

Relationship Between Partial Carbon Dioxide Pressure and Strong Ions in Humans: A Retrospective Study

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Little is known about the role of a strong ions in humans with respiratory abnormalities. In this study, we investigated the associations between partial carbon dioxide pressure ($p\text{CO}_2$) and each of sodium ion (Na^+) concentrations, chloride ion (Cl^-) concentrations and their difference ($\text{SID}_{\text{Na-Cl}}$). Blood gas data were obtained from patients in a teaching hospital intensive care unit between August 2013 and January 2017. The association between $p\text{CO}_2$ and $\text{SID}_{\text{Na-Cl}}$ was defined as the primary outcome. The associations between $p\text{CO}_2$ and $[\text{Cl}^-]$, $[\text{Na}^+]$ and other strong ions were secondary outcomes. $p\text{CO}_2$ was stratified into 10 mmHg-wide bands and treated as a categorical variable for comparison. As a result, we reviewed 115,936 blood gas data points from 3,840 different ICU stays. There were significant differences in $\text{SID}_{\text{Na-Cl}}$, $[\text{Cl}^-]$, and $[\text{Na}^+]$ among all categorized $p\text{CO}_2$ bands. The respective $p\text{CO}_2$ $\text{SID}_{\text{Na-Cl}}$, $[\text{Cl}^-]$, and $[\text{Na}^+]$ correlation coefficients were 0.48, -0.31 , and 0.08. $\text{SID}_{\text{Na-Cl}}$ increased and $[\text{Cl}^-]$ decreased with $p\text{CO}_2$, with little relationship between $p\text{CO}_2$ and $[\text{Na}^+]$ across subsets. In conclusion, we found relatively strong correlations between $p\text{CO}_2$ and $\text{SID}_{\text{Na-Cl}}$ in the multiple blood gas datasets examined. Correlations between $p\text{CO}_2$ and chloride concentrations, but not sodium concentrations, were further found to be moderate in these ICU data.

Key words: acid-base phenomena, Stewart approach, strong ion difference, chlorine ion, partial carbon dioxide pressure

Acid-base disorders are relatively common among critically ill patients and are associated with poor clinical outcomes [1-3]; therefore, unraveling the mechanisms underlying these disorders and elucidating the related phenomena have been a primary focus in medical research. In the late 1970s, Peter Stewart advocated for a “physicochemical” or “strong ion” approach to the evaluation of acid-base phenomena [4]. In the “Stewart” approach, each variable is classified as either a dependent or independent determinant of the hydrogen ion concentration of a solution, influencing pH via the dissociation of water to maintain electrical neutrality [5,6]. There are three independent variables

according to this approach: 1) the strong ion difference (SID), defined as the difference between the concentrations of positive and negative ions that are dissociated completely within the physiological pH range, 2) the partial pressure of carbon dioxide ($p\text{CO}_2$), and 3) the total concentration of weak acids (A_{TOT}).

While traditional approaches to acid-base disorders suggest that respiratory abnormalities are compensated for by changes in the bicarbonate ion (HCO_3^-) concentration, the Stewart approach proposes that the bicarbonate ion concentration is a dependent variable and thus subject to change per independent variable flux in a given solution. From a physicochemical perspective, this means that other independent variables should also

change along with shifts in $p\text{CO}_2$, ultimately resulting in bicarbonate ion concentration changes. Although some experimental studies using the Stewart approach have proposed that any deviations in $p\text{CO}_2$ might affect SID compensation [7, 8], the evidence of associations among those independent variables, especially in humans, is limited.

There are 2 main extracellular strong ions in the human body: sodium ions (Na^+) and chlorine ions (Cl^-). We hypothesize that differences in the concentrations of these 2 strong ions ($\text{SID}_{\text{Na-Cl}}$) may change along with shifts in $p\text{CO}_2$ due to the dominance of one or the other in human plasma. To assess this hypothesis, we investigated the association between $p\text{CO}_2$ and $\text{SID}_{\text{Na-Cl}}$ and how these strong ions, or other strong ions such as calcium (Ca^{2+}), potassium (K^+), and lactate (Lac^-), might change along with shifts in $p\text{CO}_2$.

