ANESTHESIOLOGY

Combining the Physical–Chemical Approach with Standard Base Excess to Understand the Compensation of Respiratory Acid–Base Derangements: An Individual Participant Meta-analysis Approach to Data from Multiple Canine and Human Experiments

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ABSTRACT

Background: Several studies explored the interdependence between $Paco_2$ and bicarbonate during respiratory acid–base derangements. The authors aimed to reframe the bicarbonate adaptation to respiratory disorders according to the physical–chemical approach, hypothesizing that (1) bicarbonate concentration during respiratory derangements is associated with strong ion difference; and (2) during *acute* respiratory disorders, strong ion difference changes are not associated with standard base excess.

Methods: This is an individual participant data meta-analysis from multiple canine and human experiments published up to April 29, 2021. Studies testing the effect of acute or chronic respiratory derangements and reporting the variations of $Paco_2$, bicarbonate, and electrolytes were analyzed. Strong ion difference and standard base excess were calculated.

Results: Eleven studies were included. $Paco_2$ ranged between 21 and 142 mmHg, while bicarbonate and strong ion difference ranged between 12.3 and 43.8 mM, and 32.6 and 60.0 mEq/l, respectively. Bicarbonate changes were linearly associated with the strong ion difference variation in acute and chronic respiratory derangement (β-coefficient, 1.2; 95% CI, 1.2 to 1.3; $P < 0.001$). In the acute setting, sodium variations justified approximately 80% of strong ion difference change, while a similar percentage of chloride variation was responsible for chronic adaptations. In the acute setting, strong ion difference variation was not associated with standard base excess changes (β-coefficient, –0.02; 95% CI, –0.11 to 0.07; $P = 0.719$), while a positive linear association was present in chronic studies (β-coefficient, 1.04; 95% CI, 0.84 to 1.24; $P < 0.001$).

Conclusions: The bicarbonate adaptation that follows primary respiratory alterations is associated with variations of strong ion difference. In the acute phase, the variation in strong ion difference is mainly due to sodium variations and is not paralleled by modifications of standard base excess. In the chronic setting, strong ion difference changes are due to chloride variations and are mirrored by standard base excess.

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EDITOR'S PERSPECTIVE

What We Already Know about This Topic

- Previous studies on the adaptation to acute and chronic respiratory acid–base derangements have mainly focused on bicarbonate (Boston rules) and base excess changes, without investigating the associated electrolyte variations.

What This Article Tells Us That Is New

- The authors take an individual participant meta-analysis approach to data from multiple canine and human experiments, combining the physical–chemical approach with standard base excess to better understand the compensation of respiratory acid–base derangements. They find that bicarbonate adaptation that follows primary respiratory alterations is associated with variations of strong ion difference.
- In the acute phase, the variation in strong ion difference is mainly due to sodium variations and is not paralleled by modifications of standard base excess.
- In the chronic setting, strong ion difference changes are due to chloride variations and are mirrored by standard base excess.

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During the last century, acid–base equilibrium disturbances have been approached in several different ways.[1] According to an oversimplified interpretation of the Henderson-Hasselbalch equation, the $Paco_2$ and the concentration of bicarbonate (HCO_3^-) are the two determinants of pH. Primary changes of these parameters are used to classify the acid–base derangements as respiratory or metabolic, respectively. However, carbon dioxide and bicarbonate are two interdependent variables as described by the law of mass action (*i.e.,* $CO_2 + H_2O \Leftrightarrow H_2CO_3 \Leftrightarrow H^+ + HCO_3^-$). Schwartz and Relman performed *in vivo* experiments exploring the dependence between $Paco_2$ and bicarbonate during acute and chronic respiratory acidosis or alkalosis.[2,3] These studies, conducted on healthy humans and dogs, led to the development of four empiric equations to predict the compensatory variation of bicarbonate in response to respiratory acid–base disorders: the so-called "Boston rules" (Supplementary materials, Table S1, https://links.lww.com/ALN/D285).

The Boston rules are easy to remember and apply at the bedside to deduce the presence of primary respiratory or mixed acid–base disorders. However, several limitations need to be acknowledged. First, to be applied, the knowledge of the time course of the respiratory disorder is required. However, the patient's medical history may not always be available, especially during emergencies or when dealing with unconscious patients. Second, these equations were obtained from healthy humans and dogs without renal impairment and with normal hemoglobin and albumin concentrations, the major determinants of the noncarbonic buffer power.[4] Nevertheless, they are commonly applied to critically ill patients, in whom these factors are often altered by acute illness, drug administration, or intravenous fluid infusion.[5,6] Third, they do not give any insight into the electrolyte changes leading to the metabolic compensation of the respiratory disorder.

In the sixties, Siggaard-Andersen developed the base excess concept to quantitatively isolate the metabolic acid–base status of patients, independently from coexisting respiratory derangements.[7]

Last, Stewart introduced a physical–chemical approach to acid–base, in which the major novelty was to integrate the concept of electrical neutrality, thus recognizing the critical role of electrolytes and their charges in maintaining acid–base balance.[8,9] This model considers three independent variables regulating the concentration of hydrogen ions in plasma: $Paco_2$, the total concentration of weak acids (mainly represented by albumin and phosphates), and the strong ion difference. The strong ion difference is the net difference in charge carried by strong cations and anions, *i.e.,* ions that can be considered as completely dissociated in solution. According to this approach, to compensate for an acid–base disequilibrium generated by a primary carbon dioxide increase (*i.e.*, a primary respiratory acidosis), the strong ion difference should increase alkalinizing the solution, and *vice versa*.

