ORIGINAL ARTICLE

Respiratory Electrodialysis

A Novel, Highly Efficient Extracorporeal CO_2 Removal Technique

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Abstract

Rationale: We developed an innovative, minimally invasive, highly efficient extracorporeal CO_2 removal ($ECCO_2R$) technique called respiratory electrodialysis (R-ED).

Objectives: To evaluate the efficacy of R-ED in controlling ventilation compared with conventional $ECCO_2R$ technology.

Methods: Five mechanically ventilated swine were connected to a custom-made circuit optimized for R-ED, consisting of a hemofilter, a membrane lung, and an electrodialysis cell. Electrodialysis regionally modulates blood electrolyte concentration to convert bicarbonate to CO_2 before entering the membrane lung, enhancing membrane lung CO_2 extraction. All animals underwent three repeated experimental sequences, consisting of four steps: baseline (1 h), conventional $ECCO_2R$ (2 h), R-ED (2 h), and final NO-$ECCO_2R$ (1 h). Blood and gas flow were 250 ml/min and 10 L/min, respectively. Tidal volume was set at 8 ml/kg, and respiratory rate was adjusted to maintain arterial P_{CO_2} at 50 mm Hg.

Measurements and Main Results: During R-ED, chloride and H^+ concentration increased in blood entering the membrane lung, almost doubling CO_2 extraction compared with $ECCO_2R$ (112 ± 6 vs. 64 ± 5 ml/min, $P < 0.001$). Compared with baseline, R-ED and $ECCO_2R$ reduced minute ventilation by 50% and 27%, respectively. Systemic arterial gas analyses remained stable during the experimental phases. No major complication occurred, but there was an increase in creatinine level.

Conclusions: In this first *in vivo* application, we proved electrodialysis feasible and effective in increasing membrane lung CO_2 extraction. R-ED was more effective than conventional $ECCO_2R$ technology in controlling ventilation. Further studies are warranted to assess the safety profile of R-ED, especially regarding kidney function.

Keywords: extracorporeal circulation; carbon dioxide; respiratory insufficiency; hypercapnia

At a Glance Commentary

Scientific Knowledge on the Subject: Extracorporeal CO_2 removal ($ECCO_2R$) has been suggested for the treatment of patients with acute and chronic respiratory failure. The current $ECCO_2R$ technology, although perfected compared to the past, still has room for improvement.

What This Study Adds to the Field: We developed respiratory electrodialysis, an innovative extracorporeal CO_2 removal technique that selectively modulates pH and electrolyte concentration and highly enhances CO_2 removal by applying an electrical field to blood. Respiratory electrodialysis, requiring a minimally invasive approach, could greatly affect the way we treat patients suffering from respiratory failure and other conditions.

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Endotracheal intubation and mechanical ventilation are the conventional treatments for respiratory failure, and they unfortunately are often associated with severe complications (i.e., ventilator-associated pneumonia, ventilator-induced lung injury, diaphragmatic dysfunction) (1–3). Extracorporeal CO_2 removal ($ECCO_2R$) can partially replace lung gas exchange function, sparing patients from the detrimental consequences of intubation and mechanical ventilation, possibly reducing patient mortality (4–9). Recent applications of CO_2 removal have been aimed at low invasiveness, through low extracorporeal blood flows (10, 11). With current technology this approach may be limited by a relatively low amount of CO_2 removal (12–15). We aimed at significantly increasing the amount of CO_2 removed from a given blood flow, so as to achieve a greater decrease of ventilation and expand the spectrum of potential clinical applications (16–18).

We present here a technique that can remove up to 50% of total CO_2 production from 250 ml/min of blood flow and, by a possible scaling up, remove total CO_2 production from about 500 ml/min.

Membrane lungs can only remove dissolved CO_2 from blood. This gaseous form represents only a small part of the total blood CO_2 content, whereas the

