



Mechanical Ventilation

Electrolyte shifts across the artificial lung in patients on extracorporeal membrane oxygenation: Interdependence between partial pressure of carbon dioxide and strong ion difference ☆☆☆★



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ABSTRACT

Purpose: Partial pressure of carbon dioxide (P_{CO_2}), strong ion difference (SID), and total amount of weak acids independently regulate pH. When blood passes through an extracorporeal membrane lung, P_{CO_2} decreases. Furthermore, changes in electrolytes, potentially affecting SID, were reported. We analyzed these phenomena according to Stewart's approach.

Methods: Couples of measurements of blood entering (venous) and leaving (arterial) the extracorporeal membrane lung were analyzed in 20 patients. Changes in SID, P_{CO_2} , and pH were computed and pH variations in the absence of measured SID variations calculated.

Results: Passing from venous to arterial blood, P_{CO_2} was reduced (46.5 ± 7.7 vs 34.8 ± 7.4 mm Hg, $P < .001$), and hemoglobin saturation increased (78 ± 8 vs $100 \pm 2\%$, $P < .001$). Chloride increased, and sodium decreased causing a reduction in SID (38.7 ± 5.0 vs 36.4 ± 5.1 mEq/L, $P < .001$). Analysis of quartiles of ΔP_{CO_2} revealed progressive increases in chloride ($P < .001$), reductions in sodium ($P < .001$), and decreases in SID ($P < .001$), at constant hemoglobin saturation variation ($P = .12$). Actual pH variation was lower than pH variations in the absence of measured SID variations (0.09 ± 0.03 vs 0.12 ± 0.04 , $P < .001$).

Conclusions: When P_{CO_2} is reduced and oxygen added, several changes in electrolytes occur. These changes cause a P_{CO_2} -dependent SID reduction that, by acidifying plasma, limits pH correction caused by carbon dioxide removal. In this particular setting, P_{CO_2} and SID are interdependent.

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1. Introduction

Venovenous extracorporeal membrane oxygenation (ECMO), also known as “extracorporeal gas exchange,” is a temporary support of the failing respiratory system [1,2] that is increasingly used as an adjunct to mechanical ventilation in patients who cannot be safely treated with mechanical ventilation alone [3,4]. Moreover, ECMO is increasingly used as a first-line treatment, that is, as an alternative to mechanical ventilation in patients bridged to lung transplantation [5], patients with exacerbation of chronic obstructive pulmonary disease

(COPD) [6,7], and patients with acute respiratory distress syndrome (ARDS) [8,9]. During ECMO, a fraction of the patient's venous blood is drained from a catheter placed in a large vein, pumped through a membrane lung, and delivered back into the patient's venous system. The membrane lung is ventilated with varying amounts of oxygen mixtures (sweep gas flow [GF]), and gas exchange—oxygenation and carbon dioxide removal—takes place at the interface between blood and membrane fibers, similarly to the alveolar-capillary membrane of natural lungs.

When considering Stewart's approach to acid-base and electrolyte equilibrium [10,11], 1 of the 3 independent variables, the partial pressure of carbon dioxide (P_{CO_2}), is acutely reduced when the blood passing through the membrane lung is ventilated, causing a reduction in plasma bicarbonate ion concentration (HCO_3^-) and an increase in plasma pH. Furthermore, although the total amount of weak acids (A_{TOT}) is expected to remain unchanged, electrolyte variations caused by changes in P_{CO_2} and hemoglobin (Hb) saturation have been described in vitro [12] and in experimental models [13,14]. These electrolyte variations can potentially lead to variations in plasma SID therefore affecting plasma pH and the final effect of ECMO in correcting arterial pH.

☆ Competing interests: The authors declare that they have no conflict of interest regarding the present study.

☆☆ Authors' contribution: TL and LG conceived the study; TL and MC contributed to data acquisition; TL, ES, EC, and LZ performed data analysis; TL, ES, and EC drafted the manuscript; AP, MC, PC, and LG critically revised the manuscript for important intellectual content; all authors read and approved the final version of the manuscript.

