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The End of the Bicarbonate Era? A Therapeutic Application of the Stewart Approach

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Critically ill patients frequently present with disorders of acid-base homeostasis (1), making arterial blood gas interpretation a cornerstone activity in the clinical assessment of patients by intensivists. Many of us are unaware we've been taught to interpret acid-base homeostasis in the "bicarbonate era" (2), where focus on the Henderson-Hasselbach equation for dissociation of carbon dioxide has led us to beleive bicarbonate is a major determinant of acid-base status (3). However, when we try to understand some of the commonly encountered acid-base abnormalities in critical illness, such as hyperchloremia (4), the Henderson-Hasselbach equation leaves us yearning for a better explanation.

Forty years ago, the Canadian physiologist Peter Stewart provided a better explanation. He described an approach to understanding acid-base where bicarbonate is not the major determinant of acid-base status (5). Although referred to as the "modern" approach (2), Stewart's explanation incorporated time-tested concepts of physical chemistry, such as conservation of mass, dissociation of electrolytes, and electroneutrality, some of which date back to the 18th century (6). Therefore, it is perhaps more accurate to refer to Stewart's work as the physicochemical approach. Stewart applied these physicochemical principles by using simple algebra to demonstrate that plasma pH (and bicarbonate concentration) is determined by the partial pressure of carbon dioxide (PCO_2), the strong ion difference and the concentration of weak acids (primarily albumin and phosphate).

The strong ion difference in plasma is determined by the relatively higher concentration of sodium compared to chloride, and the difference is typically about 40 mEq/L (5). The electroneutrality of plasma is maintained because the charge gap between these two strong ions is made up by the dissociation of weak acids into their respective anions, as well as the dissociation of dissolved carbon dioxide into bicarbonate. By showing that plasma proteins (weak acids) and dissolved strong ions also participate in acid-base homeostasis, the

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physicochemical approach provides an explanation for acid-base disorders commonly encountered in critical illness, such as hypoalbuminemia and hyperchloremia. However, although this approach is mathematically accurate (7), it oversimplifies some of the mechanistic insights (8), which is perhaps why reception has been mixed, ranging from full embracement at the bedside (9) to outright hostility (10).

Unfortunately, the controversy has left many of us wondering whether it is truly important to learn the physicochemical approach. After all, intensivists really only have access to two tools for rapid manipulation of plasma pH in the setting of acidosis- hyperventilation to lower partial pressure of carbon dioxide or administration of sodium bicarbonate. Nonetheless, the understanding of these interventions may be improved with the physicochemical approach. For example, although the Henderson-Hasselbach equation predicts hyperventilation lowers pH, it doesn't allow us to understand it does this by removing carbon dioxide without changing the strong ion difference and doesn't predict the effect remaining weak acids will have on the final observed pH.

Similarly, the physicochemical approach helps us understand that administration of sodium bicarbonate increases pH by increasing the concentration of plasma sodium relative to chloride, rather than simply adding bicarbonate buffer to the system. This is because sodium fully dissociates in solution, whereas bicarbonate exists in equilibrium with dissolved carbon dioxide (PCO_2) i.e. it behaves like a weak acid. In fact, the physicochemical approach helps us understand the potential harmful effects of a rapid bolus of sodium bicarbonate, because it predicts an increase in the local PCO_2. Since carbon dioxide rapidly diffuses across cellular membranes, this may rapidly increase intracellular PCO_2, worsening intracellular acidosis (11).

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Here, Zanella et al report their ingenious alternative method of therapeutically increasing the strong ion difference in plasma (12). The authors used electrodialysis cell technology to defy the principles of electroneutrality and remove chloride ions from plasma, while maintaining the concentration of sodium ions. As a result, they increased the strong ion difference and raised pH back to normal levels. They tested this technology in animal models of both metabolic and respiratory acidosis and showed that the effect was maintained even after discontinuing the electrodialysis. Their work not only validates a direct therapeutic application of the physicochemical approach, it provides fascinating insights into acid-base homeostasis. Prior to initiation of electrodialysis, renal chloride excretion was increased in response to both metabolic and respiratory acidosis. Once pH was restored by lowering plasma chloride with electrodialysis, renal chloride excretion was reduced. Homeostatic mechanisms involving chloride shifts have been previously shown to play an important role in the maintenance of pH through mechanisms involving circulating red blood cells (13) as well as the kidney (14). This leads one to conclude that lowering plasma chloride with electrodialysis augments the natural homeostatic response to acidosis, unlike the administration of concentrated sodium bicarbonate, which also increases plasma sodium.

