Quantitative Analysis of Acid-Base Disorders in Patients With Chronic Respiratory Failure in Stable or Unstable Respiratory Condition

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BACKGROUND: The Stewart approach theorizes that plasma pH depends on P_{aCO_2}, the strong ion difference, and the plasma total concentration of non-volatile weak acids (A_{tot}). The conventional approach measures standardized base excess, bicarbonate (HCO_3^-), and the anion gap. OBJECTIVE: To describe acid-base disorders with the Stewart approach and the conventional approach in patients with chronic respiratory failure. METHODS: This was an observational prospective study in a medical intensive care unit and a pneumology ward of a university hospital. There were 128 patients included in the study, of which 14 had more than one admission, resulting in 145 admissions. These were allocated to 4 groups: stable respiratory condition and elevated HCO_3^- (Group 1, $n = 23$), stable respiratory condition and non-elevated HCO_3^- (Group 2, $n = 41$), unstable respiratory condition and elevated HCO_3^- (Group 3, $n = 44$), and unstable respiratory condition and non-elevated HCO_3^- (Group 4, $n = 37$). Elevated HCO_3^- was defined as ≥ 3 standard deviations higher than the mean value we found in 8 healthy volunteers. Measurements were taken on admission. RESULTS: In groups 1, 2, 3, and 4, the respective mean ± SD values were: HCO_3^- 33 ± 3 mM, 26 ± 3 mM, 37 ± 4 mM, and 27 ± 3 mM ($P < .001$); strong ion difference 45 ± 3 mM, 38 ± 4 mM, 46 ± 4 mM, and 36 ± 4 mM ($P < .001$); and A_{tot} 12 ± 1 mM, 12 ± 1 mM, 10 ± 1 mM, 10 ± 2 mM ($P < .001$). Non-respiratory disorders related to high strong ion difference were observed in 12% of patients with elevated HCO_3^-, and in none of those with non-elevated HCO_3^- ($P = .003$). Non-respiratory disorders related to low strong ion difference were observed in 9% of patients with non-elevated HCO_3^-, and in none of those with elevated HCO_3^- ($P = .02$). Hypoalbuminemia was common, especially in unstable patients (group 3, 66%; group 4, 65%). Normal standardized base excess (16%), HCO_3^- (28%), and anion gap (30%) values were common. The Stewart approach detected high effective strong ion difference in 13% of normal standardized base excess, and in 20% of normal anion gap corrected for albuminemia, and low effective strong ion difference in 22% of non-elevated HCO_3^-. CONCLUSIONS: In patients with chronic respiratory failure the acid-base pattern is complex, metabolic alkalosis is present in some patients with elevated HCO_3^-, and metabolic acidosis is present in some with non-elevated HCO_3^-. The diagnostic performance of the Stewart approach was better than that of the conventional approach, even when corrected anion gap was taken into account. *Key words: chronic respiratory failure; acute respiratory failure; acid-base balance; metabolic alkalosis; respiratory acidosis.* [Respir Care 2010;55(11):1453–1463. © 2010 Daedalus Enterprises]

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The authors have disclosed no conflicts of interest.

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Introduction

In the chronic respiratory failure setting, the analysis of acid-base disturbances is expected to be complex, as shown in the examples below. Elevated plasma bicarbonate is traditionally thought to be a marker of renal compensation for chronic hypercapnia in stable patients. However, diuretics and steroids, which are commonly used in these patients, may contribute to the elevated plasma bicarbonate.[1] Should these patients develop acute respiratory failure and receive mechanical ventilation with excessive minute ventilation, mixed respiratory and metabolic alkalosis would occur, exposing them to the risk of severe cardiac arrhythmias[2] or seizures,[3] via alkalosis-induced acute profound hypophosphatemia.[4]

Mixed alkalosis is difficult to assess with the conventional approach to analysis of acid-base disturbances. In cystic fibrosis, metabolic acidosis may be predominant, even when no diuretics are used.[5,6] In acute-on-chronic respiratory failure, metabolic acidosis may well be present, depending on the cause of the acute respiratory failure. It may also be difficult to reveal with the conventional approach. Furthermore, the clinical symptoms of acute respiratory failure in acute asthma may be the expression of metabolic acidosis rather than respiratory acidosis.[7] Some causes of chronic respiratory failure, such as chronic lung fibrosis, are typically associated with respiratory alkalosis due to hypoxemia-induced increased minute ventilation.[8]

Finally, under-nutrition is common in patients with chronic respiratory failure and is associated with hypoalbuminemia. Hypoalbuminemia is also very common in the critically ill, which includes patients with acute-on-chronic respiratory failure. Hypoalbuminemia is a cause of metabolic alkalosis and may thereby limit respiratory or metabolic acidosis. Moreover, hypoalbuminemia lowers the measured anion gap, and these values must be corrected. For all of these reasons, the Stewart approach is an attractive choice for this setting.