The current work aims to re-examine data from published studies focused on bicarbonate adaptation to acute and chronic respiratory alterations, according to the physical–chemical and base excess approaches. We hypothesized the presence of an association between bicarbonate concentrations and strong ion difference during acute and chronic respiratory derangements. Moreover, as opposed to chronic experiments, we hypothesized that during acute $Paco_2$ changes, strong ion difference variations are not associated with standard base excess changes.

Materials and Methods

Design and Data Sources

This study followed an individual participant data meta-analysis approach to data extracted from multiple canine and human experiments.[10] A structured, systematic search of the literature was performed according to the methods of Preferred Reporting Items for Systematic Reviews and Meta-Analyses checklist (https://links.lww.com/ALN/D286) to retrieve studies describing respiratory acid–base alterations.[11] Moreover, the Strengthening the Reporting of Observational Studies in Epidemiology checklist (https://links.lww.com/ALN/D287) was used to guide reporting of the results of the study.[12]

We searched into MEDLINE database for any type of publication published up to April 29, 2021. The research was performed using the following Medical Subject Headings research string: "respiratory acid-base imbalance/analysis" OR "respiratory acid-base imbalance/blood" OR "acute respiratory acidosis," "acute hypercapnic acidosis" OR "acute hypercapnia" OR "carbon dioxide titration" OR "acidosis, respiratory" OR "chronic respiratory acidosis" OR "chronic

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hypercapnic acidosis" OR "chronic hypercapnia" OR "acute respiratory alkalosis" OR "acute hypocapnic alkalosis" OR "acute hypocapnia" OR "chronic respiratory alkalosis" OR "chronic hypocapnic alkalosis" OR "chronic hypocapnia."

Studies Screening and Data Extraction

We selected publications written in English describing experimental *in vivo* studies conducted on humans or dogs, testing the effect of the induction of an acute or chronic respiratory acidosis or alkalosis. In order to be included in the analyses, values of $Paco_2$, pH, HCO_3^-, sodium, chloride, and potassium before and after the induction of the respiratory alteration had to be reported.

We excluded studies reporting data about subjects or animals with pre-existing chronic respiratory, renal, metabolic, or cardiac impairment, and studies in which the subject received *per* protocol intravenous fluids and/or drugs (*e.g.*, normal saline, sodium bicarbonate, diuretics) that could alter the acid–base balance significantly.

Two authors (F.Z. and A.D.) independently selected eligible articles using Rayyan software.[13] As a first step, duplicated studies were identified and removed. The relevance of each article was evaluated by examining the title, abstract, and full text. Data from the included studies were manually extracted. Each manuscript could include more groups (*e.g.*, different inspiratory carbon dioxide concentrations). Reported average values of each group were used as this. If the study reported only disaggregated data, the average of the variables of interest was calculated for each group and used for analysis. Based on the time interval between the respiratory alteration onset and the following measurement, the acid–base derangements were classified as "acute" if the measurement were obtained within 2 h, or "chronic" when more than 72 h were intercurred. For further details, refer to Supplemental Table S2 (https://links.lww.com/ALN/D285).

A simplified strong ion difference was calculated from the electrolytes retrieved in the selected manuscripts as follows:

$$Strong\ ion\ difference = [Na^+] + [K^+] - [Cl^-]$$

where $[Na^+]$, $[K^+]$, and $[Cl^-]$ are sodium, potassium, and chloride concentrations expressed as millimoles/liter.

The difference between sodium and chloride concentration (Na-Cl) was also calculated as a proxy of the strong ion difference.

For every set of experimental data, the relative contribution of sodium (ΔNa%) and chloride (ΔCl%) to total strong ion difference variation was computed using the difference in sodium and chloride (ΔNa^+ and ΔCl^-, respectively) between the points with the highest and lowest $Paco_2$ as follows:

$$\Delta Na\% = \frac{\Delta Na^+}{\Delta strong\ ion\ difference}$$

$$\Delta Cl\ \% = \frac{\Delta Cl^-}{\Delta strong\ ion\ difference}$$

To address the *in vivo* alteration of the metabolic component of acid–base equilibrium, independently from the coexisting respiratory derangements, standard base excess was calculated for every pH and bicarbonate couple as follows:

$$Standard\ base\ excess = \left(HCO_3^- - 24.8\right) + \beta \cdot (pH - 7.40)$$

considering a noncarbonic buffer power (β) of the extracellular fluid of 16.2 mM.[7,14]

Statistical Analysis

Results are presented as mean ± SD. The normality of each distribution was tested *via* the Shapiro–Wilk test. Data from respiratory acidosis and alkalosis of the same timeframe (*i.e.*, acute or chronic) were pooled and analyzed together. Within each time group, the different contributions of sodium and chloride to strong ion difference variation were evaluated *via* Student's paired *t* test, or Wilcoxon signed-rank test. A P value < 0.05 was considered statistically significant.

Model Development and Comparison

For every couple of continuous variables, changes of the dependent variable over the explanatory one were modeled according to a polynomial multilevel linear regression model (generalized linear mixed models) with random intercept and random slope both at group level, as previously described.[4] Random intercept and random slope were included in the model according to model-based likelihood ratio tests, with a cutoff P value of 0.050. The exponential power of the polynomial function was assessed by comparing models of increasing degree by model-based likelihood ratio tests (cutoff P value 0.05). Interaction between the explanatory variables and the time group (*i.e.*, acute coded as "0" and chronic coded as "1") was also included in the model according to model-based likelihood ratio tests (cutoff P value 0.001). The models were weighted for the sample size, *i.e.*, the number of subjects forming the group. To compare the potential differences, the model generated by pooling together the different studies was plotted against the Boston rules (simplified linear equations) and the original equations from which they were derived. Statistical analyses were performed using the SAS 9.4 statistical package (Statistical Analysis Software Institute Inc., USA).