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The aim of the present study was to describe, in a cohort of critically ill patients with respiratory failure supported with ECMO, the variations in electrolytes and therefore SID occurring across the membrane lung as a consequence of extracorporeal gas exchange. In particular, we aimed to (i) describe accurately the electrolyte changes occurring across the membrane lung and (ii) investigate the possible impact of these electrolyte variations on plasma pH according to Stewart's quantitative approach to acid-base and electrolyte equilibrium.

Some of the results of the present study have been previously reported in the form of abstracts [15,16].

2. Materials and methods

This is a retrospective analysis of clinical data routinely collected in our intensive care unit. The study was approved by the institutional review board of our hospital; informed consent was waived because of the retrospective nature of the study.

All patients admitted to the general intensive care unit "Emma Vecla" of the Fondazione IRCCS Ca' Granda–Ospedale Maggiore Policlinico, Milan, Italy, between January 2010 and June 2011 requiring ECMO support were enrolled in the study.

Couples of measurements of blood gases and electrolytes (ABL 800 Flex; Radiometer GmbH, Willich, Germany) performed simultaneously, for clinical purposes, before (prelung, venous) and after (postlung, arterial) the membrane lung (Maquet Cardiopulmonary AG, Rastatt, Germany) were recorded. Moreover, settings of blood flow (BF) and sweep GF at the moment of sample drawing were recorded.

2.1. Definitions and calculations

Strong ion difference was calculated as reported in Eq. (1).

$$[SID] = [Na^+] + [K^+] + 2 \times [Ca^{2+}] - [Cl^-] - [Lac^-] \quad (1)$$

where Na^+ , K^+ , Ca^{2+} , Cl^- and Lac^- refer to plasma sodium, potassium, ionized calcium, chloride and lactate concentrations, respectively. All values are expressed as millimolar.

Theoretical postlung pH was calculated (MATLAB R2008a; The Math Works, Inc, Natick, MA) using premembrane lung acid-base values and the actual variation in P_{CO_2} as previously reported [17] (see also the electronic supplementary material for more details).

Actual and theoretical pH variations (ΔpH_A and ΔpH_T) induced by the passage of blood through the ventilated membrane lung were defined as follows:

$$\Delta pH_A = pH_{POST} - pH_{PRE} \quad (2)$$

$$\Delta pH_T = \text{theoretical } pH_{POST} - pH_{PRE} \quad (3)$$

Variations in other measured variables were defined similarly:

$$\Delta X = X_{POST} - X_{PRE} \quad (4)$$

where ΔX denotes the variation in any measured variable (X); footnotes POST and PRE denote blood exiting and entering the membrane lung, respectively.

2.2. Statistical analysis

Data are reported as mean \pm SD unless otherwise stated. A paired *t* test or the Wilcoxon signed rank test was used, as appropriate, to compare prelung and postlung values. Moreover, data were divided into quartiles of P_{CO_2} variations (ΔP_{CO_2}), and the mean values of the resulting 4 groups were tested for statistical difference via one-way

analysis of variance (ANOVA) or the Kruskal-Wallis test, as appropriate. Tukey or Dunn test was used for post hoc multiple comparisons.

The correlation between ΔP_{CO_2} and ΔpH_A and between ΔP_{CO_2} and ΔpH_T was assessed via linear regression analysis. Slopes of the resulting regressions were compared using the test for equality of slopes. Statistical significance was defined as $P < .05$. Analysis was performed with SAS v.9.2. (SAS, Cary, NC) and SigmaPlot v.12.0 (Systat Software Inc, San Jose, CA).

3. Results

Twenty patients were supported with ECMO during the study period. A total of 403 premembrane and postmembrane lung sample couples were collected (806 blood gas analyses), with a median number of 29 (interquartile range, 15–63) sample couples per patient.

Table 1 summarizes the most relevant demographic and clinical characteristics of the study population.

3.1. Prelung and postlung blood gases and electrolytes

Prelung and postlung values of blood gases and electrolytes are reported in Table 2. A significant reduction in P_{CO_2} associated with a consequent increase in pH and a reduction in HCO_3^- concentration was observed in postlung samples. Saturation of Hb increased significantly in blood passing through the membrane lung. Plasma concentration of chloride increased ($P < .001$), and concentration of sodium decreased ($P < .001$), causing a significant reduction in SID ($P < .001$) in postlung values. Moreover, a simultaneous variation of other electrolytes was observed: slight, although significant increase of lactate and minimal, although significant decrease for other cations (potassium and ionized calcium).