However, we should be cautiously enthusiastic. Modifying pH by removing chloride and manipulating the strong ion difference will not treat the underlying cause of the acid-base disorder any more than lowering PCO_2 or administering bicarbonate does, unless of course the primary derangement is hyperchloremia, elevated PCO_2, or hyponatremia. While acidosis with hyperchloremia is quite common in critical illness (4), prevention of hyperchloremia by using the physicochemical approach to guide fluid choice and composition is perhaps a simpler and wiser alternative. Furthermore, hyperventilation, sodium bicarbonate administration and chloride electrodialysis do not directly treat elevated lactate levels, the most common cause of acidosis in critical illness (1). However, Zanella et al make no such

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claims. They simply use the physicochemical approach to elegantly show that increasing the strong ion difference restores pH to normal levels. It's conceivable the same result could be more easily obtained by conventional dialysis, where the dialysate solutions are engineered to target a given strong ion difference. Either way, the manipulation of strong ion difference to achieve specific therapeutic effects is slowly gaining traction and similar approaches have recently been shown to enhance respiratory support (15, 16). Whatever the future holds for these therapies, it behooves us to start teaching the physicochemical approach to our medical students and junior colleagues sooner rather than later.

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Extracorporeal Chloride Removal by Electrodialysis (CRe-ED): A Novel Approach to Correct Acidemia.

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Authors' contributions:

A.Z. conceived the study, collected, interpreted and analyzed data, searched literature, and wrote the manuscript; A.Z., D.S. and A.P. developed the CRe-ED prototype; P.C. conceived the study, interpreted data and revised the manuscript; L.C., E.R. and E.S. collected, interpreted and analyzed data, searched literature, and wrote the manuscript; D.S. and T.L. interpreted data and revised the manuscript; V.S., S. A. D., T.M., F.M., M.C., F.Z collected data and revised the manuscript; M.F.

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collected and interpreted data, and revised the manuscript; D.D. performed surgery on animals; S.G., L.G. and A.P. interpreted data and revised the manuscript.

All authors gave final approval of the version to be published and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy and integrity of any part of the work are appropriately investigated and resolved.

Conflict of interest statement:

A.Z., P.C., D.S., L.G. and A.M.P are inventors of a patent owned with the “Università degli Studi di Milano-Bicocca”, with the “Università degli Studi di Milano” and with the Fondazione IRCCS Ca’ Granda, Ospedale Maggiore Policlinico, Milano” titled: “Extracorporeal circuit system for the treatment of hydroelectrolyte and acid-base blood imbalances”. Application number: WO2016024217.

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At a Glance Commentary

Scientific Knowledge on the Subject:

Acidemia is a severe complication among critically ill patients. Despite being controversial, sodium bicarbonate is frequently used to increase blood pH. This treatment increases the strong ion difference (SID) by elevating sodium concentration, and raises blood pH. However, sodium bicarbonate administration can lead to several side effects including hypernatremia, hyperosmolality and intracellular acidosis.

What This Study Adds to the Field:

This proof of concept study shows the feasibility, safety, and effectiveness of extracorporeal chloride removal through electrodialysis to correct acidemia. Plasma chloride reduction mimics the physiologic renal response to acidosis. Extracorporeal chloride removal by electrodialysis quickly corrects blood pH without altering plasma osmolarity and maintains its effects up to several hours following treatment suspension.

This article has an online data supplement, which is accessible from this issue's table of content online at www.atsjournals.org.

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Abstract

Rationale: Acidemia is a severe condition among critically ill patients. Despite lack of evidence, sodium bicarbonate is frequently used to correct pH. However, its administration is burdened by several side effects. We hypothesized that the reduction of plasma chloride concentration could be an alternative strategy to correct acidemia.

Objectives: To evaluate feasibility, safety, and effectiveness of a novel strategy to correct acidemia through Extracorporeal Chloride Removal by Electrodialysis (CRe-ED).

Methods: Ten swine (6 treatments, 4 controls) were sedated, mechanically ventilated and connected to an electrodialysis extracorporeal device capable of removing selectively chloride. In random order, an arterial pH of 7.15 was induced either through reduction of ventilation (respiratory acidosis) or through lactic acid infusion (metabolic acidosis). Acidosis was subsequently sustained for 12-14 hours. In treatment pigs, soon after reaching target acidemia, electrodialysis was started in order to restore pH.