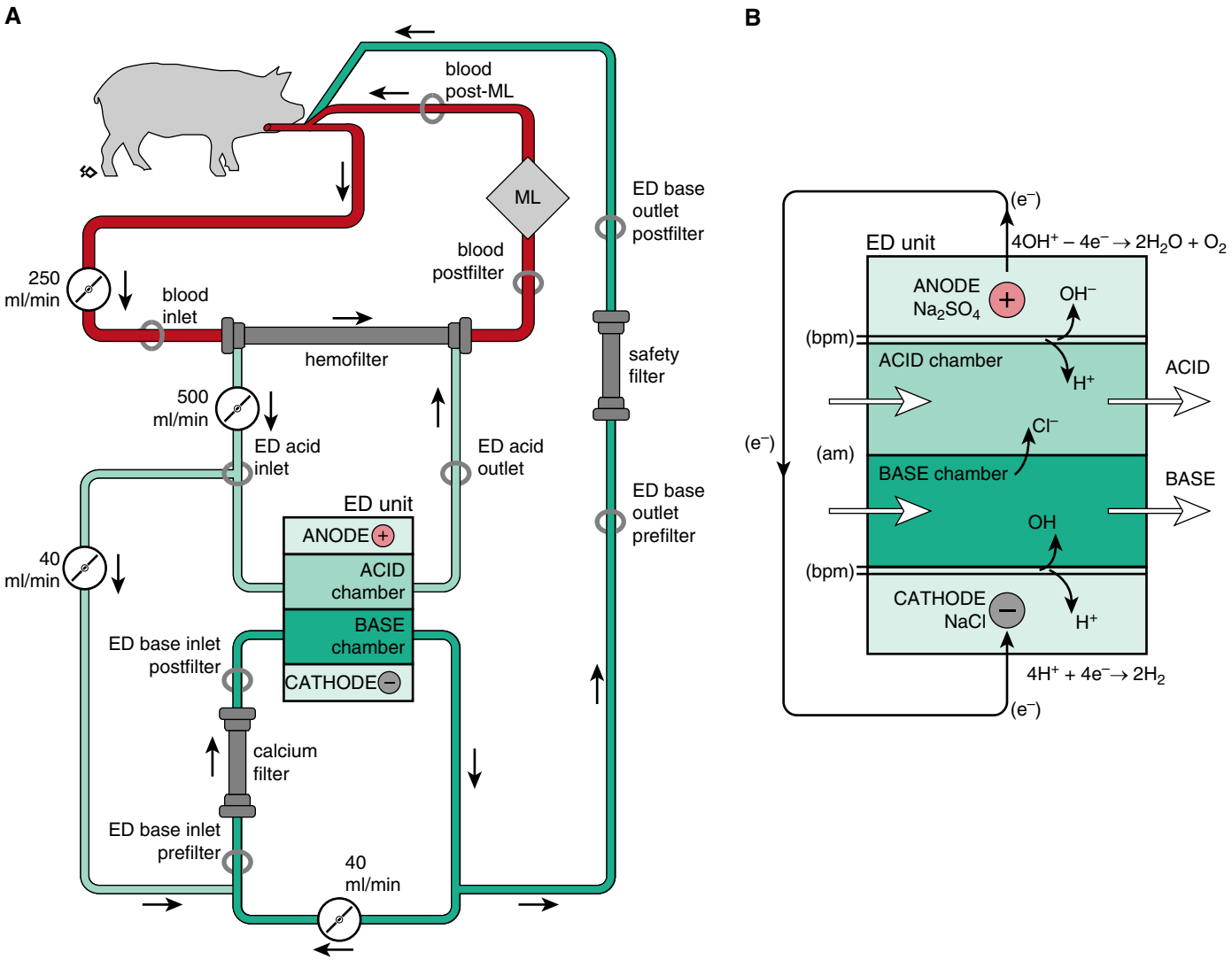

Figure 1. (*A*) Extracorporeal circuit. Blood circuitry (*red*), acid hemodiafiltrate (*light green*), and basic hemodiafiltrate (*dark green*). Blood flowed (250 ml/min) through a hemofilter and a membrane lung (ML). Hemodiafiltrate was generated by the hemofilter (500 ml/min), flowed toward the electrodialysis (ED) acid chamber, and returned to the hemofilter. Before the ED acid chamber, a fraction of the hemodiafiltrate (40 ml/min) was diverted toward a calcium filter, into the ED base chamber, and reinfused at the end of the blood circuit. A safety filter was placed before the reinfusion of ultrafiltrate into the blood. A fraction of hemodiafiltrate (40 ml/min) recirculated from the outlet of the ED base chamber before the calcium filter. Nine different withdrawal ports were arranged in the circuit: blood inlet, blood postfilter, blood post-ML, ED acid inlet, ED acid outlet, ED base inlet prefilter, ED base inlet postfilter, ED base outlet prefilter, and ED base outlet postfilter. (*B*) ED unit. The ED unit contained a customized four-chamber cell, with a bipolar (bpm), anionic (am), and bipolar membrane inserted from the anode to the cathode. These divide the ED cell into an anode, acid chamber, base chamber, and cathode. Through the anionic membrane, anions (mainly chloride) moved from the "base" chamber to the "acid" chamber.

majority is chemically combined with water to form bicarbonate ions. The former and the latter are in a chemical equilibrium that can be altered by shifts in acid–base status. Specifically, the lower the pH, the higher the partial pressure of carbon dioxide (P_{CO_2}) (19).

To exploit bicarbonate for gas exchange, we developed an innovative lung support technique, called respiratory electrodialysis (R-ED), by combining a hemofilter, a membrane lung, and an electrodialysis unit. By applying electrodialysis to hemodiafiltrate, the pH and the electrolyte concentration are selectively modulated in specific sections of the extracorporeal circuitry.