Results

Study Description

A total of 3378 citations were identified. Eleven articles published between 1961 and 1994 matched the inclusion criteria (Supplemental Figure S1, https://links.lww.com/ALN/D285), three performed on humans and eight on dogs. A total of 31 dogs and 19 humans from four different studies were included in the acute respiratory derangement

Table 1. Studies Description

	Article	Species	Method of Carbon Dioxide Alteration	Range of Inspiratory Fraction of Carbon Dioxide	Sampling Time	Participants Included
Respiratory acidosis						
Acute (≤ 2 h)	Cohen *et al.*[15]	Dog	Incremental inspiratory fraction of carbon dioxide	0–18%	≤ 2 h	21 (3 groups)
	Brackett *et al.*[3]	Human	Incremental inspiratory fraction of carbon dioxide	0–10%	≤ 2 h	7 (1 group)
Chronic (≥ 72 h)	Polak *et al.*[16]	Dog	Incremental inspiratory fraction of carbon dioxide	0–13%	≥ 4 days	2 (2 groups)
	Schwartz *et al.*[17]	Dog	Incremental inspiratory fraction of carbon dioxide	0–17%	≥ 4 days	1 (1 group)
	Sapir *et al.*[18]	Dog	Incremental inspiratory fraction of carbon dioxide	0–13%	≥ 4 days	1 (1 group)
	Madias *et al.*[19]	Dog	Incremental inspiratory fraction of carbon dioxide	0–6%	≥ 5 days	9 (1 group)
Respiratory alkalosis						
Acute (≤ 2 h)	Arbus *et al.*[20]	Human	Hyperventilation in mechanical ventilation		≤ 2 h	12 (1 group)
	Javaheri *et al.*[21]	Dog	Hyperventilation in mechanical ventilation		≤ 2 h	10 (1 group)
Chronic (≥ 72 h)	Gennari *et al.*[23]	Dog	Decremental FIO_2	21–9%*	≥ 5 days	22 (2 groups)
	Gougoux *et al.*[24]	Dog	Decremental FIO_2	21–9%*	≥ 7 days	25 (4 groups)
	Krapf *et al.*[25]	Human	Decremental FIO_2 (altitude)		≥ 4 days	4 (1 group)

This table reports the different characteristics of the hypercapnic and hypocapnic protocols included in the study. In the "Participants Included" column, the number of subjects included in the original study and the number of groups extracted for the analyses are reported.

*Range of inspiratory fraction of oxygen

FIO_2, inspiratory fraction of oxygen.

group, while 60 dogs and 4 humans from seven studies were included in the chronic respiratory derangement group. Six articles focused on respiratory acidosis induced by increases in inspiratory fraction of carbon dioxide.[3,15–19] Five articles explored respiratory alkalosis, which was induced either through an increase in mechanical ventilation (acute) or by decreasing the inspiratory fraction of oxygen,[20,21] thus exploiting the hypoxic respiratory drive,[22] in spontaneously breathing dogs (chronic).[23–25] A summary of the analyzed studies is reported in table 1.

Effects of $Paco_2$ Changes on pH, Strong Ion Difference, Bicarbonate, and Standard Base Excess

A range of $Paco_2$ between 21 and 142 mmHg was explored. The resulting pH and bicarbonate values ranged from 6.93 to 7.55 and from 12.3 to 43.8 mM, respectively. The relationship between pH *versus* $Paco_2$ (Supplemental Figure S2, https://links.lww.com/ALN/D285) and bicarbonate *versus* $Paco_2$ (fig. 1A, and Supplemental Figure S3, https://links.lww.com/ALN/D285) differed according to the duration of the respiratory disorder ($P < 0.001$ for both). For a similar perturbation of $Paco_2$, smaller changes in pH and greater bicarbonate variations were observed in chronic compared to acute disorders.

Both in acute and chronic respiratory disorders, a rise in strong ion difference was observed after the increase in $Paco_2$ (observed range, 32.6 to 60.0 mEq/l; fig. 1B, and Supplemental Figure S4, https://links.lww.com/ALN/D285). Similar to the bicarbonate *versus* $Paco_2$ curve, the $Paco_2$-induced strong ion difference variation was more pronounced in the chronic group. A similar slope (β-coefficient, 1.2; 95% CI, 1.2 to 1.3; $P < 0.001$ for both) between bicarbonate and strong ion difference was observed in the acute and chronic settings (fig. 1C, and Supplemental Figure S5, https://links.lww.com/ALN/D285).

A statistically significant but clinically negligible relationship was found between standard base excess and $Paco_2$ in the acute response to $Paco_2$ variations (β-coefficient, –0.01; 95% CI, –0.02 to –0.01; $P < 0.001$). On the contrary, a positive, clinically relevant linear association was present in the chronic time group (β-coefficient, 0.29; 95% CI, 0.29 to 0.32; $P < 0.001$; fig. 2A, and Supplemental Figure S6, https://links.lww.com/ALN/D285). In the acute setting, no relationship was found between standard base excess and HCO_3^- (β-coefficient, 0.02; 95% CI, –0.01 to 0.06; $P = 0.238$; fig. 2B, and Supplemental Figure S7, https://links.lww.com/ALN/D285), or between standard base excess and strong ion difference (β-coefficient, –0.02, 95% CI, –0.11 to 0.07; $P = 0.719$; fig. 2C, and Supplemental Figure S8, https://links.lww.com/ALN/D285). Differently, in the chronic time frame, both the associations of parameters were positively correlated (β-coefficient, 0.88; 95% CI, 0.80 to 0.95; $P < 0.001$; and β-coefficient, 1.04; 95% CI, 0.84 to 1.24; $P < 0.001$, respectively).