3.2. Analysis in quartiles of P_{CO_2} variation

To analyze the effects of different ΔP_{CO_2} on plasma acid-base variables and electrolyte concentrations, data were divided into quartiles of ΔP_{CO_2} . As variations in Hb saturation were similar in the different quartiles, this allowed us to normalize the samples for possible effects of Hb saturation changes. Results are summarized in Table 3. Fig. 1 represents the observed variations of SID associated to ΔP_{CO_2} .

3.3. Calculation of ΔpH_T

Theoretical ΔpH_T were significantly higher than the ΔpH_A (0.12 ± 0.04 vs 0.09 ± 0.03 , $P < .0001$). As shown in Fig. 2, both ΔpH_A and calculated pH correlated linearly to ΔP_{CO_2} ($r^2 = 0.69$, $P < .0001$ and $r^2 = 0.73$, $P < .0001$, respectively). Regression slopes significantly differed between calculated and ΔpH_A ($P < .001$).

Table 1
Demographic and clinical characteristics of the study population

Characteristics	(n = 20)
Age (y)	41 \pm 18
Female sex–n (%)	8 (40)
Days on ECMO	15 \pm 11
Cause of lung failure–n (%)	
ARDS	13 (65)
Bridge to lung transplantation	5 (25)
Primary graft dysfunction	1 (5)
COPD exacerbation	1 (5)
Spontaneous breathing–n (%)	8 (40)
Survival–n (%)	12 (60)

Abbreviations: *Primary graft dysfunction*, primary graft dysfunction after lung transplantation; *spontaneous breathing*, patients who have been treated with ECMO as an alternative to mechanical ventilation, in the absence of endotracheal intubation and invasive mechanical ventilation; plus-minus values are means \pm SD.

Table 2
Blood gases and electrolytes of prelung and postlung samples

Variables	Pre-lung	Post-lung	Difference	P
pH	7.412 ± 0.055	7.501 ± 0.062	0.089 ± 0.029	<.001
H ⁺ (nEq/L)	39.0 ± 5.1	31.9 ± 4.6	−7.2 ± 2.4	<.001
Pco ₂ (millimeters of mercury)	46.5 ± 7.7	34.8 ± 7.4	−11.7 ± 3.5	<.001
PO ₂ (millimeters of mercury)	45 ± 7	438 ± 136	393 ± 136	<.001
SO ₂ (%)	78 ± 8	100 ± 2	22 ± 8	<.001
Na ⁺ (milliequivalents per liter)	139.6 ± 5.8	138.6 ± 5.8	−1.0 ± 0.7	<.001
K ⁺ (milliequivalents per liter)	3.91 ± 0.47	3.88 ± 0.47	−0.03 ± 0.097	<.001
Cl [−] (milliequivalents per liter)	105.5 ± 7.4	106.7 ± 7.4	1.2 ± 1.0	<.001
Ca ²⁺ (milliequivalents per liter)	2.30 ± 0.15	2.24 ± 0.15	−0.06 ± 0.05	<.001
Lactate (milliequivalents per liter)	1.6 ± 0.8	1.7 ± 0.9	0.1 ± 0.1	<.001
Hco ₃ [−] (milliequivalents per liter)	29.3 ± 5.3	26.8 ± 5.4	−2.5 ± 0.8	<.001
SID (milliequivalents per liter)	38.7 ± 5.0	36.4 ± 5.1	−2.3 ± 1.3	<.001
BE (milliequivalents per liter)	4.7 ± 5.7	3.6 ± 5.7	−1.1 ± 0.7	<.001

Abbreviations: H⁺, hydrogen ion; PO₂, partial pressure of oxygen; SO₂, Hb level saturation; Na⁺, sodium; K⁺, potassium; Cl[−], chloride; Ca²⁺, calcium; BE, base excess; nEq/L, nanoequivalents per liter. Data are expressed as mean ± SD; P value, P value of the paired t test.