Blood is regionally acidified, bicarbonate is exchanged with chloride, and the P_{CO_2} is increased, leading to facilitated membrane lung CO_2 removal.

Here, we describe the first successful *in vivo* application of the electrodialysis technique. We report how R-ED, with minimally invasive extracorporeal support, could largely reduce the ventilatory needs of healthy swine when compared with a standard $ECCO_2R$ technology.

Methods

After anesthesia and instrumentation, five healthy Yorkshire swine (52 ± 2 kg) were mechanically ventilated with inspired oxygen fraction of 50%, positive end-expiratory pressure of 5 cm H_2O, and tidal volume of 8 ml/kg. Respiratory rate was adjusted throughout the whole experiment to maintain an arterial P_{CO_2} of 50 mm Hg. Via a double-lumen 14F catheter inserted into the right external jugular vein, the animals were connected to a custom-made extracorporeal circuit (*see* online data supplement for details). Unfractionated heparin was continuously infused to achieve an activated clotting time twice the baseline.

The extracorporeal circuit was composed of a blood circuit and an electrodialysis circuit (Figure 1A). In the blood circuit, blood flowed (250 ml/min) through a hemofilter and a pediatric membrane lung. In the electrodialysis circuit, hemodiafiltrate was generated by the hemofilter (500 ml/min), flowed through the electrodialysis acid chamber, and returned to the hemofilter. Before the electrodialysis acid chamber, 40 ml/min of hemodiafiltrate was diverted toward a calcium filter, into the electrodialysis base chamber, and finally returned after a safety filter to the reinfusion lumen of the catheter. To prevent calcium precipitation inside the electrodialysis cell, a fraction of the alkaline hemodiafiltrate (40 ml/min) was recirculated from the outlet of the electrodialysis base chamber before the calcium filter. Thus, calcium precipitated before electrodialysis to be trapped by the calcium filter. The electrodialysis unit was customized with a bipolar, an anionic, and a bipolar membrane (Figure 1B; *see* online supplement).

All animals underwent three repeated experimental sequences consisting of four steps each:

- Baseline (1 h): no extracorporeal blood treatment.
- $ECCO_2R$ (2 h): gas flow 10 L/min, electrodialysis circuit excluded.
- R-ED (2 h): gas flow 10 L/min, electrodialysis circuit functioning, and electrodialysis cell supplied by an electric current of 10 A. Calcium gluconate was infused to maintain arterial concentration of ionized calcium within the normal range.
- Final: NO-$ECCO_2R$ (1 h): same as Baseline.

R-ED and $ECCO_2R$ steps were randomized. Experimental sequences were followed by a 1-h equilibration period.

At the end of each step, hemodynamic and ventilatory parameters were recorded; samples from the femoral artery, pulmonary artery, and extracorporeal circuit were collected for gas analyses and electrolytes; expired CO_2 concentration of membrane lung and natural lung were measured to compute membrane lung CO_2 extraction, natural lung CO_2 extraction, total CO_2 production ($\dot{V}_{CO_2}$), and alveolar ventilation. At the end of Baseline and R-ED steps, plasma-free hemoglobin concentration was measured. After instrumentation and at the end of the experiment, blood was sampled for biochemistry measures (*see* online supplement).

Statistical Analysis

Data are presented as mean ± SD unless otherwise stated. Different steps were compared with one-way analysis of variance for repeated measurements or Kruskal-Wallis test, when appropriate. Two-way analysis of variance was used to compare samples along the extracorporeal circuit during $ECCO_2R$ and R-ED. Tukey test was used for *post hoc* multiple comparisons. A P value < 0.05 was deemed statistically significant. Analyses were performed using JMP 11.0 (SAS, Cary, NC).