Effects of $Paco_2$ Changes on Electrolytes and Strong Ion Difference

In both time groups, a positive linear association was found between sodium and $Paco_2$ (fig. 3A, and Supplemental Figure S9, https://links.lww.com/ALN/D285), while chloride variations were negatively associated with $Paco_2$ only in chronic experiments (fig. 3B, and Supplemental Figure S10, https://links.lww.com/ALN/D285). A significant association ($P < 0.001$) was found between potassium

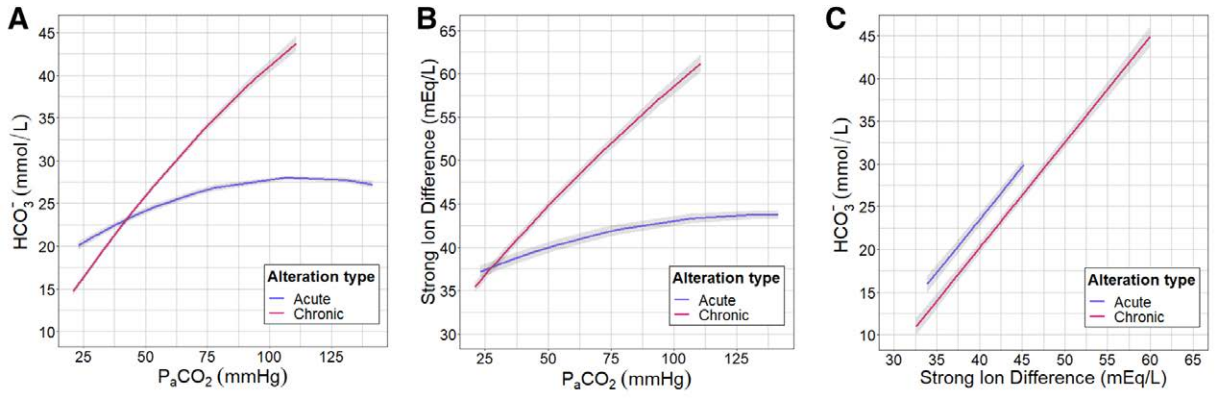

Fig. 1. The graphs show the relationships between bicarbonate and $Paco_2$ (*A*), strong ion difference and $Paco_2$ (*B*), and bicarbonate and strong ion difference (*C*). The polynomial multilevel linear regression model is represented as a *colored line* with its 95% CI. The acute (less than 2 h) $Paco_2$ variations are represented in *blue*, while the chronic ones (above 72 h) are represented in *red*.

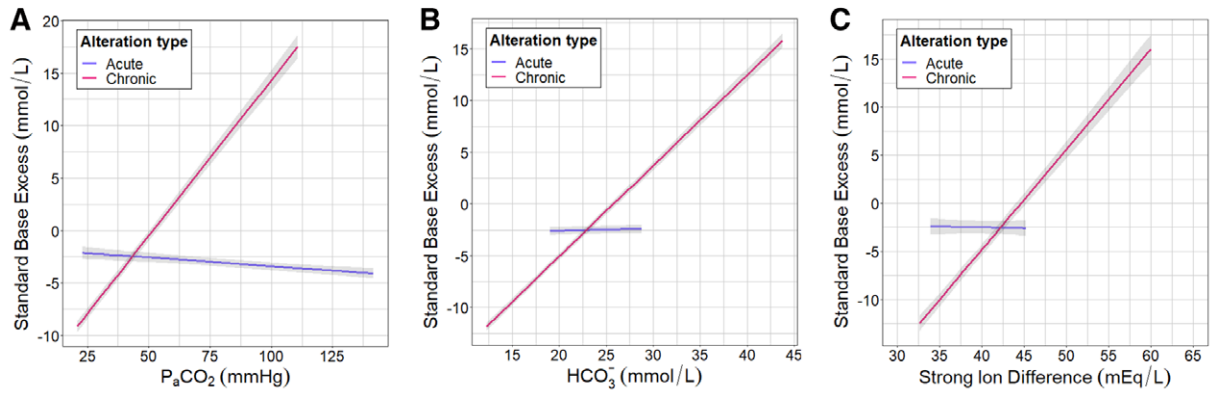

Fig. 2. The graphs show the relationships between the standard base excess and $Paco_2$ (*A*), standard base excess and $Paco_2$ (*B*), and standard base excess and HCO_3^- (*C*), respectively. The polynomial multilevel linear regression model is represented as a *colored line* with its 95% CI. The acute (less than 2 h) $Paco_2$ variations are represented in *blue*, while the chronic ones (above 72 h) are represented in *red*.

and $Paco_2$ in both timeframes (Supplemental Figure S11, https://links.lww.com/ALN/D285). However, potassium variations were quantitatively negligible, and thus, the Na-Cl difference strictly paralleled strong ion difference changes in response to $Paco_2$ modifications within a clinically relevant range of $Paco_2$ (Supplemental Figure S12, https://links.lww.com/ALN/D285).

Finally, the behavior of sodium (fig. 4A, and Supplemental Figure S13, https://links.lww.com/ALN/D285) and chloride (fig. 4B, and Supplemental Figure S14, https://links.lww.com/ALN/D285) variations and their impact on strong ion difference was different between time groups. In particular, sodium was the main determinant of strong ion difference variations during acute respiratory alterations ($\Delta Na\% = 80 \pm 27\%$ *vs.* $\Delta Cl\% = 16 \pm 30\%$ of strong ion difference variation, $P = 0.040$), while chloride played the major role in chronic alterations ($\Delta Na\% = 18 \pm 23\%$ *vs.* $\Delta Cl\% = 80 \pm 22\%$ of strong ion difference variation, $P = 0.002$).