Measurements and Main Results: During respiratory acidosis, electrodialysis reduced plasma chloride concentration by 26±5 mEq/L within 6 hours (final pH=7.36±0.04). Control animals exhibited incomplete and slower compensatory response to respiratory acidosis (final pH=7.29±0.03, $p<0.001$). During metabolic acidosis, electrodialysis reduced plasma chloride concentration by 15±3 mEq/L within 4 hours (final pH=7.34±0.07). No effective compensatory response occurred in controls (final pH=7.11±0.08; $p<0.001$). No complications occurred.

Conclusions: We described the first in-vivo application of an extracorporeal system targeted to correct severe acidemia by lowering plasma chloride concentration. The

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CRe-ED proved to be feasible, safe, and effective. Further studies are warranted to assess its performance in presence of impaired respiratory and renal functions.

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INTRODUCTION

Metabolic and respiratory acidosis are pathological conditions frequently occurring in critically ill patients, and are associated with increased morbidity and mortality (1-4). Cardiac arrhythmias, organ failure, suppression of the immune response, release of pro-inflammatory cytokines and bacterial proliferation are severe complications associated with acidemia (5-7).

The treatment of acidosis is primarily aimed at correction of the underlying cause. In case of persistent severe acidemia (blood pH<7.15), sodium bicarbonate is frequently administered in order to correct blood pH (6,8,9), although its efficacy to improve survival has been observed only in a selected subgroup of critically ill patients (10) and patients with sepsis (11). Indeed, intravenous infusion of sodium bicarbonate can cause side effects such as hypernatremia and hyperosmolarity (12). In addition, being bicarbonate hydrated carbon dioxide, its intravenous infusion causes a transient rise in plasma partial pressure of carbon dioxide, potentially leading to paradoxical intracellular acidosis (13). Furthermore, in respiratory acidosis the correction of the underlying cause may not be effectively achieved, especially when lung parenchyma is acutely (or chronically) responsible for the insufficient carbon dioxide elimination (14).

According to Stewart's acid-base approach, the Strong Ion Difference (SID), i.e., the difference between the concentrations of strong cations ($[Na^+]+[K^+]+[Ca^{2+}]+[Mg^{2+}]$) and strong anions ($[Cl^-]+[Lac^-]$), is one of the three independent variables determining blood pH (7,15,16). Sodium bicarbonate infusion causes an increase in plasma sodium concentration leading to SID increase and, consequently, of pH. We hypothesized that the reduction of plasma chloride concentration, mimicking the

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physiologic renal response occurring during chronic respiratory acidosis, could be an alternative strategy to normalize blood pH by increasing plasma SID during experimental acidemia (16-18).

Many studies focused on the role of chloride in acid-base equilibrium (19,20). Chloride is the most represented anion in the extracellular fluid, and variations in chloride levels significantly affect the acid-base status (19). Hypo- or hyper-chloremia are frequently observed in acid-base derangements, especially in the ICU setting (20). Of note, the infusion of 0.9% NaCl-containing solutions is known to induce hyperchloremic acidosis through SID reduction (21,22). Conversely, hypochloremic alkalosis is a frequent consequence of loop-diuretic administration, because of urinary chloride loss through Na^+-K^+-$2Cl^-$ pump inhibition (23).

We developed an extracorporeal device to remove chloride in order to decrease its plasma concentration (Chloride Removal Electrodialysis, CRe-ED), thereby increasing SID and pH. This novel technique features an electrodialysis cell, as we previously described (24,25). Here we report the first *in-vivo* application of CRe-ED. In a swine randomized controlled crossover model of metabolic and respiratory acidosis, we tested feasibility, safety and effectiveness of this novel approach to correct severe acidemia.

Some of the results of these studies have been previously reported in the form of an abstract (26).

Methods

The study protocol was approved by the Italian Ministry of Health. Ten healthy piglets (24±2 kg, mean±SD) were anesthetized, surgically instrumented, mechanically

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ventilated (tidal volume (Vt): 10 mL/kg; respiratory rate (RR): 10 breaths per minute; PEEP: 5 cmH_2O) and connected to an extracorporeal circuit through a double-lumen 14Fr catheter positioned in the external jugular vein. The extracorporeal circuit consisted of a blood circuit, composed of two in-series hemofilters, an electrodialysis circuit and a circuit for lactic acid infusion (acid infusion circuit), connected to the first and the second hemofilter, respectively (**Figure 1** and online data supplement). Anticoagulation was performed with continuous intravenous heparin infusion.

Study design

Six piglets were assigned to the CRe-ED treatment (*treatment group*) and four were controls (*control group*) (**Figure 2**). Regardless of treatment allocation, each swine randomly underwent both respiratory and metabolic acidosis (crossover randomization).

