Acute hypercapnia may have hemodynamic consequences and lead to pulmonary hypertension and right heart failure [8]. It is to avoid the problems associated with hypercapnia that extracorporeal CO_2 removal (ECCO₂R) systems have been created. ECCO₂R allowed ventilation in a protective manner without the consequences of hypercapnia and acidosis [2].

Terragni et al. [9] tested ultra-protective ventilation conditions which, in combination with ECCO₂R, made it possible to reduce ventilator-induced lung injury. In the Supernova study, ECCO₂R made it possible to apply protective ventilation in patients with moderate ARDS. A reduction in tidal volume to 3–4 mL/kg of ideal body weight and a plateau pressure <25 mm H₂O could be applied in 82% of patients admitted to the study with a baseline PCO_2 variation of less than 20%. The side effect rate was 39% with 6 serious adverse events, including a cerebral hemorrhage and a pneumothorax [10]. Regarding chronic obstructive pulmonary disease (COPD) where hypercapnia is chronic, the literature includes 3 studies that showed a benefit in terms of a reduction in the number of intubations but no benefit in terms of survival, probably due to a lack of power [11]. The reduction in PCO_2 is variable according to the studies. The ECLAIR study reported a PaCO_2 reduction of 17.5 mm Hg at 1 h and 29.5 mm Hg at 24 h. Likewise, ECCO₂R has been shown to reduce the intubation rate by 56% and the duration of mechanical ventilation by 60% in COPD patients [12]. However, the same authors reported 44% of major adverse events, including 36% of major bleeding (pulmonary hemorrhage, bleeding from tracheostomy, hemothorax, bleeding from gastric ulcer, rectal ulcer, esophageal varices, and retroperitoneal hematoma) events which constitute a main limitation to the dissemination of this technique in intensive care [12]. The authors could not demonstrate

relevant coagulopathy in ECCO₂R patients with bleeding complications. The extracorporeal surface and blood flow of the midflow device may induce unmeasured clotting disorders and contribute to hemorrhagic complications, such as platelet dysfunction, acquired von Willebrand syndrome, hyperfibrinolysis, or factor XIII deficiency [12]. Other complications were device-related (air detection or disconnection) [12].

ECCO₂R within a continuous renal replacement therapy (CRRT) circuit (ECCO₂R-CRRT) is an interesting approach recently developed by some authors [13–15] in order to extract CO_2 and at the same time as conventional dialysis [2]. We present in Figure 2 a model of CRRT-ECCO₂R. However, there is no demonstrated benefit in placing the oxygenator before or after the renal filter [14]. The current indication for CRRT coupled with ECCO₂R is the association of hypercapnic respiratory acidosis with AKI requiring CRRT. The indications for CRRT are currently the same as in AKI without respiratory failure [16]. ECCO₂R-CRRT is frequently used in patients with COPD at lower cost than standard ECCO₂R [15].

In terms of acid-base equilibrium, the most commonly encountered perturbation in such patients is respiratory acidosis, which is commonly associated with a metabolic alkalosis [17]. Studies in rabbits have shown that chronic respiratory acidosis leads to an expression of the luminal Na/H antiporter and basolateral Na/HCO₃ co-transporter in proximal tubule cells [18]. This phenomenon is also accompanied by hypochloremia, which is explained by the existence of a Cl/HCO₃ exchanger called pendrin (SLC26A4, PDS) at the level of the apical domain of type B and non-A-non-B intercalated cells. The expression of pendrin is downregulated during hypercapnia, which provides collecting tubules the potential for increased bicarbonate reabsorption and chloride excretion [19, 20]. Due to its dual function of bicarbonate secretion

Fig. 2. Schema of a combined ECCO₂R and RRT. Hemofilter is a classic device (e.g., AN69ST Gambro®) with pre- and postdilution reinjection that could be, for example, normal saline and reinjection fluid with or without bicarbonate. The hemofiltered blood then passes through a pediatric oxygenator (e.g., Liliput2 ECMO LivaNova®). In counter current flow, air or oxygen is circulated. The exchange of CO₂ takes place from oxygen-laden blood to gas which does not contain it. RRT, renal replacement therapy; ECCO₂R, extracorporeal CO₂ removal.

and chloride reabsorption in the distal tubules, it is thought that pendrin plays an important role in systemic acid-base and electrolyte balance as well as vascular volume in homeostasis under basal conditions. Pendrin is upregulated by bicarbonate loading and downregulated in acidosis [21].