Models Comparison

The model developed in the current work resembles the equations derived from the four original studies (fig. 5, and Supplemental Table S1, https://links.lww.com/ALN/D285). Conversely, as compared to our model, the simplified, linear Boston rules overestimate the bicarbonate compensations during hypercapnia.

Discussion

In this study, we used an individual participant data meta-analysis method to describe the metabolic compensation to primary acute or chronic respiratory acid–base derangements according to the physical–chemical approach. Our results

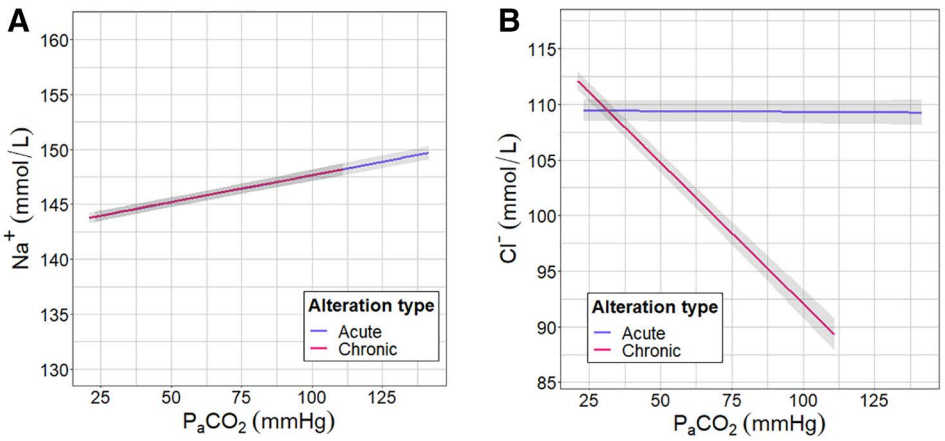

Fig. 3. The graphs show the relationships between sodium and $Paco_2$ (*A*), and chloride and $Paco_2$ (*B*). The polynomial multilevel linear regression model is represented as a *colored line* with its 95% CI. The acute (less than 2 h) $Paco_2$ variations are represented in *blue*, while the chronic ones (above 72 h) are represented in *red*.

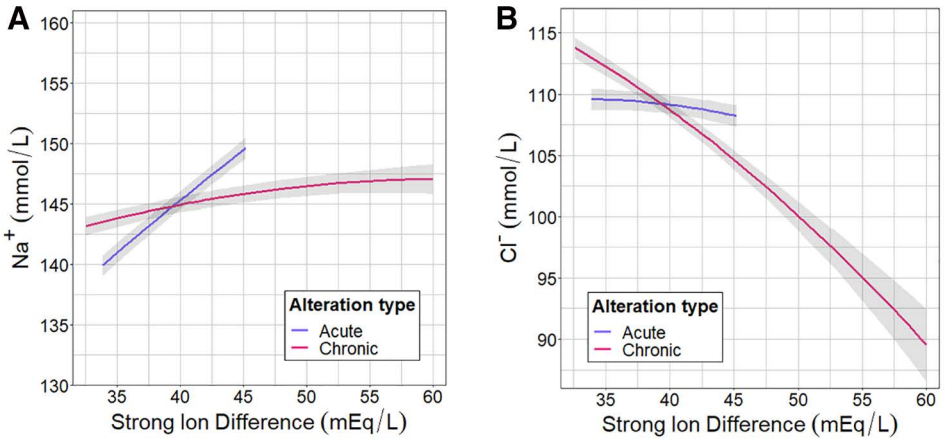

Fig. 4. The graphs show the relationships between sodium and strong ion difference (*A*), and chloride and strong ion difference (*B*), respectively. The polynomial multilevel linear regression model is represented as a *colored line* with its 95% CI. The acute (less than 2 h) $Paco_2$ variations are represented in *blue*, while the chronic ones (above 72 h) are represented in *red*.

confirmed the key role of time in determining the degree of $Paco_2$-associated bicarbonate changes, which resulted associated with strong ion difference variations. In particular, in the acute setting, sodium variations were the major determinant of strong ion difference changes, while chloride was the key electrolyte in chronic experiments. Last, no association was found between strong ion difference variations and standard base excess in acute respiratory acid–base disorders, while this relationship was present in the chronic phase.

Strong Ion Difference–Bicarbonate Relationship

Several electrolytes contribute to the change in strong ion difference, which is paralleled by bicarbonate variations, regardless of the length of the respiratory alterations. According to the electrical neutrality concept, the sum of all cations (*e.g.*, sodium, potassium) is equal to the sum of negative charges, deriving from strong anions (*e.g.*, chloride), dissociated weak noncarbonic acids, and bicarbonate. In the current study, the contribution of unmeasured anions (*e.g.*, lactate) is likely negligible, as only healthy subjects were studied.[26,27] Indeed, the observed stability of the anion gap (Supplemental Table S3, https://links.lww.com/ALN/D285) confirmed that unmeasured anions were likely constant during the experiments. According to these premises, changes in bicarbonate were paralleled by strong ion difference variations regardless of the timing of the respiratory derangement.