At baseline, respiratory rate was adjusted in order to achieve an arterial pH between 7.38 and 7.42. Thereafter, pH was lowered to reach a target of 7.15±0.02 through either a decrease in minute ventilation by respiratory rate reduction (respiratory acidosis), or by a continuous infusion of 1.5 M lactic acid into the acid infusion circuit (metabolic acidosis).

In the *treatment* group, once the target pH was reached, CRe-ED was started and continued until normalization of arterial pH. Thereafter, CRe-ED was stopped and animals were monitored for 8 hours. In contrast, in the control group, CRe-ED was not applied, and, after induction of acidosis, animals were monitored for a total period comparable with the CRe-ED duration plus 8-hr monitoring period after CRe-ED treatment (14 hours of respiratory acidosis and 12 hours of metabolic acidosis). Arterial pCO_2 (±3 mmHg) and lactate (±1 mEq/L) were kept constant throughout all

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the experiments until the end of observation period, by modulating respiratory rate and lactic acid infusion, respectively.

Before the second phase of the assigned acidosis, plasma chloride concentrations were restored to baseline values (±2 mEq/L) by the infusion of 1.5 M hydrochloric acid through the acid infusion circuit (re-chloration phase).

Data collection

At the end of each step (i.e., baseline, start and end of CRe-ED treatment, 4h and end (8h) of observation period), every hour during CRe-ED treatment and every two hours during the control observation period, we collected hemodynamic and ventilator parameters; laboratory biomarkers, and blood gas analyses and electrolytes from arterial line and extracorporeal circuit; urinary output, pH and urinary electrolytes (27); glomerular filtration rate.

Statistical Analysis

Data are presented as mean±standard deviation unless otherwise specified. Differences among groups were tested by a 2-way analysis of variance for repeated measurements over time. Multiple comparisons analyses were tested among different time points versus baseline, start and end of CRe-ED treatment using Dunnet's test. A p-value<0.05 (two-tailed) was deemed statistically significant.

Please refer to the online data supplement for detailed methods.

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Results

Respiratory acidosis

During respiratory acidosis, targeted pH was achieved by decreasing minute ventilation from 4.0±0.8 L/min to 1.8±0.2 ($p<0.001$) in the treatment group, and from 3.7±0.7 to 1.6±0.2 L/min ($p<0.001$) in the control group (**Table 1**). An increase in pCO_2 from 45±6 mmHg to 91±12 mmHg ($p<0.001$) and from 49±4 mmHg to 95±6 mmHg ($p<0.001$) was recorded in the treatment and control groups, respectively. Subsequently, pCO_2 was kept constant during the whole experiment in both groups (**Figure 3A**).

In the treatment group, after the application of CRe-ED, plasma chloride concentration decreased from 103.7±3.4 mEq/L to 78.2±8.0 mEq/L ($p<0.001$) (**Figure 3B**), thereby leading to an increase in plasma SID from 41.4±4.4 mEq/L to 64.2±9.5 mEq/L, ($p<0.001$), and an increase in HCO_3^- from 30.7±3.6 mEq/L to 54.3±6.6 mEq/L, ($p<0.001$) (**Table 1**). As plasma chloride concentration decreased and SID increased, arterial pH increased from 7.16±0.01 to 7.40±0.01 ($p<0.001$). Correction of pH during CRe-ED treatment was achieved in 333±59 minutes (range, 255-430 minutes) (**Figure 3C**). During the 8-h observation period, pH slightly decreased from 7.40±0.01 to 7.36±0.04 ($p<0.001$), as plasma chloride concentration increased from 78.2±8.0 mEq/L to 84.8±4.6 mEq/L ($p<0.001$) (**Figure 3B,C**).

In control animals, we observed a slower compensatory response to respiratory acidosis: SID and HCO_3^- progressively increased from 41.7±3.5 to 53.3±3.9 mEq/L (acidosis induction to end of observation, $p<0.001$), and from 32.6±2.8 to 43.6±2.3 mEq/L ($p<0.001$), respectively **(Table 1)**. Accordingly, over the whole 14 hours of respiratory acidosis, pH increased in the control group from 7.16±0.01 to 7.29±0.03,

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though up to a lower level as compared to the treatment group (p<0.001) **(Figure 3C)**.