The mortality of the COPD patients is independent of the level of PCO₂ but is clearly related to the presence of acidosis (pH < 7.25) [22, 23]. Ucgun et al. [24] also showed a link between the presence of renal compensation and mortality. The overall mortality of their patients was 59% for a HCO₃ < 20 mEq/L. This mortality fell to 19% for a HCO₃ > 28 mEq/L. In their series, one-third of patients had HCO₃ levels above 28 mEq/L. Although administration of bicarbonate has not shown any benefit in terms of survival in metabolic acidosis in intensive care [25], it is interesting to note that the use of CRRT-ECCO₂R allows both the extraction of CO₂ and the concomitant reproduction of renal metabolic compensation in patients with hypercapnic chronic respiratory failure and concomitant

impaired renal failure. We wish to describe the different possibilities offered by the association of CRRT and ECCO₂R (CRRT-ECCO₂R), in terms of optimization of the pH and extraction of CO₂.

Dialysate Solution

In a recent study, Jonckheer et al. [26] measured the levels of CO₂ and O₂ pre- and postfilter and in the effluent in patients treated with CRRT under standard conditions. The VCO₂ drops significantly between the prefilter and the postfilter measurements (from 110.5 ± 9.6 mL to 84.5 ± 6.5 mL/min [*p* > 0.01]). VCO₂ in the effluent was measured at 26.0 ± 5.8 mL. This withdrawal corresponds to approximately 14% of the CO₂ exhaled by a patient. For oxygen, the VO₂ prefilter was measured at 10.9 ± 3.9 mL/min and postfilter at 10.9 ± 3.6 mL/min (*p* = 0.33). VO₂ was measured at 0 mL/min in the effluent. CRRT does not extract oxygen at standard dialysate flow rates [26]. In the

Fig. 3. Mechanism of CO₂ removal by RRT. RRT, renal replacement therapy.

model used by Jonckheer et al. [26], the reinjection liquid was 0.9% NaCl, therefore free of bicarbonate (Fig. 3).

In the CRRT-ECCO₂R, the CRRT device is used as a pump in charge of circulating the blood through a pediatric oxygenator. CO₂ is transported in the blood in dissolved form in plasma (5%), bound to hemoglobin (15%), or as bicarbonate (80%) [27]. If a clinician only uses the Hemosol B0[®] compartment A, the lack of HCO₃ in the dialysate induces bicarbonate extraction, as the sieving and extraction coefficients are close to 1 (Fig. 4). According to some authors, this extraction could reduce the total CO₂ [28]. Cove et al. [29] tested the effect of bicarbonate removal on pH and plasma CO₂ in an in vitro model. They used an adult-size renal filter and then used dialysates with several different bicarbonate concentrations. Using bicarbonate-free dialysate, they removed 94 mL/min of CO₂. With the same dialysis conditions using a dialysate containing 32 mEq/L of HCO₃, CO₂ removal dropped to 5 mL/min. However, they showed that with no HCO₃, the pH was improperly modified with a trend to acidosis [29]. CO₂ extraction is limited because the pH becomes acidic due to incomplete regeneration of systemic bicarbonate.

Assuming that 80% of plasma CO₂ is in the form of bicarbonate [27], a recent work has shown that an acetazolamide-impregnated membrane can also extract up to 36% more CO₂ than a standard membrane [30]. In a second article, the same author showed that when using 2.2% SO₂ as a flushing gas, the CO₂ extraction capacity could be doubled by acidifying the acetazolamide-containing membrane, which accelerated the conversion of bicar-

Blood		Dialysate with only compartment A
Ca ²⁺ : 1.12–1.32 mmol/L	←	Ca ²⁺ : 1.75 mmol/L
Mg : 0.63–1.05 mmol/L	→	Mg : 0.5 mmol/L
Cl ⁻ : 98–107 mmol/L	→	Cl ⁻ : 2.25 mmol/L
Lactate : 0.7–2.0 mmol/L	←	Lactate : 71.6 mmol/L
Na ²⁺ : 135–145 mmol/L	→	
K ⁺ : 3.5–4.5 mmol/L	→	
HCO ₃ ⁻ : 23–29 mmol/L	→	

Fig. 4. Effect of exposure to compartment A of hemosol B₀ during RRT in a patient without ionic anomalies. Bicarbonate diffuses in the effluent. This explains the disappearance of renal compensation by elevation of bicarbonate in a patient with COPD. RRT, renal replacement therapy. COPD, chronic obstructive pulmonary disease.

bonate to CO₂ while maintaining a physiological pH [31]. Note that CO₂ extraction is limited by secondary metabolic acidosis in patients with AKI/CKD when using a liquid of substitution free of bicarbonate. We cannot use HEMOSOL compartment A only in this renal suffering population without dangerous hemodynamic risks. It would, therefore, be more prudent to use acetazolamide coated membrane.