Methods

Design. We utilized a single-center retrospective study design. The study protocol was approved by the Okayama University Hospital Ethics Committee (approval no. 1710-032). The committee waived any requirement for informed consent due to this study utilizing an existing database.

Participants. All blood gas data that were obtained from surgical and medical patients in an intensive care unit (ICU) at our hospital between August 2013 and January 2017 and were linked to the electronic medical records were included in this study.

Blood gas sampling. Blood samples were collected into standard, prepared, heparinized blood gas syringes and measured without delay using a blood gas analyzer (ABL 800; Radiometer Co., Copenhagen, Denmark) in the ICU. The analyzer measured whole blood samples at 37°C . The hospital laboratory in which all analyses were conducted complies with the standards set by the National Association of Testing Authorities. During the study period, blood gas analyses were performed in the ICU at the discretion of intensivists or trained nursing staff.

Primary and secondary outcomes. The association between $p\text{CO}_2$ and $\text{SID}_{\text{Na-Cl}}$ was defined as the primary outcome. $\text{SID}_{\text{Na-Cl}}$ was calculated using the following equation: $\text{SID}_{\text{Na-Cl}} = [\text{Na}^+] - [\text{Cl}^-]$. The associations between $p\text{CO}_2$ and $[\text{Na}^+]$, $[\text{K}^+]$, $[\text{Ca}^{2+}]$, $[\text{Cl}^-]$, $[\text{Lac}^-]$, and bicarbonate ion concentration ($[\text{HCO}_3^-]$) were sec-

ondary outcomes.

Statistical analyses. Data are presented as the number (percentage) or mean \pm standard deviation (SD), as appropriate. $p\text{CO}_2$ was stratified into 10 mmHg-wide bands and treated as a categorical variable for comparison given the potential for non-linear relationships between $p\text{CO}_2$ and $\text{SID}_{\text{Na-Cl}}$, $[\text{Na}^+]$, $[\text{K}^+]$, $[\text{Ca}^{2+}]$, $[\text{Cl}^-]$, $[\text{Lac}^-]$, and $[\text{HCO}_3^-]$. Between- and within-group comparisons were performed using unpaired *t*-tests and analyses of variance (ANOVAs), respectively. Associations between variables were also assessed by Pearson's Correlation Coefficients. Linear regression analyses were further performed to estimate the independent associations between each ion and $p\text{CO}_2$.

To assess associations between $p\text{CO}_2$ and the other variables, we analyzed all available blood gas sample data (Dataset A) and also performed two subgroup analyses. One of the subgroups consisted of blood gas data from patients without metabolic changes (Dataset B) [9]. The other subgroup consisted of the subset of data from Dataset A with a pH ranging from 7.35 to 7.45 (Dataset C). All analyses were performed independently within each dataset. Significance was defined as a *p*-value of less than 0.05. All statistical analyses were performed using commercially available statistical software (2013 SAS Institute Inc, Cary, NC, USA) and R 3.3.3 (R Foundation for Statistical Computing, Vienna, Austria).

Results

We reviewed 115,936 blood gas data points from 3,840 different ICU stays from possibly duplicated patients during the study period (Dataset A). The mean age of those cases was 42.6 years (± 30.4). All primary departments responsible for the ICU cases are shown in Table 1.

A total of 20,481 data points from patients without metabolic acidosis and/or alkalosis were available (Dataset B) and 70,834 data points with a pH between 7.35 and 7.45 were available (Dataset C). Figure 1 depicts the process by which each dataset was created.