Table 1 summarizes respiratory, hemodynamic, plasma electrolytes, acid-base status and renal function changes over time among the groups during respiratory acidosis. Plasma biochemistry and respiratory variables in both groups, as well as electrolytes concentrations in the treatment group along the withdrawal port of the extracorporeal circuit are reported in Table E1-E4.

Urinary response

At acidosis induction, urinary pH (pH_u) decreased in the treatment (acidosis induction versus baseline, 4.9±0.3 versus 5.8±0.5, p=0.013) and control group (4.7±0.2 versus 5.5±0.5, p=0.118), although only in the treatment group pH reduction reached statistical significance **(Figure 4A)**. No significant change of urinary chloride and ammonium concentration was observed in both treatment and control groups (**Table 2** and **Figure 4 A-C**).

In the treatment group, during CRe-ED treatment, urinary chloride concentration significantly decreased from 179.3±29.2 to 34.3±14.1 mEq/L (p<0.001) and urinary anion gap (AG) increased accordingly from -79.6±32.6 to 79.9±65.3 (p<0.001) (**Table 2**). Consequently, pH_u increased from 4.9±0.3 up to 6.9±1.0 (p<0.001) and remained stable during the 8h observation (**Figure 4A**, **Table 2**). Overall, the restoration of baseline blood pH required the removal of 392±65 mEq of chloride ions, of which 336±54 mEq were removed by CRe-ED and 56±37 mEq by the renal system, mainly excreted during the acidosis induction phase (**Figure 4B**).

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In the control group, a total of 248±65 mEq of chloride were removed by the kidneys during the entire 14-h period of respiratory acidosis, causing constantly negative values of urinary anion gap **(Table 2)**, and leading to a decrease in plasma chloride concentration from 105±4 (acidosis induction) to 92±5 mEq/L (end of observation) (p<0.001) (**Figure 4B**). Of note, after the induction of respiratory acidosis, creatinine clearance increased from 69.1±13.7 (baseline) to a maximum value of 141.4±29.9 mL/min (p=0.002) (**Table 1**).

Metabolic acidosis

Metabolic acidosis was induced and maintained by infusing 2.2±0.4 mL/kg/h of 40% lactic acid (3.5±1.3 mmol/min) on the acid infusion circuit. From baseline to the end of lactic acidosis induction, plasma lactate concentration increased from 0.6±0.2 to 13.1±1.5 mmol/L (p<0.001) in the treatment group and from 0.6±0.2 to 12.9±1.5 mmol/L (p<0.001) in the control group (**Figure 5A**). As a consequence, plasma SID decreased from 38.7±5.4 to 26.5±2.7 mEq/L in the treatment group (p<0.001) and from 42.6±6.1 to 28.6±5.2 mEq/L in the control group (p=0.001), while HCO_3^- decreased from 28.5±5 to 16.0±2.4 mEq/L in the treatment group (p<0.001), and from 29.1±1.4 to 16.6±1.4 mEq/L in the control group (p<0.001) (**Table 3**). Targeted arterial pH was similarly achieved in both treatment and control groups (7.16±0.02 and 7.16±0.02 respectively, p<0.001 versus baseline) (**Figure 5B**).

In the treatment group, plasma chloride was removed by CRe-ED, and its concentration decreased from 106±4 to 91±6 mEq/L, from the beginning to the end of CRe-ED treatment, respectively (p<0.001) (**Figure 5C**). Consequently, plasma SID and HCO_3^- significantly increased **(Table 3)** and arterial pH returned to baseline after 199±43 minutes of CRe-ED treatment (range, 135-255 minutes) (**Figure 5C**). Of

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note, arterial pH remained stable from the end of the CRe-ED treatment to the end of the observation period (**Figure 5C**). In contrast, after infusion of lactic acid in the control group, no spontaneous correction of acidosis was observed (**Figures 5C**).

Table 3 summarizes **respiratory,** hemodynamic, plasma electrolytes, **acid-base status and renal function** changes over time among the groups during lactic acidosis. Plasma biochemistry and respiratory variables in both groups, as well as electrolyte concentrations in the treatment group along the withdrawal port of the extracorporeal circuit are reported in Table E5-E8.

Urinary response

During acidosis, in both treatment and control groups, urinary pH (pH_u) decreased **(Figure 6A)** while urinary ammonium and chloride concentration increased only in the control group (**Table 2** and **Figures 6 A-C**).