Impact of the Buffer

Previous studies have used buffer-free solutions containing sodium salts of organic anions (lactate, acetate, malate, succinate, fumarate, and citrate). It has been shown that only lactate and acetate are sufficiently rapidly metabolized to bicarbonate (0.1 mmol/kg/min). This means that the same amount of bicarbonate can be removed: 40–75 mL of CO₂ (2 mL/kg/min). Alkalization with NaOH gave many side effects, such as electrolyte disturbances, hemolysis, arrhythmias, and cardiac arrest. Alkalinization with tris(hydroxymethyl)aminomethane (“Tris”) gave refractory hypotension after 8–12 h [32].

Table 1. Hemosol B₀ composition before reconstitution

<i>1,000 mL of electrolyte solution (small compartment A) contains</i>	
Calcium chloride, 2H ₂ O	5.145 g
Magnesium chloride, 6H ₂ O	2.033 g
Lactic acid	5.4 g
<i>1,000 mL of buffer solution (large compartment B) contains</i>	
Sodium hydrogen carbonate	3.09 g
Sodium chloride	6.45 g

The Hemosol B₀[®] compartment A contains 60 mmol/L of lactate (Tables 1, 2), which leads to a certain degree of acidification of the system which has been described as facilitating the extraction of CO₂ [33, 34]. Lactate is a physiological substrate for many tissues and is then metabolized by the body. Experimental work by Zanella has shown that an infusion of 5 mEq/min of lactic acid into the circuit before the oxygenator membrane allowed maximum CO₂ extraction. The pH obtained in the circuit before the membrane decreased to around 6.90 (0.5 pH unit) and the pCO₂ increased up to 140 mm Hg. This pH at 6.90 is safe for blood elements because human blood tolerates similar pH in the muscle during strenuous exercise [28]. On the other hand, under standard conditions without acidification, PCO₂ drops to around 25 mm Hg with a postmembrane pH rise of up to 7.85 which could be dangerous for the blood. The authors highlight the benefit of acidification with lactic acid, which can buffer postmembrane blood alkalization [33].

However, we have observed that in a patient with COPD with compensatory respiratory alkalosis treated accidentally with a dialysate with only the compartment A, the gradient between the dialysate and the blood is such that the bicarbonate removed by CVVH induces a net effect of acidification of the pH that can fall below 7.25. Again, the use of CVVH brings an interesting advantage to resolve this problem. It has been clearly shown that administering intravenous bicarbonate while increasing pH also increases PCO₂ [35], which is the opposite of the expected effect of ECCO₂R. Other authors have shown that the administration of bicarbonate via a CVVH machine is not accompanied by a concomitant rise in PCO₂ [36, 37] (Fig. 5).

According to the theory of Stewart, the pH has 3 main determinants: PaCO₂, strong ion difference (SID), and the presence of weak acid. Romano et al. [36] compared blood pH of pigs hemodialyzed with either 20 mEq/L ("group 20") or 40 mEq/L ("group 40") of bicarbonate in the dialysate. They postulated that the improved control of blood pH in the animals in group 40 was achieved by

Table 2. Hemosol B₀ composition after reconstitution

		In mmol/L	In mEq/L
Calcium	Ca ²⁺	1.75	3.50
Magnesium	Mg ²⁺	0.5	1.0
Sodium	Na ⁺	140	140
Chloride	Cl ⁻	109.5	109.5
Lactate		3	3
Hydrogen carbonate	HCO ₃ ⁻	32	32

higher SID values, due to lower chloride infusion in this group without elevation of PCO₂. They put forward 3 hypotheses to explain the absence of elevation of CO₂.