Primary outcome. There were significant differences in $\text{SID}_{\text{Na-Cl}}$ among the categorized $p\text{CO}_2$ data points in Datasets A, B, and C ($p < 0.0001$) (Fig. 2, 3, and 4, respectively). The $p\text{CO}_2$ and $\text{SID}_{\text{Na-Cl}}$ correlation coefficient was 0.48 ($p < 0.0001$) in Dataset A. A signif-

icant correlation between $p\text{CO}_2$ and $\text{SID}_{\text{Na-Cl}}$ was also found in Datasets B ($r=0.59$, $p<0.0001$) and C ($r=0.55$, $p<0.0001$).

Secondary outcomes. In Dataset A, there were significant differences in $[\text{Cl}^-]$ and $[\text{Na}^+]$ among the categorized $p\text{CO}_2$ levels ($p<0.0001$ and $p<0.0001$, respectively). Fig. 2 shows $[\text{Cl}^-]$ and $[\text{Na}^+]$ differences among the categorized $p\text{CO}_2$ levels in Dataset A. The $p\text{CO}_2$ and $[\text{Cl}^-]$ and $[\text{Na}^+]$ correlation coefficients were -0.31 ($p<0.0001$) and 0.08 ($p<0.0001$), respectively.

When identical analyses were done in the two subgroups (Datasets B and C), similar relationships emerged (Fig. 3 and 4). In Dataset B, there were signif-

icant differences in $[\text{Cl}^-]$ and $[\text{Na}^+]$ among the categorized $p\text{CO}_2$ levels ($p<0.0001$). The correlation coefficients for $p\text{CO}_2$ and $[\text{Cl}^-]$ and $[\text{Na}^+]$ were -0.35 ($p<0.0001$) and 0.15 ($p<0.0001$), respectively. In Dataset C, the correlation coefficients for $p\text{CO}_2$ and $[\text{Cl}^-]$ and $[\text{Na}^+]$ were -0.41 ($p<0.0001$) and 0.04 ($p<0.0001$), respectively.

Table 1 Baseline study population characteristics

Variable	Mean \pm SD or n (%)
Number of patients	3,840
Age, years	42.6 \pm 30.4
Weight, kg	44.0 \pm 24.5
Male, n (%)	2,102 (54.70)
Primary treating department, n (%)	
Cardiovascular surgery	1,127 (29.37)
Respiratory surgery	925 (24.11)
Neurosurgery	879 (22.91)
Hepato-Biliary-Pancreatic Surgery	169 (4.4)
Gastrointestinal Surgery	128 (3.3)

SD, standard deviation.

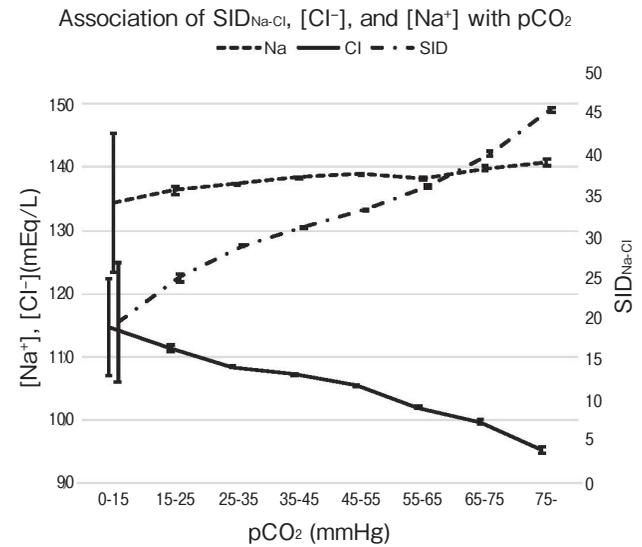


Fig. 2 Association between strong ion differences, chloride ion concentrations, and sodium ion concentrations and partial carbon dioxide pressure in Dataset A. $\text{SID}_{\text{Na-Cl}}$, difference in sodium ion concentration and chloride ion concentration; Cl^- , chloride ion; Na^+ , sodium ion; $p\text{CO}_2$, partial carbon dioxide pressure $\text{SID}_{\text{Na-Cl}}$ increased and chloride ion concentration decreased with an increase in $p\text{CO}_2$, and there was a weak relationship between $p\text{CO}_2$ and sodium ion concentration in Dataset A.