4. Discussion

In the present study, we describe, in a cohort of critically ill patients with respiratory failure supported with ECMO, the electrolyte variations occurring in the blood passing through the membrane lung as a consequence of extracorporeal oxygenation and carbon dioxide removal and analyze these variations according to Stewart's approach to acid-base and electrolyte equilibrium.

It is worth underlining that, in this setting, we can exclude electrolyte exchanges with the interstitium [18], electrolyte variations due to electrolyte excretion through the kidney [19,20], and electrolyte changes caused by the infusion of fluids [21,22]. The observed electrolyte variations can therefore only be the results of (i) movements from blood cells, mainly red blood cells, to plasma (and vice versa) and (ii) pH-mediated changes in the affinity of electrolytes to proteins and therefore variations in their ionized concentration [23–25]. In this regard, our model can be considered “*in vivo-in vitro*”, as the system is, aside from gas exchange, completely closed to external influences.

When analyzing the overall pre- and post-samples, we observed the expected variations in Hb saturation, Pco₂, Hco₃[−], and pH due to extracorporeal gas exchange. Furthermore, slight, but statistically significant changes in several electrolytes were recorded (Table 2). Changes in chloride concentrations due to variations in Pco₂ (and Hco₃[−] concentrations) have been first described at the beginning of the 20th century by the Dutch physiologist Hamburger [26] and have been recently rediscussed

[27]. Classically, the *chloride shift* is defined as the exchange between chloride and Hco₃[−] caused by the addition to venous plasma of the carbon dioxide produced by cellular metabolism. In this condition, the increase of plasma Pco₂ and Hco₃[−] is associated with the entrance of chloride into red blood cells, with ensuing reduction in plasma chloride concentration [27]. In our study, we had the opposite condition, as metabolically produced carbon dioxide was removed by the membrane lung. Accordingly, we observed a reduction in Hco₃[−] and a significant increase in plasma chloride concentration (Table 2), a “reverse Hamburger effect.” We also observed a minimal, although statistically significant increase in lactate; the other measured anion, a significant decrease in plasma sodium; and minimal, although significant reductions in potassium and ionized calcium.

To understand the physicochemical mechanisms underlying the observed electrolyte variations, it is necessary to split the venoarterial transition into 2 parts (i) oxygenation of Hb and (ii) reduction in carbon dioxide content.

The oxygen added to the system binds to Hb causing a change in its quaternary structure from the taut (“T”), deoxygenated, to the relaxed (“R”) oxygenated state [27,28]. This conformational change leads to the release of hydrogen ions with consequent reduction in Hb's pKa and increased carbon dioxide release from Hb (Haldane effect). Furthermore, oxygenation of Hb causes (i) the extrusion of electrically charged 2,3-diphosphoglyceric acid from Hb and (ii) the unbinding from Hb of chloride anions, which are added to the