The traditional approach defines acids as H^+ donors and bases as H^+ acceptors. It works out the carbonic acid/bicarbonate couple as the single buffer system. The traditional approach uses the Henderson-Hasselbalch equation alone, with a respiratory component (the carbonic acid) and a metabolic component (the bicarbonate):

$$pH = pK + \log([HCO_3^-]/(P_{aCO_2} \times 0.03)) \quad (1)$$

This approach is limited for complex disorders and does not quantify the abnormalities.[9] The additional use of standardized base excess[10] and anion gap[11] introduced a degree of quantification in the assessment of the metabolic component. The anion gap is defined as the difference between the concentration of $Na^+ + K^+$ and the concentration of $Cl^- + HCO_3^-$. However, standardized base excess requires a normal concentration of body water, and the anion gap is affected by the albumin concentration.[12] Another approach was therefore introduced by Stewart[13] to eliminate the limitations described above. In Stewart's concept, the origin of protons (H^+) and, hence, their plasma concentration, results from the dissociation of water, which results from the presence of totally dissociated strong ions, which are chemically non-reacting. Stewart's approach also applies total ion dissociation, electroneutrality, and mass conservation, through 6 equations, which, when solved simultaneously, give the plasma pH. According to this concept, the plasma pH depends on 3 variables: P_{aCO_2}, the strong ion difference, and the plasma total concentration of non-volatile weak acids (A_{tot}). Those 3 variables are thought to act independently of each other. The strong ion difference is the difference between the sums of all the strong cations and all the strong anions. The complete state of plasma electroneutrality reads as follows:

$$([Na^+] + [K^+] + [Ca^{++}] + [Mg^{++}] - [Cl^-] - [XA^-]) + [H^+] - [OH^-] - [HCO_3^-] - [CO_3^-] - [Alb^-] - [Pi^-] = 0 \quad (2)$$

where XA is the unmeasured anions, Alb^- is plasma albuminate, and Pi^- is inorganic phosphate. The expression in parenthesis is the strong ion difference. After eliminating the negligible concentrations of H^+, OH^-, and CO_3^-, Equation 2 reads as follows:

$$\text{Strong ion difference} - [HCO_3^-] - [Alb^-] - [Pi^-] = 0 \quad (3)$$

The expression in parenthesis in Equation 2 is the apparent strong ion difference, whereas the strong ion difference in Equation 3 is the effective strong ion difference, which takes into account the requirement for electroneutrality.

How does a change in the strong ion difference influence pH? If the concentration of cations is lower than that of anions, electroneutrality requires an increase in positive charges. Where do the positive charges come from? The difference in electrical charges forces the molecules that are not dissociated or partly dissociated to fully dissociate, to recover electroneutrality. The major source of positive charge is water. If all the molecules in the water are already dissociated, the source of positive charges is the water itself, which dissociates into H^+ and OH^-. So a decrease in strong ion difference (lack of positive charges) would increase water dissociation and produce H^+ and, hence, acidosis. By contrast, an increase in strong ion difference would increase water dissociation and produce OH^- and alkalosis.

In unselected intensive care unit (ICU) patients, the Stewart approach is useful for revealing acid-base disturbances,[14] but was not found to be superior to the conventional approach if the anion gap was corrected for albumin.[15] A more recent study reported that the Stewart approach identified more acid-base disturbances in ICU patients than did the conventional approach, even with corrected anion gap.[16]

However, few studies have been carried out in this field. In a study of patients with acute respiratory failure of various origins, including acute-on-chronic respiratory failure, we found that the diagnostic performance of the Stewart approach was better than that of the conventional approach, even with corrected anion gap.[17] However, in the patients with chronic respiratory failure in that study the plasma bicarbonate was as normal as could have been expected, given the established chronic hypercapnia. Therefore we undertook the present study to describe the acid-base disorders in patients with chronic respiratory failure, and to compare the diagnostic performance of the conventional approach and the Stewart approach in this population. As the primary objective was to investigate the impacts of respiratory condition and plasma bicarbonate on the biochemical pattern, 4 groups of patients were a priori defined as follows:

Group 1: stable condition and elevated bicarbonate
Group 2: stable condition and non-elevated bicarbonate
Group 3: unstable condition and elevated bicarbonate
Group 4: unstable condition and non-elevated bicarbonate

Methods

Patients

From October 1, 2008, to May 28, 2009, 844 patients were prospectively screened for eligibility: 381 in the 14-bed medical ICU, and 463 in the 12-bed pneumology ward at the Croix-Rousse Hospital, which is part of the University of Lyon, Lyon, France.