In the treatment group, during CRe-ED treatment, pH_u remained significantly lower compared to baseline (from 5.0±0.4 versus 5.7±0.7, p=0.016), did not differ compared to acidosis induction (versus 4.7±0.3, p=0.569) and remained stable during the 8h of observation (**Figure 6A** and **Table 2**). Furthermore, urinary chloride concentration decreased from 85.8±51.6 (acidosis induction) to 34.5±16.7 mEq/L (end of treatment) (p=0.160) **(Figure 6B)** and urinary AG increased accordingly from -1.4±54.5 to 46.8±45.4 (p=0.123), although these differences did not reach statistical significance (**Table 2**). Overall, normal arterial pH was restored by the removal of 185±56 mEq of chloride, of which 159±55 mEq were removed by CRe-ED and 26±9 mEq by urinary output, mainly excreted during the acidosis induction phase (**Figure 6B**).

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In the control group, cumulative urinary chloride excretion was 77±46 mEq (**Figure 6B**).

In all the treated animals by CRe-ED, no treatment was withdrawn due to the development of complications, including cardiac arrhythmias, pulmonary hypertension, or visible signs of hemolysis.

Discussion

In this experimental proof of concept study, we were able to reduce plasma chloride concentration *in vivo* through an extracorporeal device characterized by an electrodialysis cell (CRe-ED), aimed at selective chloride removal. The removal of plasma chloride rapidly corrected the acidemia regardless of the respiratory or metabolic origin of the acidosis. Indeed, during respiratory acidosis, six hours of CRe-ED treatment increased arterial pH from 7.16 to 7.40 by decreasing chloride concentration from 104 to 78 mEq/L. During metabolic acidosis, less than four hours of CRe-ED treatment were necessary to increase arterial pH from 7.16 to 7.40, through a reduction of chloride from 106 to 92 mEq/L. Within the same time frame, six and four hours, control swine subjected to comparable acidosis were able to increase arterial pH up to 7.29±0.03 only during respiratory acidosis while no modifications of pH were recorded during metabolic acidosis.

This is the first *in vivo* application of an extracorporeal electrodialytic device aimed at restoring physiologic pH during severe acidosis through selective plasma chloride removal. Chloride is the main anion in the extracellular fluid, and it has a key role in the regulation of acid-base equilibrium. As an example, because of SID reduction, hyperchloremia is a well-known cause of metabolic acidosis, as reported after administration of normal saline (19,20). Conversely, gastrointestinal, renal or sweat

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chloride loss may lead to hypochloremia, which, by increasing SID, causes metabolic alkalosis (28). Hypochloremia is likewise found in hypercapnic patients suffering from chronic obstructive pulmonary disease as a response to chronic respiratory acidosis (29). Selective binding and removal of hydrochloric acid from the gastrointestinal tract has been recently introduced as a novel treatment for chronic metabolic acidosis in patients suffering from chronic kidney disease. In a recently published randomized clinical trial, veverimer was able to achieve in 12 weeks a least squares mean change from baseline of blood bicarbonate of +4.4 mEq/L compared to +1.8 mEq/L of the placebo group (30).

In our experimental setting, investigating acute acidosis, CRe-ED normalized pH from 7.15 to 7.40 extremely rapidly. This was achieved through an average reduction of about 26 and 15 mEq/L in plasma chloride concentration, leading to an increase in blood bicarbonate of about 24 and 12 mEq/L, during respiratory and metabolic acidosis, respectively. According to Stewart's model, these decreases in chloride concentrations lead to an equivalent increase in SID, provided that strong cation concentrations remain constant. Sodium bicarbonate is a known therapeutic option to treat metabolic acidosis (6,12). However, if identical pH corrections were performed by administering sodium bicarbonate, a similar increase in SID would have been achieved at the cost of a marked increase of sodium concentration, with an increase in plasma osmolarity, and the consequent water shifts from the intracellular toward the extracellular fluid compartment. Indeed, sodium bicarbonate is burdened by side effects, such as increased plasma osmolarity, intracellular acidosis, and even risk of myelinolysis, when rapidly administered (6,12,13,31).