First, this result could be explained by Gattinoni's "open system" theory in which CO₂ clearance by the lungs attenuates the effect on blood pH of CO₂ elevation secondary to sodium bicarbonate infusion. This theory implies the preservation of the integrity of the capillary alveolar membrane. They expected an increase in the total venous blood content of CO₂ in group 40 secondary to the influx of bicarbonate from dialysate, which would result in increased CO₂ transfer in the lungs. However, neither the venous blood CO₂ content nor the venous-arterial difference of CO₂ was different between the groups; thus, it is difficult to ascribe the lack of PaCO₂ elevation to enhanced pulmonary elimination.

The second possibility is a volume of CO₂ distribution so large in the tissues that the plasma value would be unchanged. The third explanation is related to the slower infusion rate in the CVVH circuit which would explain the absence of a PCO₂ peak [33].

The compensatory metabolic alkalosis of chronic COPD can be very important. It is not uncommon to observe values around 50 mmol/L of bicarbonate. The metabolic acidosis induced by the fall of the bicarbonate linked to the dialysis can have a beneficial effect by acidifying the blood at the prerenal filter level and thus favoring CO₂ extraction. But in case of a too deep metabolic acidosis (pH < 7.25), a respiratory deterioration can oc-

Fig. 5. Evolution of a patient with COPD treated by ECCO₂R with Hemosol® compatibility A. After initiation of the treatment, the PCO₂ decreases but the bicarbonate falls with a pH below 7.25. The addition of bicarbonate (compartment B + 100 mL NaHCO₃ 8.4%) in the CVVH circuit normalizes the pH without concomitant elevation to PCO₂. ECCO₂R, extracorporeal CO₂ removal; COPD, chronic obstructive pulmonary disease.

Fig. 6. Theoretical model of dialysis with dialysate without bicarbonate but with lactate buffer. There is a clear CO₂ extraction in CO₂ form but also in the form of bicarbonate. Citrate and lactate acidify the blood supply by diffusion, making it even easier to extract C.

cur, presenting as polypnea, which can worsen the clinical status of COPD patients. The addition of bicarbonate with compartment B (which should in principle be the rule in all dialysis) and the addition of bicarbonate (e.g., 100 mL NaHCO₃ 8.4%) in the dialysate can mimic the renal compensation lost by the addition of CRRT.

Fig. 7. The calcium citrate complex which retains a negative charge after binding of a calcium ion explaining the risk of alkalization due to citrate anticoagulation.

Impact of Anticoagulation

Trisodium citrate is the anticoagulant of choice in CRRT. Citrate acts as a weak acid. The presence of acid alters the Henderson-Hasselbach equation and disrupts the balance between different forms of CO₂ and potentially influences CO₂ extraction during CRRT [26]. The addition of citrate to blood results in the formation of citrate-calcium complex (CCC), effectively decreasing the level of ionizing calcium producing the anticoagulant effect. Again, according to Stewart's theory, the pH has 3 main determinants: PaCO₂, SID, and the presence of a weak acid (Fig. 6). Sodium citrate contains 3 Na⁺ ions which are released and replaced by a Ca²⁺ ion which leaves free a residual anion charge (Fig. 7). All citrate is in

CCC form except in case of hypocalcemia [38]. The net acidifying effect is very weak because the CCC is quickly eliminated by the body. Similarly, the 3 Na⁺ released will increase the SID and induce an alkalization that also counteracts the acidifying effect. The hypothetical possibility of acidification of the blood prefilter with citrate is negligible and is not found in practice [26].

Conclusion

In practical terms, it is important to keep in mind to provide bicarbonate in the dialysate pockets (compartment B of Hemosol B0®) to prevent metabolic acidosis secondary to bicarbonate extraction by the CVVH as compartment A does not contain any. Acidification with lactic acid is still an experimental treatment for which no recommendation yet exists and as such administration should only be done with monitoring of the prerenal membrane, postrenal membrane, and patient pH. Furthermore, high postmembrane pH after buffering of lactic acid could be deleterious.

Slow administration of supplementary bicarbonate 8.4% through the CRRT circuit could be useful to avoid a deleterious metabolic acidosis and mimic a potential re-

nal compensation which could be lifesaving for patients with COPD. Further RCTs are necessary to validate this hypothesis.

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Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

P.H., D.D.B., and S.R. designed the manuscript. All authors participated in drafting and reviewing. All authors read and approved the final version of the manuscript. Patients provided informed consent.

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