The inclusion criteria were:

- Age $\geq$ 18 years old
- Well documented ventilatory defect on a pulmonary function test carried out prior to the current admission, or, if that was not available, ongoing long-term domiciliary oxygen therapy, or home mechanical ventilation for chronic respiratory failure
- Admission for acute respiratory failure, defined as either dyspnea increased above baseline and/or respiratory rate $>$ 25 breaths/min, use of accessory respiratory muscles, and/or $P_{aCO_2} > 45$ mm Hg with arterial pH < 7.36, and/or $P_{aO_2}/F_{IO_2} < 300$ mm Hg, and/or either invasive or noninvasive mechanical ventilation
- Respiratory assessment of a patient in stable respiratory condition

The exclusion criteria were:

- No pulmonary function test results available in a patient without long-term oxygen therapy or home mechanical ventilation
- Repeat admissions of a given patient to the ICU or pneumology ward during the same hospital stay

Stable respiratory condition was defined as absence of increase in dyspnea or absence of acute respiratory failure or absence of hospitalization or assessment for impairment in the respiratory condition in the last month. Unstable respiratory condition was defined as acute respiratory failure, whose criteria were are indicated above. The patients in stable respiratory condition included in the study were those admitted to the pneumology ward for systematic respiratory assessment. Patients in unstable condition were admitted to either the pneumology ward or the ICU. In our laboratory we tested 8 healthy volunteers (6 non-smoker men, mean $\pm$ SD age 47 $\pm$ 21 y) to determine normal values. They underwent the same measurements as the patients. Elevated HCO_3^- was defined as $\geq$ 3 standard deviations higher than the mean value we found in the 8 healthy volunteers.[17]

The study was approved by the Comité de Protection des Personnes [CPP] Sud-Est III. The requirement for informed consent was waived because the protocol was part of the routine management of these patients.

Measurements

Our routine management of patients in stable condition admitted for acute respiratory failure or respiratory assessment includes taking arterial blood samples to measure arterial pH, P_{aO_2}, P_{aCO_2}, plasma electrolytes, albumin, total protein, and lactate. For the purposes of this study, the results kept were those obtained from samples taken both at ICU admission and during the first day of hospital assessment, for stable patients. After sampling, the blood was immediately sent to the clinical biochemistry laboratory. Arterial pH (pH electrode), P_{aO_2} (Clarke's electrode), P_{aCO_2} (P_{CO_2} electrode) were measured with the Omni S device (Roche Diagnostics France, Meylan, France). Sodium (Na^+), potassium (K^+), and chloride (Cl^-) were determined with an ion-selective electrode, with an indirect potentiometric method. Calcium (Ca^{++}) was determined with the Ortho Cresol Phtalein photometric method; phosphate (PO_4^{--}) with the phosphomolybdate method, magnesium (Mg^{++}) with the methylthymol blue complexometric procedure, albumin with the bromocresol purple-dye-binding method, total protein with the Biuret method,

Table 1. Diagnostic Criteria of Acid-Base Disorders From the Conventional Approach Used in the Present Study[23]

	HCO_3^- (mM)	P_{aCO_2} (mm Hg)	Standardized Base Excess (mM)
Metabolic acidosis	< 22	$= 40 + SBE$	< -5
Metabolic alkalosis	> 26	$= 40 + (0.6 \times SBE)$	$> +5$
Acute respiratory acidosis	$((P_{aCO_2} - 40)/10) + 24$	> 45	$= 0$
Chronic respiratory acidosis	$((P_{aCO_2} - 40)/3) + 24$	> 45	$= 0.4 \times (P_{aCO_2} - 40)$
Acute respiratory alkalosis	$((40 - P_{aCO_2})/5) + 24$	< 35	$= 0$
Chronic respiratory alkalosis	$((40 - P_{aCO_2})/2) + 24$	< 35	$= 0.4 \times (P_{aCO_2} - 40)$

SBE = standardized base excess

and lactate with a method that uses oxidation of lactate to pyruvate. All the tests were carried out with a Dimension RXL analyzer (Dade Behring, Newark, Delaware).

Calculated Variables

HCO_3^- and base excess[18] values were calculated from the measured pH and P_{aCO_2}, with the Henderson-Hasselbalch and Van Slyke equations, respectively.[19] Standardized base excess[20] was computed as:

$$\text{Standardized base excess} = ([HCO_3^-] - 24.4) + ((8.3 \times [\text{albumin}] \times 0.15) + (0.29 \times [PO_4^-] \times 0.32)) \times (pH - 7.4) \quad (4)$$

with [albumin] in g/dL and $[PO_4^-]$ in mg/dL.