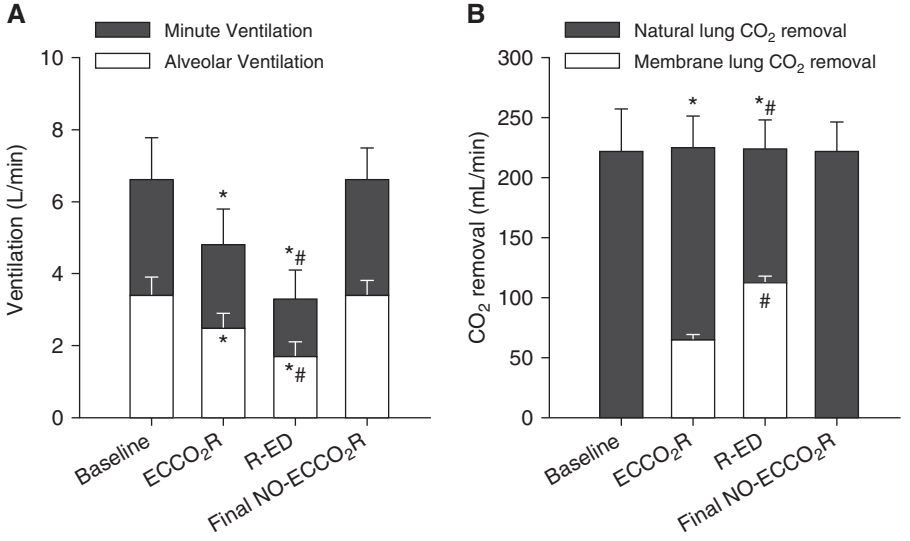

Figure 2. (*A*) Minute and alveolar ventilation (L/min). (*B*) Natural lung and membrane lung CO_2 removal (ml/min). Total CO_2 production (V_{CO_2}, ml/min) may be computed as the sum of natural lung and membrane lung CO_2 removal. Mean ± SD reported. $^*P < 0.05$ versus Baseline and Final NO–extracorporeal CO_2 removal ($ECCO_2R$), $^{\#}P < 0.05$ versus $ECCO_2R$. R-ED = respiratory electrodialysis.

Table 1. Respiratory Parameters

	Baseline	$ECCO_2R$	R-ED	Final NO-$ECCO_2R$
Minute ventilation, L/min	6.6 ± 1.2	4.8 ± 1.0*†	3.3 ± 0.8*†‡	6.6 ± 0.9
Respiratory rate, rate/min	16 ± 3	12 ± 2*†	8 ± 2*†‡	16 ± 2
Tidal volume, ml/kg	7.9 ± 0.1	8.0 ± 0.1	8.0 ± 0.1	7.9 ± 0.1
Alveolar ventilation, L/min	3.4 ± 0.5	2.5 ± 0.4*†	1.7 ± 0.4*†‡	3.4 ± 0.4
Peak pressure, cm H_2O	24 ± 3	22 ± 2*†	20 ± 2*†‡	24 ± 4
Plateau pressure, cm H_2O	17 ± 2	17 ± 2	16 ± 2	17 ± 3

Definition of abbreviations: $ECCO_2R$ = extracorporeal CO_2 removal; R-ED = respiratory electrodialysis.
Data are reported as mean ± SD.
*$P < 0.05$ versus Baseline.
†$P < 0.05$ versus $ECCO_2R$.
‡$P < 0.05$ versus Final NO-$ECCO_2R$

Results

R-ED reduced minute volume by half compared with Baseline and Final NO-$ECCO_2R$, and almost doubled the membrane lung CO_2 removal when compared with $ECCO_2R$, achieving a supplemental 31% minute ventilation reduction (Figure 2, Table 1). Variations in alveolar ventilation perfectly resembled variations in minute ventilation. Due to the study design, changes in minute ventilation were achieved by modification of respiratory rate, whereas tidal volume and plateau pressure were stable throughout the whole experiment. This reduction of ventilatory needs was secondary to a significant increase in the ratio between membrane lung CO_2 removal and $\dot{V}CO_2$ (Figure 2B; *see* Table E1 in the online supplement). Indeed, during $ECCO_2R$, membrane lung CO_2 removal was 64 ± 5 ml/min (i.e., 28% of $\dot{V}CO_2$), whereas during R-ED, membrane lung CO_2 removal reached 112 ± 6 ml/min (i.e., 50% of $\dot{V}CO_2$). $\dot{V}CO_2$ was constant during all four steps. Therefore, natural lung CO_2 removal was significantly lower during R-ED compared with $ECCO_2R$ (113 ± 24 vs. 161 ± 35 ml/min, respectively; $P < 0.001$). No alteration in arterial pH and PCO_2 was detected during the whole experiment (Table 2).

During R-ED, higher levels of membrane lung CO_2 removal were achieved by selective modulation of the acid–base balance and the electrolyte concentration in the extracorporeal blood (Figure 3, Table E2). The concentration of chloride ions increased across the hemofilter (from 99 ± 4 to 108 ± 4 mmol/L, $P < 0.05$). Chloride ions partially replaced bicarbonate ions (from 34.6 ± 1.8 to 30.0 ± 1.8 mmol/L, $P < 0.05$) (Figures 3A and 3B), leading to a significant reduction in pH (from 7.37 ± 0.02 to 6.77 ± 0.04, $P < 0.05$) (Figure 3C), which was associated with a 255% increase in PCO_2 (from 61.0 ± 3.1 to 216.7 ± 15.5, $P < 0.05$) (Figure 3D). The subsequent passage of blood across the membrane lung led to a significant reduction of PCO_2 and bicarbonate ions, which restored pH back to physiological values. Notably, alterations in the acid–base balance and electrolyte concentration in the extracorporeal blood due to R-ED was limited to specific sections of the extracorporeal circuitry. Indeed, inlet and mixed venous blood showed no differences during R-ED and $ECCO_2R$ (Figure 3, Tables E2 and E3).