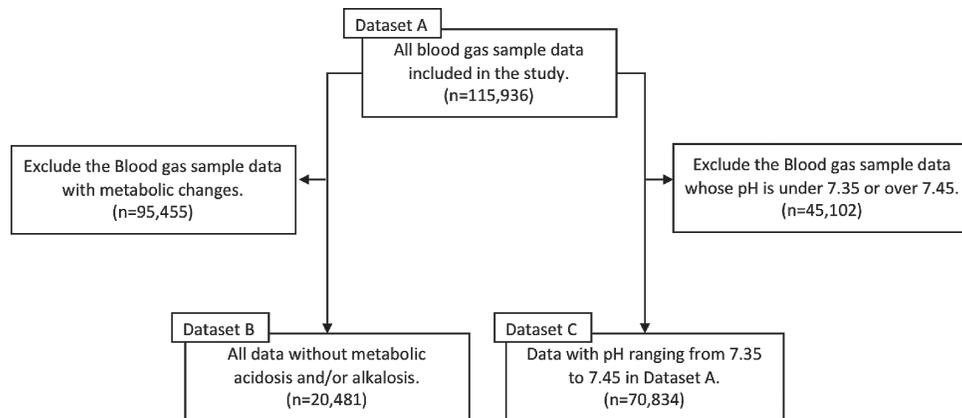


Fig. 1 Dataset creation flow chart. Dataset A contained all available blood gas sample data. Dataset B consisted of blood gas data from patients without metabolic changes. Dataset C consisted of the subset of data from Dataset A with a pH ranging from 7.35 to 7.45.

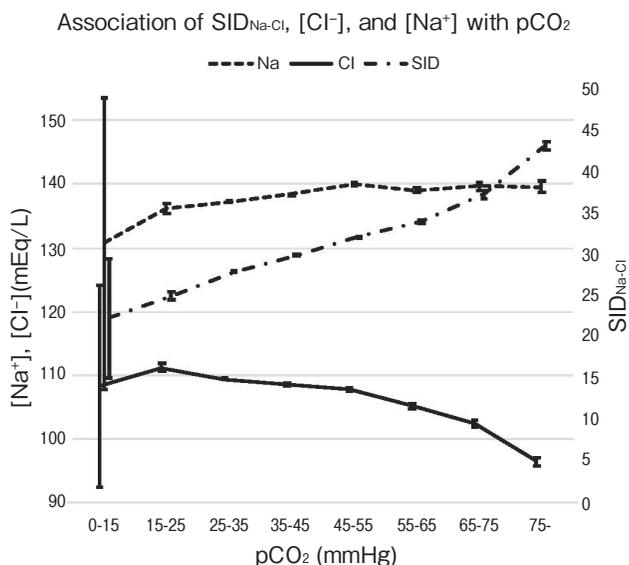


Fig. 3 Association between strong ion differences, chloride ion concentrations, and sodium ion concentrations and partial carbon dioxide pressure in Dataset B. SID_{Na-Cl} , difference of sodium ion concentration and chloride ion concentration; Cl^- , chloride ion; Na^+ , sodium ion; pCO_2 , partial carbon dioxide pressure. Similar to the findings in Dataset A, SID_{Na-Cl} increased and chloride ion concentration decreased with an increase in pCO_2 , and there was a weak relationship between pCO_2 and sodium ion concentration in Dataset B.