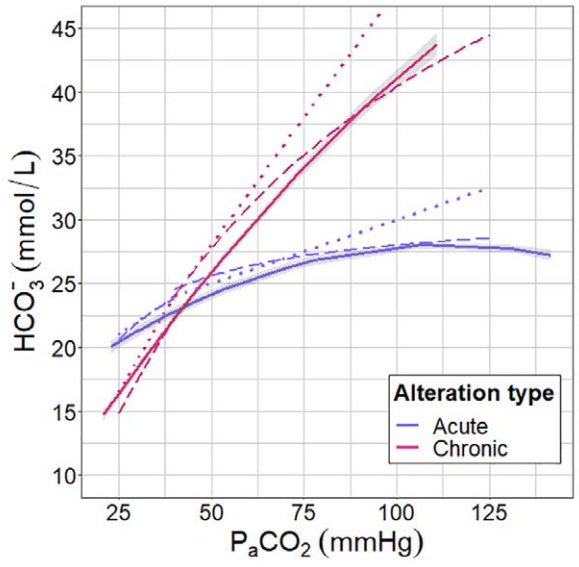

Fig. 5. The graph compares the experimental bicarbonate and $Paco_2$ models obtained by pooling the data from the different studies (continue *red* and *blue lines* with the *gray* 95% CI) to two different models: the *dotted lines* represent the four simplified, linear Boston rules, while the *dashed lines* represent the original equations from which the Boston rules were derived. The polynomial multilevel linear regression model is represented as a *colored line* with its 95% CI. The acute (less than 2 h) $Paco_2$ variations are represented in *blue*, while the chronic ones (above 72 h) are represented in *red*.

Mechanisms of Metabolic Compensation

Both in the acute and chronic settings, we observed an increase in sodium and a decrease in plasma chloride concentration, moving from hypocapnia to hypercapnia. The entity of sodium variations was modest and similar in acute and chronic conditions. The small magnitude of sodium variations is not surprising, as sodium is the primary determinant of osmolarity, and its concentration is strictly regulated by several hormones.[28] On the contrary, moving from acute to chronic hypercapnia, the chloride decrease became more remarkable, reaching variations up to 20 mM (fig. 3B). Consequently, sodium played a major role in acute respiratory derangements, while chloride was the key electrolyte in chronic adaptation (fig. 4). These different behaviors can be explained by two physiologic mechanisms.

During acute hypercapnia, carbon dioxide is hydrated to bicarbonate prevalently within red blood cells. This process transiently increases intracellular osmolarity fostering the shift of water from the extra to the intracellular space, ultimately increasing plasma sodium concentration. In contrast, chloride decreases during acute hypercapnia due to the Hamburger effect.[29,30] Last, a quantitatively less important cause of both sodium and chloride acute shifts is their direct pH-dependent release from plasma proteins.[4,31]

During chronic hypercapnia, the kidneys are responsible for the observed chloride variation, mainly due to the excretion of ammonium chloride.[32] While the renal response to an acid–base disorder is extremely powerful and rapidly established,[33] it requires up to 1 week to fully compensate for respiratory acid–base alterations.[17,19,32]

To summarize, the compensation for a respiratory derangement can be divided into two distinct phases. Acutely, the degree of carbon dioxide variation and the noncarbonic buffer power are the determinants of pH. In this context, the strong ion difference variation is a consequence of water and electrolyte shifts between intra- and extracellular fluids, as the amount of electrolytes removed from or added to the system by the kidneys is limited per definition.[34] Accordingly, these variations in strong ion difference are not paralleled by changes in standard base excess (fig. 2C, and Supplemental Figure S8, https://links.lww.com/ALN/D285).

On the contrary, during chronic carbon dioxide exposure, pH is determined by $Paco_2$, noncarbonic buffer power, and strong ion difference variations induced by active renal electrolyte manipulation. In this context, the strong ion difference change represents the metabolic adaptation and is mirrored by standard base excess. Of note, a similar relationship between standard base excess and acute or chronic $Paco_2$ variations was described in humans by Schlichtig *et al.*[35]

Last, in line with previous studies,[4,36] our data from acute experiments underline the dependency of "plasma" strong ion difference on $Paco_2$. While one might argue that this observation discredits the physical–chemical approach, we think that a reallocation of independent variable status from "plasma" to "extracellular" strong ion difference (*i.e.*, strong ion difference of whole blood and interstitial fluid) reconciles the model. Of note, standard base excess describes the metabolic status of the same compartment, which remains stable during electrolyte shifts between red blood cells and plasma, as no electrolytes are added and/or removed.

Clinical Implications

The Boston school described the secondary adaptation of bicarbonate to primary respiratory derangements and developed four different equations, which were simplified to linear equations: the Boston rules (Supplemental Table S1, https://links.lww.com/ALN/D285).[3,17,20,23] Not surprisingly, our model, which includes the results of these studies, is in line with the original equations (fig. 5). Conversely, a different behavior was observed when the simplified Boston equations were compared to the model. For instance, the simplified, linear rules have lower performances than the original equations. The chronic respiratory Boston equation describes a complete metabolic compensation to chronic respiratory acidosis, requiring several

days.[17,19,32] As compared to the original equation, the simplified Boston rule for chronic acidosis overestimates the bicarbonate adaptation, becoming less precise at higher $Paco_2$. For example, considering a pure, chronic respiratory acidosis at 75 mmHg $Paco_2$, the difference in bicarbonate between the simplified and the original equation is about 5 mM. If a complete evaluation, including the measurement of electrolytes and the application of the electrical neutrality concept, is not performed, the lower-than-expected value of bicarbonate could misleadingly suggest a concomitant metabolic acidosis. Despite similar limits, the simplified rule for acute acidosis seems more reliable.