Electrolyte concentrations and pH of the hemodiafiltrate during R-ED are shown in Figure 4 and Table E4. Passage of hemodiafiltrate through the electrodialysis acid chamber increased chloride concentration (from 110 ± 6 to 115 ± 6 mmol/L, $P < 0.05$), leading to a pH reduction (from 7.07 ± 0.28 to 6.60 ± 0.25, $P < 0.05$). Passage of hemodiafiltrate through the electrodialysis base chamber reduced chloride concentration (from 83 ± 8 to 60 ± 5 mmol/L, $P < 0.05$), leading to a rise in pH (from 11.01 ± 0.4 to 12.54 ± 0.34, $P < 0.05$). As expected, hemodiafiltrate entering the calcium filter was extremely alkaline (i.e., 11.00 ± 0.52), which led to calcium precipitation inside the calcium filter (2.8 ± 0.7 to 0.3 ± 0.1 mg/dl, electrodialysis base inlet prefilter and electrodialysis base inlet postfilter, respectively; $P < 0.05$) and magnesium (0.6 ± 0.2 to 0.3 ± 0.2 mg/dl, electrodialysis base inlet prefilter and electrodialysis base inlet postfilter, respectively; $P < 0.05$) (Figures 4C and 4D). No alteration in electrolyte concentration was associated with the passage of hemodiafiltrate through the safety filter.

Arterial electrolyte concentrations remained stable during all experimental steps, except for magnesium concentration. Indeed, at the end of the R-ED step, arterial concentration of magnesium was lower than Baseline (Table 2). Remarkably, we were able to keep the arterial ionized calcium concentration constant by infusing 1.6 ± 0.4 g/h of calcium gluconate, corresponding to 3.7 ± 1.0 mmol of calcium per hour. There was no clinically significant hemodynamic alteration associated with the application of R-ED (Table E5).

During R-ED, concentration of plasma-free hemoglobin was similar to Baseline (median, 4.8; interquartile range [IQR], 9.0–3.2; vs. median, 4.8; IQR, 5.8–3.2 mg/dl; $P = 0.89$) and always lower than the

Table 2. Arterial Blood Gas Analyses and Electrolyte Concentrations

	Baseline	$ECCO_2R$	R-ED	Final NO-$ECCO_2R$
pH	7.43 ± 0.03	7.43 ± 0.02	7.43 ± 0.02	7.43 ± 0.03
PCO_2, mm Hg	49.9 ± 1.5	50.0 ± 1.3	50.1 ± 1.2	49.9 ± 1.0
HCO_3^-, mmol/L	32.3 ± 1.7	32.9 ± 1.5	32.5 ± 1.5	32.9 ± 1.7
PO_2, mm Hg	207 ± 72	185 ± 66	180 ± 66	191 ± 64
Oxygen saturation, %	98.6 ± 1.0	98.1 ± 1.1	98.1 ± 1.2	98.2 ± 0.9
Hemoglobin, mg/dl	8.6 ± 1.3	8.6 ± 1.4	8.8 ± 1.5	8.7 ± 1.3
Lactate, mmol/L	0.8 ± 0.3	0.7 ± 0.2	0.7 ± 0.2	0.7 ± 0.2
Na^+, mmol/L	137 ± 3	136 ± 4	137 ± 4	137 ± 3
K^+, mmol/L	4.1 ± 0.3	4.2 ± 0.3	4.1 ± 0.3	4.2 ± 0.2
Cl^-, mmol/L	98 ± 4	99 ± 4	99 ± 4	99 ± 3
Ca^{2+}, mmol/L	1.21 ± 0.10	1.19 ± 0.10	1.17 ± 0.08	1.19 ± 0.09
Total calcium, mg/dl	8.8 ± 1.4	8.4 ± 1.5	8.8 ± 1.4	8.6 ± 1.4
Magnesium, mg/dl	1.6 ± 0.2	1.5 ± 0.2	1.4 ± 0.2*	1.5 ± 0.2

For definition of abbreviations, *see* Table 1.
Data are represented as mean ± SD.
*$P < 0.05$ versus Baseline.