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As mentioned above, the rationale of CRe-ED arises from the physiological response of the renal system to acidosis, and, in parallel, from the physico-chemical approach to acid-base by Peter Stewart. According to traditional knowledge of renal physiology, the kidney reacts to acid load by enhancing net acid excretion (mainly through an increased NH_4^+ excretion), and HCO_3^- reabsorption / regeneration (32). The net result will be an increase in plasma HCO_3^- concentration. However, due to electroneutrality, an increased HCO_3^- concentration will inevitably be associated with a reduction of strong anions (Cl^-), provided that osmolality remains constant. In control animals, during respiratory acidosis urinary pH decreased, paralleled by a significant increase in urinary NH_4^+ excretion. Such modifications were, however, also associated with a parallel increase in urinary Cl^- excretion, likely due to an increase in Cl^- voltage-dependent channel secretion to preserve electroneutrality after the increased activity of distal H^+-ATPase pumps (33-34). Indeed, CRe-ED treatment switched-off such compensatory mechanism, possibly as a consequence of a very rapid reduction of the available Cl^- content in the peritubular capillary, and of the increase in urinary pH. During metabolic acidosis, we observed a similar, although markedly blunted, course of urinary Cl^- and NH_4^+ concentration, while in contrast, urinary pH remains acidotic also during CRe-ED treatment. Although a full understanding of this mechanism cannot be achieved, we may speculate that a significant urinary excretion of another strong anion, i.e., lactate, was present, thereby limiting urinary pH correction despite the selective plasma Cl^- removal and the associated progressive pH correction.

In order to selectively reduce the concentration of plasma chloride while maintaining a constant plasma sodium concentration, we have modified the electrodialysis circuit previously used to enhance extracorporeal CO_2 removal (23,25). Treatment of

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metabolic acidosis by conventional continuous renal replacement therapy (CRRT) would have partially increased blood pH by removing fixed acids with little, if any, change in plasma chloride concentration (35-37), depending on the composition of the dialytic bath. Treatment of respiratory acidosis by conventional CRRT might be potentially effective at increasing blood pH through a chloride reduction exclusively in conjunction with the use of replacement fluids with low or zero chloride concentration. Unfortunately, the use of such fluids are not commercially available today. However, CRRT would have also changed plasma sodium concentration towards the concentration of the replacement solution. Therefore, the final effect on blood pH and SID would have resulted by both the modifications of chloride and sodium, thus making it impossible to assess the sole effect of chloride reduction. Indeed, CRe-ED provided an effective treatment of acidemia through a selective and controlled plasma chloride removal.

After pH correction by CRe-ED, plasma chloride concentration was lowered to 91±6 and 78±8 mEq/L during metabolic and respiratory acidosis, respectively. We recorded no major adverse events of either hemodynamic, blood gas or biochemical nature. Furthermore, no visible signs of haemolysis were detected despite the concentration of plasma chloride in the post-filter blood was as low as 85±7 mEq/L and 71±8 mEq/L after metabolic and respiratory acidosis correction, respectively, with a chloride shift across the first hemofilter of 5.0±2.1 mEq/L and 7.4±1.9 mEq/L, and an associated pH of 7.29±0.09 and 7.37±0.02, respectively. However, despite maintaining a steady plasma osmolarity, we do not know to what extent chloride removal can be forced before causing harmful side effects *in vivo*, and this issue will require future investigation. Indeed, both hyper- and hypochloremia have been associated with adverse outcomes (38-40), when associated with pathological

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conditions. Hyperchloremia was associated with immune activation, clotting impairment, decreased splanchnic perfusion, renal vasoconstriction and the consequent reduction in glomerular filtration (19,20,41). In the recent SALT randomized trial, ICU patients exposed to higher volumes of saline infusion – which was associated with higher levels of serum chloride – presented a higher incidence of the composite outcome of major adverse kidney events at 30 day follow up, compared to larger volumes of balanced crystalloid infusions. This finding suggested a potential dose-response relationship between intravenous fluid-related hyperchloremia and outcome (42). On the other hand, hypochloremia is considered a marker of illness severity (43), even though no specific threshold appears to be independently associated to unfavourable outcomes and a definite causal connection is lacking. To the best of our knowledge, no complications attributable to low chloride levels have been reported even at very low levels of chloremia (44).

As a secondary aim, our study was also designed to evaluate the hypothesis that the increment in pH achieved with a single CRe-ED treatment, would have been sustained even after the suspension of the treatment despite maintaining the underlying acidosis. This hypothesis has been partially refuted by the experimental data observed. Indeed, shortly following CRe-ED suspension during both respiratory and metabolic acidosis, pH slightly dropped to 7.36 and 7.33 at 4h, but it remained subsequently stable until the end of the observation period (7.36 and 7.34). The drop in pH was associated to an increase of plasma chloride concentration by about 7 and 4 mEq/L during the observation period of the respiratory and metabolic acidosis, respectively. Indeed, such increase in chloremia was not associated with a renal-induced chloride retaining state occurring after the achievement of very low level of hypochloremia, since urinary excretion of chloride remained active even after the end

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of CRe-ED treatment (see Figure 4c and 6c). We may speculate that plasma chloride increase may be at least partially associated with a chloride shift back into the plasma from other connecting fluid compartments, most likely from red blood cells (45,46), during a very rapid, and likely non-physiological reduction of plasma chloride concentration. In addition, intravenous administration of fluid maintenance during the observation period, which included chloride, may have played a role. Further data are warranted to evaluate the potential stability of low levels of hypochloremia over a longer period of time.