Table 3
Analysis in quartiles of carbon dioxide variations

VARIABLES	First quartile (n = 103)	Second quartile (n = 97)	Third quartile (n = 102)	Fourth quartile (n = 101)	P
ΔPco ₂ (millimeters of mercury)	−7.7 ± 1.8	−10.5 ± 0.6 ^a	−12.5 ± 0.7 ^{a,b}	−16.3 ± 2.1 ^{a,b,c}	<.001
GF/BF	1.1 ± 0.6	1.7 ± 0.7	1.7 ± 0.7	1.8 ± 0.7 ^{a,b,c}	<.001
ΔpH	0.06 ± 0.02	0.08 ± 0.02 ^a	0.09 ± 0.02 ^{a,b}	0.12 ± 0.02 ^{a,b,c}	<.001
ΔH ⁺ [nEq/L]	−4.6 ± 1.5	−6.4 ± 1.3 ^a	−7.7 ± 1.2 ^{a,b}	−9.9 ± 1.6 ^{a,b,c}	<.001
ΔNa ⁺ (milliequivalents per liter)	−0.8 ± 0.7	−0.9 ± 0.8	−1.0 ± 0.6	−1.1 ± 0.7 ^a	.002
ΔK ⁺ (milliequivalents per liter)	−0.01 ± 0.12	−0.02 ± 0.09	−0.03 ± 0.07	−0.05 ± 0.10 ^a	.02
ΔCl [−] (milliequivalents per liter)	0.9 ± 1.1	1.1 ± 0.9	1.3 ± 0.8	1.7 ± 1.1 ^{a,b,c}	<.001
ΔCa ²⁺ (milliequivalents per liter)	−0.04 ± 0.04	−0.06 ± 0.04 ^a	−0.07 ± 0.05 ^{a,b}	−0.10 ± 0.04 ^{a,b,c}	<.001
ΔHco ₃ [−] (milliequivalents per liter)	−1.7 ± 0.7	−2.4 ± 0.6 ^a	−2.7 ± 0.5 ^{a,b}	−3.2 ± 0.6 ^{a,b,c}	<.001
ΔLactate [−] (milliequivalents per liter)	0.05 ± 0.15	0.04 ± 0.10	0.06 ± 0.07	0.06 ± 0.08	.20
ΔBE (milliequivalents per liter)	−0.8 ± 0.7	−1.1 ± 0.7 ^a	−1.2 ± 0.6 ^{a,b}	−1.3 ± 0.6 ^{a,b,c}	<.001
ΔSO ₂ (%)	21.6 ± 7.9	23.0 ± 8.2	22.3 ± 7.8	20.6 ± 8.0	.12
Hb (grams per deciliter)	10.3 ± 0.9	10.3 ± 1.1	10.5 ± 0.9	10.2 ± 0.8	.03

Abbreviations: GF/BF, ratio between GF ventilating the membrane lung and BF perfusing the membrane lung; ΔpH, variations in pH; ΔH⁺, variations in hydrogen ion concentrations; ΔNa⁺, variations in sodium concentrations; ΔK⁺, variations in potassium concentrations; ΔCl[−], variations in chloride concentrations; ΔCa²⁺, variations in ionized calcium concentrations; ΔHco₃[−], variations in bicarbonate ion concentrations; ΔLactate[−], variations in lactate concentrations; ΔBE, variations in base excess; ΔSO₂, variations in Hb saturation; n, sample couples of the corresponding quartile; P value, P value of the one-way ANOVA.

^a P < .05 vs first quartile.

^b P < .05 vs 2nd quartile.

^c P < .05 vs 3rd quartile.

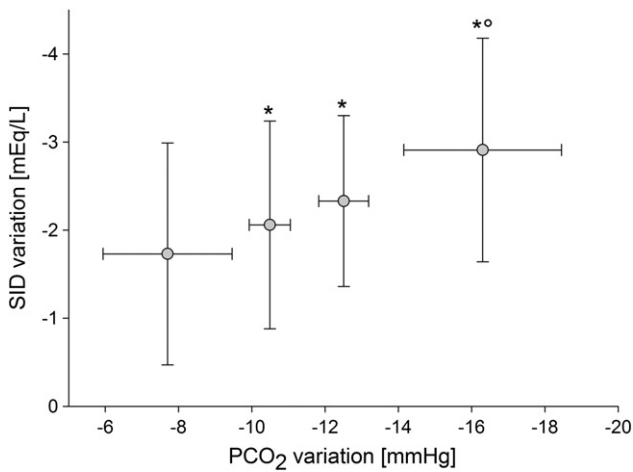


Fig. 1. Analysis of SID variations by quartiles of ΔPCO_2 . Variations in SID caused by different degrees of PCO_2 variation. Symbols and error bars represent mean \pm SD. Partial pressure of carbon dioxide variations are expressed in quartiles and are obtained by the difference between the PCO_2 measured postmembrane and premembrane. Strong ion difference variations represent the difference between SID calculated postmembrane and premembrane. $P < .001$ for the one-way ANOVA. * $P < .05$ vs first quartile; ° $P < .05$ vs second quartile.

electrochemical milieu [27,28]. Both events, besides increasing the affinity of Hb for oxygen (allosteric effect), increase the negative charges within the cytoplasm of red blood cells.