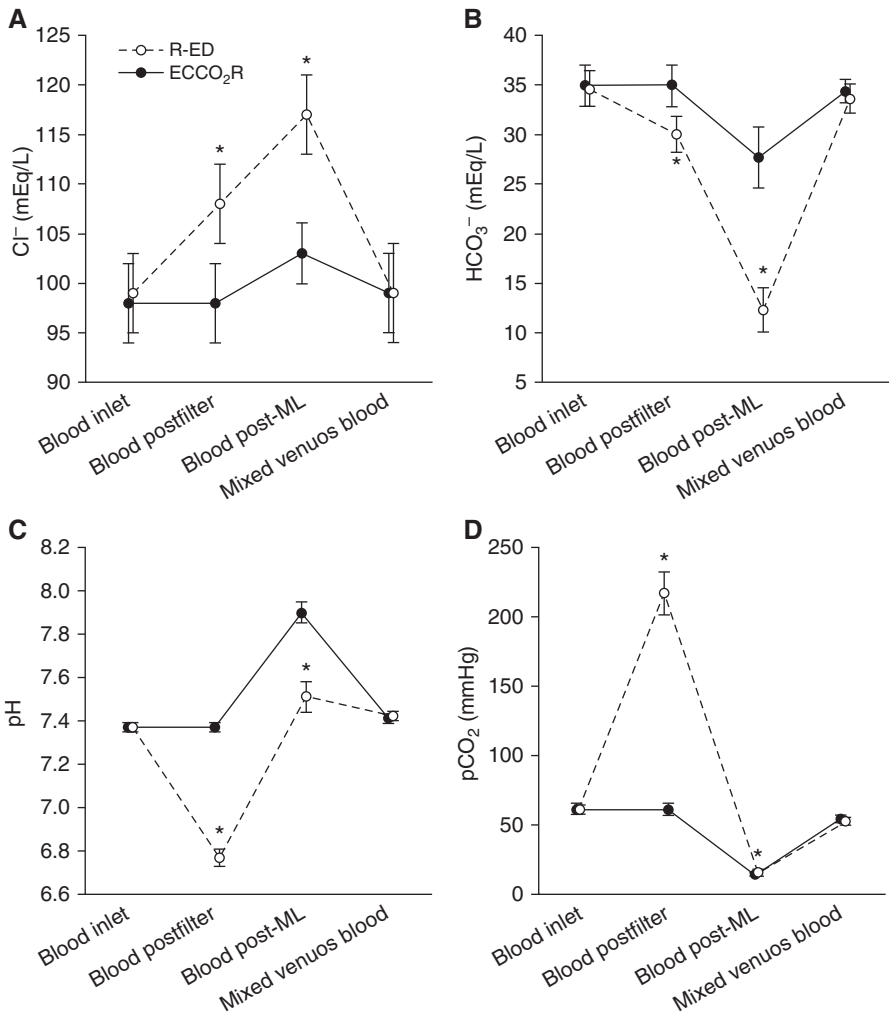

Figure 3. Meaningful acid–base and electrolyte values for the extracorporeal and mixed venous blood. (*A*) Chloride (Cl^-, mEq/L). (*B*) Bicarbonate (HCO_3^-, mEq/L). (*C*) pH. (*D*) P_{CO_2} (mm Hg). Mean ± SD reported. *$P < 0.05$ versus extracorporeal CO_2 removal ($ECCO_2R$). ML = membrane lung; R-ED = respiratory electrodialysis.

threshold (20 mg/dl) considered significant for clinically significant hemolysis. At the end of the experiment, plasma creatinine was higher than before starting the experiment (median, 0.83; IQR, 0.97–0.78 mg/dl; vs. median, 1.16; IQR, 1.40–0.94 mg/dl; $P < 0.05$). No statistically significant differences were recorded in the levels of alanine aminotransferase, aspartate aminotransferase, lactate dehydrogenase, or total protein concentration before and after the experiment (Table E6). The electrical potential difference between anode and cathode required to deliver 10 A of direct current ranged from 8.7 to 9.3 V. During ED-$ECCO_2R$, no arrhythmias or interferences in ECG signal were observed. There were no adverse effects, such as bleeding or thromboembolic episodes, or circuit malfunctions during the experiments.

Discussion

By modulating blood electrolyte concentrations, R-ED removed twice as much CO_2 as conventional $ECCO_2R$ technology. Using an extracorporeal blood flow as low as 250 ml/min and a minimally invasive 14F catheter, we reduced the minute ventilation by half in experimental healthy swine, whose total CO_2 production was similar to an adult human and arterial P_{CO_2} was 50 mm Hg.