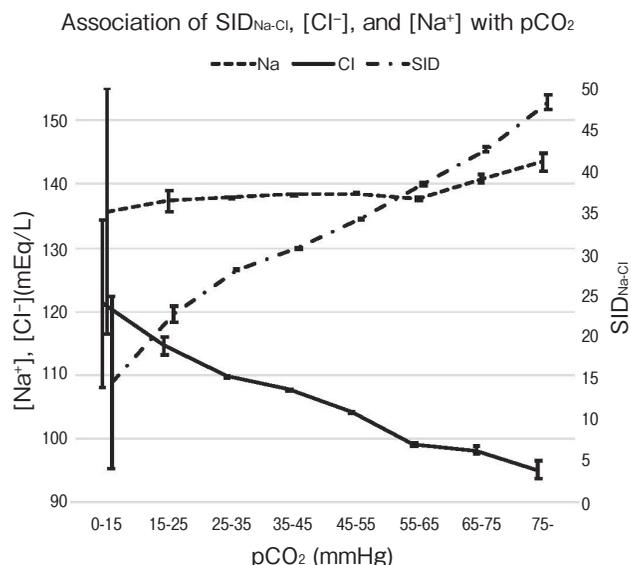


Fig. 4 Association between strong ion differences, chloride ion concentrations, and sodium ion concentrations and partial carbon dioxide pressure in Dataset C. SID_{Na-Cl} , difference of sodium ion concentration and chloride ion concentration; Cl^- , chloride ion; Na^+ , sodium ion; pCO_2 , partial carbon dioxide pressure. Similar to the findings in Dataset A and Dataset B, SID_{Na-Cl} increased and chloride ion concentration decreased with an increase in pCO_2 , and there was a weak relationship between pCO_2 and sodium ion concentration in Dataset C.

Table 2 Correlation coefficient for partial carbon dioxide pressure and other variables

Correlation coefficient (vs. pCO_2)	SID_{Na-Cl}	$[Cl^-]$	$[Na^+]$	$[Ca^{2+}]$	$[K^+]$	$[Lac^-]$	$[HCO_3^-]$
Dataset A	0.48*	-0.31*	0.08*	0.05*	0.11*	-0.10*	0.70*
Dataset B	0.59*	-0.35*	0.15*	0.10*	0.15*	-0.12*	0.96*
Dataset C	0.55*	-0.41*	0.04*	-0.05*	0.06*	-0.13*	0.91*

* $p < 0.0001$

pCO_2 , partial carbon dioxide pressure; SID_{Na-Cl} , difference in sodium ion concentration and chloride ion concentration; Cl^- , chloride ion; Na^+ , sodium ion; Ca^{2+} , calcium ion; K^+ , potassium ion; Lac^- , lactate; HCO_3^- , bicarbonate ion.

There were also strong correlations between pCO_2 and $[HCO_3^-]$ in Datasets A ($r=0.70$, $p < 0.0001$), B ($r=0.96$, $p < 0.0001$), and C ($r=0.91$, $p < 0.0001$). All correlation coefficients between pCO_2 and the other ions are summarized in Table 2.

Linear regression analyses for pCO_2 were performed with adjustment for $[Na^+]$, $[Cl^-]$, $[K^+]$, $[Ca^{2+}]$, $[Lac^-]$, and $[HCO_3^-]$. These showed significant relationships between pCO_2 and the ions listed, in all datasets, except for $[Cl^-]$ in Dataset B ($p=0.71$).

Discussion

The present retrospective study utilized a large dataset and demonstrated relatively strong correlations between pCO_2 and SID_{Na-Cl} throughout multiple datasets. Correlations between $[Cl^-]$ and pCO_2 were moderate and negative in all three datasets, whereas the correlations between $[Na^+]$ and pCO_2 were weak and inconsistent among the three datasets.

Before Peter Stewart advocated for a physicochemi-

cal approach to the evaluation of acid-base phenomena, several experimental studies had suggested an association between $p\text{CO}_2$ and SID. In early rat studies, prolonged exposure to 10% to 13% carbon dioxide resulted in respiratory acidosis and reduced serum chloride concentrations [10]. Another animal experiment in dogs investigated the response to acute acid-base disturbances of respiratory origin and revealed that changes in extracellular chloride concentrations were inversely related to deviations in $p\text{CO}_2$ from control levels [11].