On the other side of the red cell membrane, in plasma, the loss of HCO_3^- ions due to extracorporeal carbon dioxide removal further increases the negativity of the membrane potential. The final result is a slight inequality in Donnan ratios for chloride and HCO_3^- [27], which are reestablished through the extrusion of HCO_3^- and chloride from the cytoplasm of red blood cells [27]. In addition, the increased negativity of the membrane potential causes also an augmented leakage of sodium and potassium from plasma into the red blood cell and of lactate into plasma. Of note, unlike chloride and HCO_3^- , whose concentrations are regulated by a Donnan equilibrium, the concentrations of sodium and potassium are regulated by adenosine triphosphate-dependent sodium/potassium pumps.

The relative contribution of the 2 phenomena on the sole chloride shift has been investigated in previous studies performed by Prange and Westen [27] on cow's blood. The authors concluded that

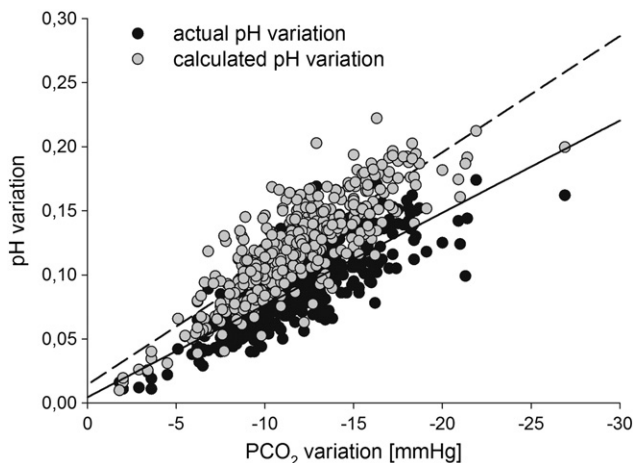


Fig. 2. Differences between ΔpH_A and calculated pH variations due to ΔPCO_2 . Correlation between ΔPCO_2 and actual (black dots) and calculated (gray dots) pH variations in premembrane and postmembrane blood samples. Continuous regression line refers to ΔpH_A ($r^2 = 0.691$, $P < .001$; $y = 0.00454 - (0.00719 \cdot \Delta\text{PCO}_2)$), whereas dashed regression line refers to calculated pH variations ($r^2 = 0.705$, $P < .0001$; $y = 0.01346 - (0.00924 \cdot \Delta\text{PCO}_2)$). Regression slopes significantly differed between calculated and ΔpH_A ($P < .001$).

approximately 75% of the chloride shift was due to the binding/unbinding of chloride to Hb, whereas only 25% was caused by carbon dioxide variations. Several aspects differ, however, between our data and data of Prange and Westen [27]. First, the blood samples of our critically ill patients on ECMO had, on average, a lower Hb concentration (10.3 vs 15.9 g/dL in the sample of Prange and Westen). As pointed out by the authors, this might have resulted in a reduced “chloride reservoir” and a reduced amount of chloride unbinding from Hb [27]. However, because the carbon dioxide component of the chloride shift is also hematocrit dependent, it would likely be reduced in equal proportion. Second, venous oxygen saturation of our samples was on average 78% therefore significantly higher and clinically more likely as compared with data of Prange and Westen [27] (28%). Consequently, we observed a significantly lower increase in Hb saturation (22% vs 70%), a significantly lower transition from T to R state of Hb and likely a lower degree of chloride unbinding from Hb. This hypothesis is also supported by our analysis in quartiles of carbon dioxide variation (Table 3), where we observed homogeneous Hb concentrations and variations in Hb saturation (Table 3). We can therefore assume the contribution of Hb oxygenation and chloride unbinding from Hb to be constant and therefore deduce that the progressive increase in observed chloride variations are the direct consequence of extracorporeal carbon dioxide removal. If we assume that only 25% of the chloride variation (0.225 mEq) observed in the first quartile is derived from carbon dioxide variation [27] and we add this amount to the difference between fourth and first quartile (0.8 mEq), we can speculate that the chloride variation deriving from carbon dioxide variation in the fourth quartile is therefore $0.8 + 0.225 = 1.025$ mEq, which roughly corresponds to 60% of the total chloride variation, significantly higher than previously reported. Of note, as stated above, the chloride unbinding from Hb in the first quartile is likely overestimated due to lower variation in Hb saturation. The percentage contribution of carbon dioxide to the chloride shift could therefore be slightly higher. Interestingly, also variations in cation concentrations (sodium, potassium, and ionized calcium) were proportional to extracorporeal carbon dioxide removal (Table 3).