Understanding compensatory mechanisms of respiratory derangements could be extremely useful during clinical practice. For instance, since chloride variations are only of a few millimoles during the acute adaptation to carbon dioxide, finding a decreased plasma chloride concentration in a patient without other causes of hypochloremia (*e.g.*, vomiting) could reveal the presence of renal adaptation to chronic hypercapnia. A second important consideration concerns the intraoperative management of patients with chronic obstructive pulmonary disease. In this context, the intraoperative use of high chloride content fluids (*e.g.*, NaCl 0.9%) could rapidly disrupt the compensatory hypochloremia.[37] Similar attention should be paid when dealing with pregnant women undergoing surgery. These patients are characterized by chronic respiratory alkalosis compensated by a reduced strong ion difference.[38] In this context, misinterpreting the low standard base excess and administering alkalinizing agents or fluids to correct metabolic acidosis could interfere with the mother's and developing fetus's physiologic homeostasis.

Timing Determination

In critically ill patients, multiple confounders altering the acid–base equilibrium might be present. The physical–chemical approach considers all measured variables, applying the key concept of electrical neutrality. However, it does not provide any tool to estimate the time that has elapsed since the onset of the disorder. In the absence of hypoalbuminemia and unmeasured anions, hints about the onset time of the respiratory disorder can be derived by calculating the difference between the actual strong ion difference and a reference value of 40 mM and comparing this value with standard base excess. Being independent of acute $Paco_2$ variations, standard base excess can differentiate between "plasma" strong ion difference variation, *i.e.,* due to electrolyte redistribution (acute) and "extracellular" strong ion difference variation, *i.e.,* true metabolic adaptation (chronic). For example, a poor quantitative agreement (*e.g.*, above 2 mM) between the absolute value of standard base excess and the strong ion difference variation defines the presence of an acute respiratory disorder whose onset is likely within 2 h from the sample collection. On the contrary, a good agreement between strong ion difference variation and standard base excess would suggest the presence of a chronic respiratory disorder.

Limitations

Several limitations need to be addressed. First, the nature of the study is a limitation *per se* as it relies on data retrieved from experimental studies performed up to 60 yr ago. Second, the chronic respiratory acidosis branch of our model relies only on canine data. However, canine and human acid–base physiologies are similar,[39,40] and data derived exclusively from human studies are in line with ours.[35] Third, we computed strong ion difference based only on sodium, potassium, and chloride. However, this simplification had minimal effect on the analyses since data were derived from healthy subjects where lactate and unmeasured anions likely have a minor role. Finally, using hypoxia to induce chronic hypocapnia could have limited the chloride increase in response to chronic alkalosis since the taut form of hemoglobin has a higher chloride binding affinity than the relaxed form.[30,41] However, this hemoglobin "chloride retention" is conceivably of minor entity (*i.e.*, less than1.5 mmol) in our population.[23,24,40,41]

Conclusions

The secondary bicarbonate adaptation after primary respiratory alterations is associated with strong ion difference variations. The variation of plasma sodium induced by $Paco_2$ is similar in acute and chronic settings. In contrast, chloride concentration is mainly altered in chronic respiratory derangements, where it becomes the major determinant of strong ion difference variations. Standard base excess does not change during acute respiratory derangements, while it accurately describes variations in strong ion difference in chronic respiratory disorders.

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Competing Interests

The authors declare no competing interests.

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Supplemental Digital Content

Online Supplemental Content, https://links.lww.com/ALN/D285
Preferred Reporting Items for Systematic Reviews and Meta-Analyses checklist, https://links.lww.com/ALN/D286
Strengthening the Reporting of Observational Studies in Epidemiology checklist, https://links.lww.com/ALN/D287