Following the Stewart approach, Sławuta *et al.* further focused on the concentration of particular ions and variables during primary respiratory disorders. In one animal study of 60 adult dogs, Sławuta *et al.* explored whether SID, A_{TOB} , and strong ion gap (SIG) changes occurred during respiratory acidosis [7]. They found that the SID and SIG values differed significantly from before to after correction for respiratory acidosis. Morgan *et al.* also adopted the Stewart approach for the assessment of venous blood samples by shifting $p\text{CO}_2$ stepwise from >200 mmHg to <20 mmHg and reported changes in strong ion concentrations accordingly [8]. They found that reduced $p\text{CO}_2$ caused significant decreases in SID and $[\text{Na}^+]$ and elevations in $[\text{Cl}^-]$.

Although a number of *in vivo* animal studies have reported associations between strong ions and the derangement of carbon dioxide, few have assessed this same phenomenon in humans. In one such study conducted by Alfaro *et al.*, metabolic contributions to chronic respiratory acid-base changes were assessed in patients with chronic obstructive pulmonary disease and chronic hypercapnia via quantitative physicochemical analysis [12]. They found that hypercapnia was associated with decreased plasma chloride but not plasma sodium. Moreover, A_{TOT} remained constant. While their study examined the association between strong ions and $p\text{CO}_2$ in real patients, the small sample size ($n=58$) and limited specificity of detected $p\text{CO}_2$ levels (participants were classified into three groups: those with $p\text{CO}_2$ less than 40 mmHg, between 40 and 50 mmHg, and above 50 mmHg) were critical limitations. Another observational human study by Wilkes *et al.* similarly reported a significant correlation between $p\text{CO}_2$ and SID [13]. However, this study also utilized a small number of samples (219 blood samples from 91 patients) and analyzed the whole dataset, including patients with metabolic acid-base disorders, due to a

primary focus on the effect of hypoproteinemia on acid-base status. A retrospective study conducted by Langer *et al.* also reported progressive decreases in SID as well as increases in chloride concentration along with decreases in $p\text{CO}_2$ among patients on extracorporeal membrane oxygenation [14]. However, they only analyzed 20 patients and the association between $p\text{CO}_2$ and SID among patients in general intensive care units still remains unclear. Our present study is thus the first to demonstrate associations between $p\text{CO}_2$ (from less than 15 mmHg to over 75 mmHg) and strong ions in humans utilizing a large sample size.

In the present study, we examined the associations between strong ion concentrations and $p\text{CO}_2$ using a large ICU blood gas database. To explore these associations, we analyzed the whole dataset (Dataset A) and performed 2 subgroup analyses (Dataset B and Dataset C). Dataset B was created with the aim of excluding data from patients with primary metabolic disorders that could obscure the association between strong ion concentrations and $p\text{CO}_2$. Dataset C was created with the aim of assessing the relationship between our independent variables in patients with successful compensation. By utilizing these multiple datasets, we revealed consistent results with relatively strong correlations between SID and $p\text{CO}_2$ and moderate correlations between chloride concentrations and $p\text{CO}_2$. On the other hand, the correlations between sodium levels and $p\text{CO}_2$ were weak in all of the datasets examined. In addition, our results reveal no strong correlation between the other strong ions, *i.e.*, $[\text{Ca}^{2+}]$, $[\text{K}^+]$, and $[\text{Lac}^-]$, and $p\text{CO}_2$. Given those findings and the low plasma concentrations of the other strong ions, it is likely that these factors play little role in the compensation for $p\text{CO}_2$ derangement.

Collectively, the above findings provide a caveat in regard to interpretation of the 3 independent variables in the physicochemical approach. In this theory, those variables independently determine the hydrogen ion concentration of a solution and pH. In considering these results, however, it is notable that SID, one of the independent variables assessed, might change along with another independent variable— $p\text{CO}_2$. In addition, chloride, and not sodium, ions may be primary contributors to these changes. This notion is supported by some physiological systems. First, the kidney has been proposed to respond to changes of $p\text{CO}_2$ by adjusting the fractional excretion of chloride [15]. Second, a

possible mechanism of chloride changes known as a “chloride shift”, which is an exchange between chloride ion and bicarbonate ion through the cellular membrane, in response to a change of $p\text{CO}_2$ could also be responsible for those association [14].