As a result of these electrolyte variations, we observed a progressive and significant increase in SID variation; that is, the greater the variation in PCO_2 (more carbon dioxide was removed extracorporeally), the greater the reduction in plasma SID (Fig. 1).

According to Stewart's theory, PCO_2 and SID are considered as independent variables regulating the acid-base equilibrium of a given solution. Our results, as opposed to the classic theory, demonstrate that plasma PCO_2 and SID are, in this particular setting, not independent from each other (Fig. 1). It is, however, worth mentioning that, in his work, Stewart modeled a single compartment, namely, separated plasma and therefore did not consider Gibbs-Donnan exchanges with red blood cells or with the interstitium [27]. Movements of electrolytes with consequent SID changes in response to ΔPCO_2 have on the contrary been discussed when dealing with whole blood, or with the 3-compartment model (interstitial, plasma, and erythrocyte) [29,30], and interstitial, plasma, and erythrocyte SID and standard base excess have consequently been proposed as better carbon dioxide invariant acid-base variables.

Finally, when calculating the ideal pH variation occurring without electrolyte changes, we observed, for any given PCO_2 decrease, a higher pH increase as compared with ΔpH_A (Fig. 2). We observed a reduction in SID when passing through the membrane lung; and because the reduction in SID has an acidifying effect, the observed electrolyte variations reduced the pH excursions caused by extracorporeal carbon dioxide removal and could therefore be considered as the contribution of red blood cells to the compensation of acute hypocapnic alkalosis [15]. Interestingly, as the slopes of the regressions in Fig. 2 were found to be statistically different, it appears that this “compensating” effect increases for higher amounts of carbon dioxide removal.

The high number of analyzed premembrane and postmembrane lung sample couples is a strength of the present study and explains

also why minimal differences in electrolyte concentration could be found statistically significant. On the other side, there are several limitations in this investigation. First, the retrospective observational nature of this study needs to be mentioned. Second, albumin and phosphates concentrations, which are the major determinants of A_{TOT} , were not reported. As these variables were not measured routinely before and after the membrane lung, we assumed, as previously reported [31], that A_{TOT} did not change importantly in the transition from venous to arterial blood.

Among the clinical options for treating acute respiratory failure, the use of ECMO is increasing; and more and more clinicians will analyze, for clinical reasons, gases and electrolytes before and after the membrane lung. The present work provides a detailed description and possible interpretation of the variations that occur across the membrane lung. Moreover, although our findings unlikely have a strong clinical impact, they fully clarify the actual efficiency of ECMO in correcting pH during severe respiratory acidosis, which may be lower than expected when high amounts of carbon dioxide are removed extracorporeally (such as in patients with severe ARDS with elevated dead-space fraction or in patients with severe COPD). Finally, Stewart's approach to acid-base and electrolyte equilibrium is gaining popularity in both the scientific and clinical community; and the present study, in our opinion, provides sound clinical evidence supporting the interdependence between P_{CO_2} and SID in the context of Stewart's theory.

In conclusion, when blood is oxygenated and cleared from carbon dioxide by using an ECMO, several variations in plasma electrolytes occur as a result of a Gibbs-Donnan phenomenon driven by changes in both carbon dioxide and Hb saturation. Plasma strong anions are increased (mainly chloride—the “chloride shift”—) and plasma strong cations reduced. These changes cause a P_{CO_2} -dependent reduction in plasma SID that, in this particular setting, becomes a dependent variable. The reduction in SID, by acidifying plasma, limits the increase in pH caused by carbon dioxide removal. This compensating effect is greater for higher amounts of carbon dioxide removal.

Additional material

Additional file 1: Electronic supplementary material. Additional materials, results and references

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <http://dx.doi.org/10.1016/j.jccr.2014.09.013>.

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