The application of CRe-ED, although still as a prototype in a pilot animal study, opens up the possibility of promising future applications, that may have an important impact in clinical settings.

First, CRe-ED may represent the only possibility of rapidly correcting acidosis when the renal system is failing. In the present study, we applied CRe-ED to healthy animals. However, patients admitted to ICU, often develop impaired renal function, a further hurdle which affects the physiologic response to acidosis (47). It is therefore conceivable that critically ill patients, such as patients with septic shock, acute respiratory failure, and other pathological processes, may benefit from CRe-ED even at greater extent.

Second, CRe-ED may represent a unique method facilitating the tolerance of hypercapnia, when related to the necessity of reducing minute ventilation during mechanical ventilation, such as during ARDS. In the present experimental setting of respiratory acidosis, chloride removal of about 400 mEq allowed to reduce minute ventilation down to 50% while keeping a constant pCO_2 (as high as about 90 mmHg). Extracorporeal chloride removal could be applied to patients with respiratory failure

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(i.e. ARDS patients) to buffer acidemia generated by permissive hypercapnia (7,48). This could be beneficial in severe ARDS patients, enabling a low tidal volume protective mechanical ventilation without the drawback of acidemia consequent to permissive hypercapnia induction. Furthermore, preclinical evidence supports the association of severe hypercapnic acidosis with immunosuppression, bacterial proliferation in sepsis and increased injury in lung cells (49-51). Caples SM et al. reported that buffering hypercapnic acidosis can protect alveolar cells and enhance the repair of wounded cells after exposure to injurious ventilation (51). The application of CRe-ED in ARDS patients could easily support even the use of ultra-low tidal volume ventilation (52).

Third, CRe-ED might be suitable as an intermittent treatment to enhance the tolerance of chronic hypercapnia, such as in the case of patients with chronic respiratory failure. Patients with chronic obstructive pulmonary disease often develop hypochloremia, which compensates for hypercapnia and a high plasma HCO_3^- concentration. However, this compensation is hardly achievable in the presence of concomitant chronic kidney disease, and may be limited by the maximal chloride excretive capability of the renal system. In this scenario, patients with end-stage respiratory failure are not only challenged by hypoxemia, but they are also unable to handle further minimal loads of CO_2. We speculate that the application of an intermittent chloride removal may increase the tolerance to higher levels of CO_2, thus extending the life span and improving the quality of life for those patients.

Fourth, therapeutic modulation of plasma chloride concentration could have some advantages in the treatment of acid-base and hydro-electrolytic imbalances. Chloride removal proved to be effective in increasing blood pH, and, in case of hyperchloremic

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acidosis, such as following administration of conspicuous amounts of normal saline, it would also effectively treat the cause of acidosis. On the opposite side, the administration of highly concentrated hydrochloric acid through a dialysis circuit, as performed during the re-chloration phases, could be a feasible and safe alternative to the historical treatment of systemic alkalosis based on direct infusion of diluted hydrochloric acid (53,54).

Our study presents also some limitations. First, this experimental investigation was a proof-of-concept study in healthy animals. Therefore, no information about the effect of normalization of respiratory or metabolic acidosis in critically ill patients, such as during respiratory failure or renal impairment can be determined. Second, we did not evaluate higher safety limits of chloride removal, both in terms of total amount of chloride to be removed and velocity of chloride shift from plasma. Third, we cannot establish the time of chloride removal by CRe-ED in humans, but we assume it may be longer relative to the time needed to remove chloride in this preclinical investigation model, based on estimated total body chloride. Fourth, during the metabolic acidosis experiment, compensatory respiratory response to acidosis was not permitted, as arterial PCO_2 was maintained constant from baseline until the end of the observation period.

In conclusion, we documented the first *in vivo* application of an extracorporeal system targeted to correction of severe acidemia by lowering plasma concentration of chloride. In two experimental models of metabolic and respiratory acidosis, CRe-ED proved to be superior in normalizing arterial pH compared to the physiological compensatory response in healthy controls. Further studies are warranted to access

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the feasibility and safety profile of CRe-ED, especially with regard of the amount and the shift velocity of plasma chloride modulation.

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