It is noted that for the large sample size in the present study, the statistical power could be too strong to detect clinically meaningless changes, and most of the p -values in univariate analyses and multivariable regression analyses were less than 0.05. In this sense, we believe that the visualizations of the associations between strong ions and $p\text{CO}_2$ are more meaningful to understand those associations. On the other hand, only $[\text{Cl}^-]$ in Dataset B had a non-independent relationship with $p\text{CO}_2$ in the linear regression analysis, possibly because the arbitrary exclusion of metabolic disorders from Dataset B and further adjustment for $[\text{HCO}_3^-]$ may have diminished the association between $[\text{Cl}^-]$ and $p\text{CO}_2$.

While it has some significant strengths, there are also several limitations of the present study that warrant further discussion. First, it utilized a retrospective design and was thus potentially subject to systematic error or bias. However, given that all electronic data were collected prospectively and are numerical in nature, it is unlikely that they were subject to such bias. However, quite a few blood gas samples were repeatedly drawn from the same patient, which could violate the independence of those data and could strengthen or weaken the real association. Although we enrolled those data to maximize the sample size, an alternative approach might be to limit inclusion to a single blood gas sample for each patient.

Second, we did not consider each patient’s clinical course in the present study. For example, our study does not have detailed information on the severity of respiratory failure in each patient, which makes it hard to detect and interpret differences in the observed associations depending on the severity. Similarly, due to the lack of detailed clinical information, the present study likely included acute respiratory disorders as well as chronic ones, whereas chronic respiratory acid-base disorders rather than acute ones are thought to be targets of compensation. Despite this, some studies have also shown that acute respiratory acid-base disorders may also result in compensation [11, 15]. In addition, it is difficult to draw a clear distinction between chronic and acute disorders in this context. In order to address

this limitation, a prospective study including only patients with similar durations of respiratory disorder and $p\text{CO}_2$ shift would be helpful.

Third, we did not account for any effect of another independent variable, A_{TOT} in the present study. Given that hypoalbuminemia and/or hypophosphatemia, which mainly affect A_{TOT} , are not rare in ICU patients [16], weak acids may drive compensation and changes in $p\text{CO}_2$. However, there is no credible evidence that living organisms regulate albumin levels to preserve acid-base homeostasis in the liver or elsewhere in the body [17-19]. Further, there is no *in vivo* correlation between changes in A_{TOT} and shifts in $p\text{CO}_2$ [8]. In other words, the contribution of A_{TOT} to compensation and shifts in $p\text{CO}_2$ is likely small, if present at all.

Finally, although the present study showed that changes in $\text{SID}_{\text{Na-Cl}}$ and chloride ion concentration are significantly and consistently associated with changes in $p\text{CO}_2$, no causal effect in this relationship can be inferred. We assessed distinct datasets, one of which excluded data for patients with primary metabolic disorders to avoid the confounding effect of metabolic acidosis and/or alkalosis on $p\text{CO}_2$. However, we might not have adjusted for all confounding factors in our estimation of the effect of $p\text{CO}_2$ on strong ions. A randomized controlled trial with patients assigned to different $p\text{CO}_2$ groups would solve this issue.

These limitations may render the generalizability and interpretation of our results somewhat tenuous. Given this, future prospective studies should be conducted, considering the limitations discussed above, to reveal the precise association between $p\text{CO}_2$ and strong ions.

In conclusion, in the present study, we found relatively strong correlations between $p\text{CO}_2$ and $\text{SID}_{\text{Na-Cl}}$ in the multiple blood gas datasets examined. Correlations between $p\text{CO}_2$ and chloride concentrations, but not sodium concentrations, were further found to be moderate in these ICU data.

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