We have previously developed an $ECCO_2R$ technique based on infusion of metabolizable acids (Acid Load CO_2 removal, $ALCO_2R$). $ALCO_2R$ increased membrane lung CO_2 removal by converting bicarbonate ions into dissolved CO_2 via acidification with metabolizable acids of blood entering a membrane lung (19–22). We present here a novel approach to acidify extracorporeal blood. We included an electrodialysis cell in our extracorporeal circulation setup to acidify blood without infusing any exogenous acid. During R-ED, regional acidification of the extracorporeal blood is achieved by electrodialysis of two hemodiafiltrate flows obtained from a standard continuous renal replacement therapy (CRRT) hemofilter. Electrodialysis shifted chloride ions between these hemodiafiltrate flows, obtaining an acidic (i.e., chloride rich) and an alkaline (i.e., chloride poor) hemodiafiltrate. The former was used to acidify blood entering the membrane lung and, therefore, enhance membrane lung CO_2 removal. The alkaline hemodiafiltrate was reinfused into the extracorporeal circuit, restoring the sodium chloride content of blood and rebalancing the electrolyte equilibrium. Due to the high pH of the alkaline hemodiafiltrate, calcium might precipitate inside the electrodialysis cell. To prevent this, we removed calcium from the hemodiafiltrate through a controlled calcium precipitation process. A fraction of the alkaline hemodiafiltrate was recirculated before the "basic" electrodialysis chamber, inducing precipitation and agglomeration of calcium and magnesium, which were trapped by a standard CRRT hemofilter. The calcium losses were corrected by means of a continuous systemic infusion of calcium gluconate. The replacement of calcium losses was feasible and effective in controlling systemic calcemia. Moreover, the calcium infusion in our experiment was well within the suggested thresholds for citrate regional anticoagulation (23). The alkaline calcium-free hemodiafiltrate was subsequently infused at the outlet of the circuitry to limit the time during which blood was exposed to this potentially harmful environment. No hemolysis was detected, and the pH of mixed venous blood was always in the normal physiological range. Previously (24), a highly alkaline solution (pH 12.04) was safely infused for up to 18 hours. In this experiment, magnesium losses were not replaced, resulting in lower systemic magnesium concentration during R-ED, but without any apparent adverse effect. Application of

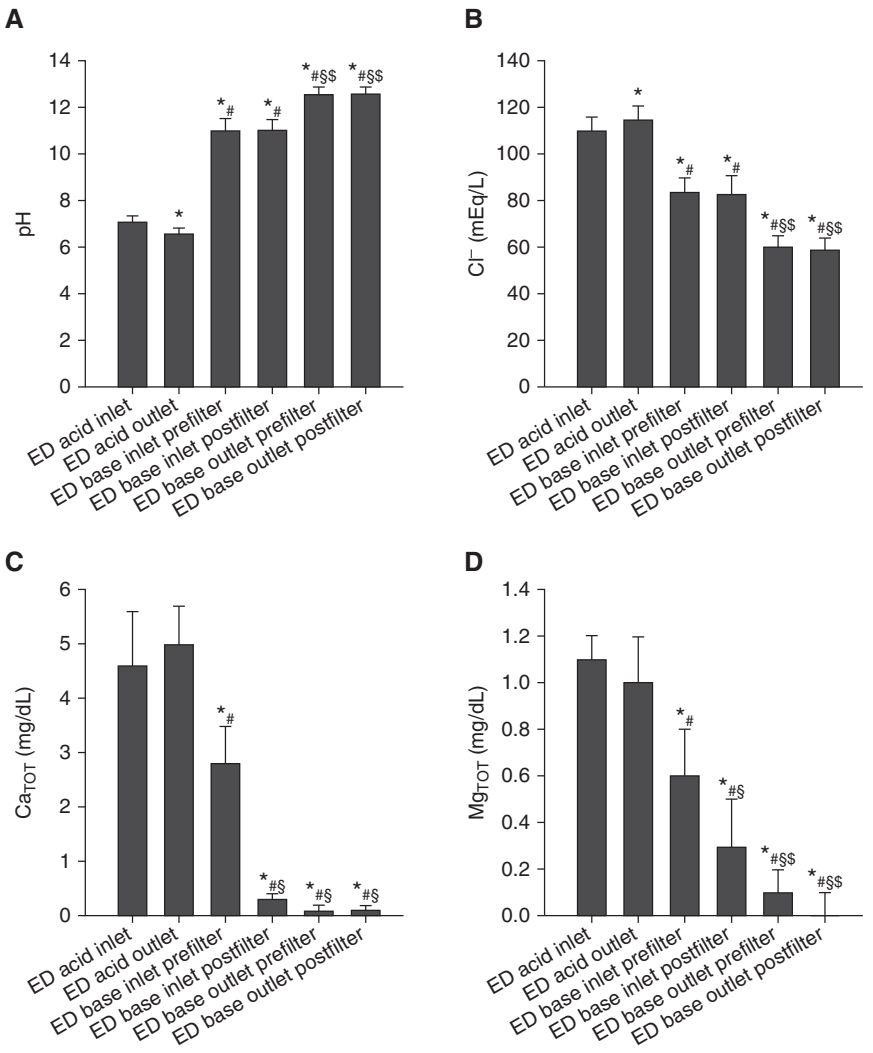

Figure 4. Meaningful acid–base and electrolyte values for the extracorporeal hemodiafiltrate. (*A*) pH. (*B*) Chloride (Cl^-, mEq/L). (*C*) Total calcium (Ca_{TOT}, mg/dl). (*D*) Total magnesium (Mg_{TOT}, mg/dl). Mean ± SD reported. $^*P < 0.05$ versus electrodialysis (ED) acid inlet, $^{\#}P < 0.05$ versus ED acid outlet, $^{\S}P < 0.05$ versus ED base inlet prefilter, $^{\$}P < 0.05$ versus ED base inlet postfilter.