References

1. Story DA: Bench-to-bedside review: A brief history of clinical acid-base. Crit Care 2004; 8:253–8
2. Schwartz WB, Relman AS: A critique of the parameters used in the evaluation of acid-base disorders. N Engl J Med 1963; 268:1382–8
3. Brackett NC, Cohen JJ, Schwartz WB: Carbon dioxide titration curve of normal man. N Engl J Med 1965; 272:6–12
4. Langer T, Brusatori S, Carlesso E, Zadek F, Brambilla P, Fusarini CF, Duska F, Caironi P, Gattinoni L, Fasano M, Lualdi M, Alberio T, Zanella A, Pesenti A, Grasselli G: Low noncarbonic buffer power amplifies acute respiratory acid-base disorders in patients with sepsis: An in vitro study. J Appl Physiol 2021; 131:464–73
5. Langer T, Ferrari M, Zazzeron L, Gattinoni L, Caironi P: Effects of intravenous solutions on acid-base equilibrium: From crystalloids to colloids and blood components. Anaesthesiol Intensive Ther 2014; 46:350–60
6. Krbec M, Waldauf P, Zadek F, Brusatori S, Zanella A, Duška F, Langer T: Non-carbonic buffer power of whole blood is increased in experimental metabolic acidosis: An in-vitro study. Front Physiol 2022; 13:1009378
7. Langer T, Brusatori S, Gattinoni L: Understanding base excess (BE): Merits and pitfalls. Intensive Care Med 2022; 48:1080–3
8. Gamble JL, Ross GS, Tisdall FF: The metabolism of fixed base during fasting. J Biol Chem 1923; 57:633–95
9. Gomez H, Kellum JA: Understanding acid base disorders. Crit Care Clin 2015; 31:849–60
10. Riley RD, Lambert PC, Abo-Zaid G: Meta-analysis of individual participant data: Rationale, conduct, and reporting. BMJ 2010; 340:c221–c221
11. Moher D, Liberati A, Tetzlaff J, Altman DG; PRISMA Group: Preferred reporting items for systematic reviews and meta-analyses: The PRISMA statement. Int J Surg 2010; 8:336–41
12. von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP: The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: Guidelines for reporting observational studies. J Clin Epidemiol 2008; 61:344–9
13. Ouzzani M, Hammady H, Fedorowicz Z, Elmagarmid A: Rayyan—A web and mobile app for systematic reviews. Syst Rev 2016; 5:210
14. Berend K: Diagnostic use of base excess in acid–base disorders. N Engl J Med 2018; 378:1419–28
15. Cohen JJ, Brackett NC, Schwartz WB: The nature of the carbon dioxide titration curve in the normal dog. J Clin Invest 1964; 43:777–86
16. Polak A, Haynie GD, Hays RM, Schwartz WB: Effects of chronic hypercapnia on electrolyte and acid-base equilibrium. I. Adaptation. J Clin Invest 1961; 40:1223–37
17. Schwartz WB, Brackett NC, Cohen JJ: The response of extracellular hydrogen ion concentration to graded degrees of chronic hypercapnia: The physiologic limits of the defense of pH. J Clin Invest 1965; 44:291–301
18. Sapir DG, Levine DZ, Schwartz WB: The effects of chronic hypoxemia on electrolyte and acid-base equilibrium: An examination of normocapneic hypoxemia and of the influence of hypoxemia on the adaptation to chronic hypercapnia. J Clin Invest 1967; 46:369–77
19. Madias NE, Wolf CJ, Cohen JJ: Regulation of acid-base equilibrium in chronic hypercapnia. Kidney Int 1985; 27:538–43
20. Arbus GS, Hebert LA, Levesque PR, Etsten BE, Schwartz WB: Characterization and clinical application of the significance band for acute respiratory alkalosis. N Engl J Med 1969; 280:117–23
21. Javaheri S, Weyne J, Demeester G, Leusen I: Effects of acetazolamide on ionic composition of cisternal fluid during acute respiratory acidosis. J Appl Physiol 1984; 57:85–91
22. Leitch AG: The hypoxic drive to breathing in man. Lancet 1981; 317:428–30
23. Gennari FJ, Goldstein MB, Schwartz WB: The nature of the renal adaptation to chronic hypocapnia. J Clin Invest 1972; 51:1722–30
24. Gougoux A, Kaehny WD, Cohen JJ: Renal adaptation to chronic hypocapnia: Dietary constraints in achieving H+ retention. Am J Physiol 1975; 229:1330–7
25. Krapf R, Beeler I, Hertner D, Hulter HN: Chronic respiratory alkalosis. N Engl J Med 1991; 324:1394–401
26. Venkatesh B, Morgan TJ: Unmeasured anions: The unknown unknowns. Crit Care 2008; 12:113
27. Forni LG, McKinnon W, Hilton PJ: Unmeasured anions in metabolic acidosis: Unravelling the mystery. Crit Care 2006; 10:220
28. Slater JDH: The hormonal control of body sodium. Postgrad Med J 1964; 40:479–96
29. Hamburger HJ: Anionenwanderungen in Serum und Blut unter dem Einfluss von CO2, Säure und Alkali. Biochem Z 1918; 86:309–24
30. Westen EA, Prange HD: A reexamination of the mechanisms underlying the arteriovenous chloride shift. Physiol Biochem Zool 2003; 76:603–14

31. Rossing TH, Maffeo N, Fencl V: Acid-base effects of altering plasma protein concentration in human blood in vitro. J Appl Physiol 1986; 61:2260–5
32. Adrogué HJ, Madias NE: Renal acidification during chronic hypercapnia in the conscious dog. Pflügers Arch Eur J Physiol 1986; 406:520–8
33. Caironi P, Langer T, Taccone P, Bruzzone P, De Chiara S, Vagginelli F, Caspani L, Marenghi C, Gattinoni L: Kidney instant monitoring (K.IN.G®): A new analyzer to monitor kidney function. Minerva Anestesiol 2010; 76:316–24
34. Narins RG, Emmett M: Simple and mixed acid-base disorders. Medicine (Baltim) 1980; 59:161–87
35. Schlichtig R, Grogono AW, Severinghaus JW: Human PaCO2 and standard base excess compensation for acid-base imbalance. Crit Care Med 1998; 26:1173–9
36. Langer T, Scotti E, Carlesso E, Protti A, Zani L, Chierichetti M, Caironi P, Gattinoni L: Electrolyte shifts across the artificial lung in patients on extracorporeal membrane oxygenation: Interdependence between partial pressure of carbon dioxide and strong ion difference. J Crit Care 2015; 30:2–6
37. Scheingraber S, Rehm M, Sehmisch C, Finsterer U: Rapid saline infusion produces hyperchloremic acidosis in patients undergoing gynecologic surgery. Anesthesiology 1999; 90:1265–70
38. Zadek F, Giudici G, Ferraris Fusarini C, Ambrosini MT, di Modugno A, Scaravilli V, Zanella A, Fumagalli R, Stocchetti N, Calderini E, Langer T: Cerebrospinal fluid and arterial acid–base equilibria in spontaneously breathing third-trimester pregnant women. Br J Anaesth 2022; 129:726–33
39. Emuakpor DS, Maas AHJ, Ruigrok TJC, Zimmerman ANE: Acid-base curve nomogram for dog blood. Pflügers Arch Eur J Physiol 1976; 363:141–7
40. Rossing RG, Cain SM: A nomogram relating pO2, pH, temperature, and hemoglobin saturation in the dog. J Appl Physiol 1966; 21:195–201
41. Prange HD, Shoemaker JL, Westen EA, Horstkotte DG, Pinshow B: Physiological consequences of oxygen-dependent chloride binding to hemoglobin. J Appl Physiol 2001; 91:33–8