R-ED for a longer time frame would warrant magnesium replacement as well.

Notably, during $ECCO_2R$ steps, blood pH at the outlet of the membrane lung was as high as 7.9. A further increase in CO_2 extraction, achievable by increasing the membrane lung exchange surface, would expose blood to an alkaline milieu for long enough to cause precipitation of calcium inside the bloodstream and subsequent thromboembolism. Contrarily, application of R-ED is devoid of these risks, because pH of extracorporeal blood is always within physiological levels and alkaline hemodiafiltrate is decalcified.

Clear advantages of R-ED over the previous applications of $ALCO_2R$ are noteworthy. Historically, $ALCO_2R$ technique was attempted with several configurations implying the infusion of exogenous substances (i.e., HCl and NaOH) (25–27). Those attempts resulted in severe clinical complications, such as hemolysis, arrhythmias, pulmonary arterial hypertension, and electrolyte derangements. Thus, these approaches have never been transferred to the clinical field. Recently, we developed an $ALCO_2R$ technique based on infusion of metabolizable acids. Though effective in increasing membrane lung CO_2 removal and safe regarding organ function, this approach has some disadvantages in that it raises $\dot{V}_{CO_2}$ and induces a slight degree of metabolic acidosis (28). In contrast, R-ED does not involve the infusion of any exogenous compounds into the extracorporeal blood. Remarkably, $\dot{V}_{CO_2}$ did not change throughout the study, and natural lung CO_2 removal returned to baseline when $ECCO_2R$ and R-ED support were suspended. Similarly, we observed the minute ventilation to be constant between Baseline and Final NO-$ECCO_2R$ steps, thus suggesting metabolic stability throughout the whole experiment.

R-ED showed a CO_2 removal that is almost double that of conventional $ECCO_2R$ technology.

R-ED is capable of removing the total adult patient CO_2 production from a blood flow as low as 500 ml/min using a double-lumen 15F to 17F cannula. Instead, if only partial CO_2 removal (i.e., about 50% of the total CO_2 production) is required, the blood flow may be reduced to 150 to 250 ml/min, theoretically allowing the application of regional anticoagulation.

Because partial CO_2 removal by R-ED can be achieved with the invasiveness and footprint of CRRT (29), it may be used on a much larger number of patients than conventional techniques. R-ED could also be used in a modular extracorporeal system capable of multiorgan support therapy (30).

The prototype arrangement we selected in the present study is complex and devoid of feedback and safety systems. Nevertheless, R-ED can be engineered and made simpler and safer. Although future studies will be required to further evaluate the safety of R-ED, we did not observe any major complications. Specifically, no hemolysis or significant changes in blood gases and ion concentration were observed in the animal systemic blood. Similarly, no hemodynamic derangements or pulmonary hypertension were detected, suggesting R-ED was not associated with pulmonary embolism or vasoconstriction. An increase in creatinine was observed at the end of the study. We have previously reported a similar increase in creatinine in healthy swine treated with both conventional $ECCO_2R$ and $ALCO_2R$ techniques (21). The study design does not permit us to evaluate specifically the effects of R-ED on kidney function. Thus, detailed studies targeting the safety profile of R-ED are warranted.

Due to the lower conductance of the extracorporeal apparatus, the low electrical current applied (i.e., 8.7–9.3 V) was not

associated with any arrhythmias or ECG alteration.

We acknowledge several limitations in this study besides the absence of a comprehensive safety evaluation. In R-ED, many variables can be set in various combinations at different levels (e.g., amperes, pumps flows, gas flow, blood flow, different membrane lung size, etc.). In the present study we evaluated a single setup, following the indications obtained from preliminary experiments. Blood flow was set at 250 ml/min, similar to the blood flow commonly used in CRRT (29). Hemodiafiltrate recirculation flow (500 ml/min) was chosen to favor a balance between the hemodiafiltrate pool and blood. We used a pediatric membrane lung (0.8 m^2) to minimize blood clotting problems at the selected blood flow.

Electrodialysis technology may have various further applications, including modulating the balance between cations and anions in blood. Thus, with an apparatus similar to the one proposed, acid–base and hydroelectrolytic derangements may also be managed.

In conclusion, we report the successful application of R-ED. By using this innovative technique, we were able to remove an amount of CO_2 equivalent to half the production of a 70-kg human (110 ml/min) using an extracorporeal blood flow of only 250 ml/min. Thus, R-ED allowed the minute ventilation to be halved. $ECCO_2R$ may prove beneficial for a large number of patients suffering from either acute or chronic respiratory failure. The possibility of decreasing the required blood flow by R-ED might substantially extend the range of application of $ECCO_2R$. Further preclinical studies are needed to evaluate the safety profile of this technique and to assess the feasibility of combining R-ED with a modular system for multiorgan support. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

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