Albuminate ($albumin^-$) and inorganic phosphate (Pi^-) were calculated[14] from the measured values of albumin, PO_4^-, and pH:

$$[\text{Albumin}^-]\,(\text{mM}) = [\text{albumin}] \times (0.123 \times pH - 0.631) \quad (5)$$

$$[Pi^-]\,(\text{mM}) = [PO_4^-] \times (0.309 \times pH - 0.469) \quad (6)$$

The anion gap was calculated as:

$$\text{Anion gap}\,(\text{mM}) = ([Na^+] + [K^+]) - ([Cl^-] + [HCO_3^-]) \quad (7)$$

The anion gap was corrected[12] for the effect of abnormal albumin concentration:

$$\text{Anion gap corrected}\,(\text{mM}) = \text{anion gap} + 0.25\,(\text{normal}\,[\text{albumin}] - \text{observed}\,[\text{albumin}])\,(\text{in g/L}) \quad (8)$$

The apparent strong ion difference was computed[13] as:

$$\text{Apparent strong ion difference}\,(\text{mM}) = ([Na^+] + [K^+] + 2 \times [Ca^{++}] + 2 \times [Mg^{++}]) - ([Cl^-] + [\text{lactate}]) \quad (9)$$

The effective strong ion difference was calculated[13] as:

$$\text{Effective strong ion difference}\,(\text{mM}) = [HCO_3^-] + [\text{albumin}^-] + [Pi^-] \quad (10)$$

The strong ion gap was obtained[21] as:

$$\text{Strong ion gap} = \text{apparent strong ion difference} - \text{effective strong ion difference} \quad (11)$$

A positive strong ion gap value represents unmeasured anions (sulfate, keto acids, citrate, pyruvate, acetate, gluconate), whereas a negative strong ion gap value represents unmeasured cations.

$[A_{tot}]$ was computed as:

$$[A_{tot}] = [\text{albumin}^-] + [Pi^-] \quad (12)$$

Unidentified strong anions (XA) were computed[14] as:

$$[\text{XA}]\,(\text{mM}) = ([Na^+] + [K^+] + 2 \times [Ca^{++}] + 2 \times [Mg^{++}]) - [Cl^-] - \text{effective strong ion difference} \quad (13)$$

XA and Cl^- were corrected for water excess/deficit by multiplying their observed values by a correcting factor (Na^+ normal/Na^+ observed).[14]

The following variables were recorded: age, sex, Simplified Acute Physiology Score II (SAPS II)[22] at ICU admission, cause of chronic respiratory failure, Global Initiative for Chronic Obstructive Lung Disease (GOLD) COPD stage (in COPD patients), FEV_1, forced vital capacity (FVC), FEV_1/FVC performed in stable condition

Table 2. Characteristics of 128 Patients With Chronic Respiratory Failure at Their First Admission to the Pneumology Ward or ICU

	Group 1*	Group 2	Group 3	Group 4
Number of patients	19	37	38	34
Age (mean ± SD y)	72 ± 9	69 ± 12	66 ± 14	68 ± 17
Male, No. (%)	9 (47)	28 (76)	20 (53)	24 (71)
Cause of Chronic Respiratory Failure, No. (%)				
COPD	14 (74)	31 (84)	25 (66)	19 (56)
Cystic fibrosis	0 (0)	0 (0)	2 (5)	1 (3)
Bronchiectasis	0 (0)	1 (3)	2 (5)	0 (0)
Other obstructive lung disease	0 (0)	0 (0)	1 (3)	1 (3)
Neuromuscular	0 (0)	2 (5)	1 (3)	3 (9)
Thoracic deformity	2 (10)	2 (5)	0 (0)	2 (6)
Tuberculosis sequelae	0 (0)	0 (0)	1 (3)	2 (6)
Obesity hypoventilation syndrome	1 (5)	1 (3)	4 (11)	1 (3)
Lung fibrosis	0 (0)	0 (0)	1 (3)	2 (6)
Other	2 (10)	0 (0)	1 (3)	3 (9)
GOLD COPD Stage, No. (%)				
0	0 (0)	0 (0)	2 (8)	2 (10)
1	0 (0)	1 (3)	1 (4)	1 (5)
2	0 (0)	7 (23)	6 (25)	3 (16)
3	4 (29)	8 (26)	4 (17)	4 (21)
4	10 (71)	15 (48)	11 (46)	9 (47)
FEV_1 (mean ± SD % predicted)	36 ± 17 (n = 18)	43 ± 19 (n = 37)	51 ± 24 (n = 34)	45 ± 27 (n = 30)
FVC (mean ± SD % predicted)	64 ± 18 (n = 18)	68 ± 20 (n = 37)	68 ± 22 (n = 34)	65 ± 25 (n = 30)
FEV_1/FVC (mean ± SD %)†	43 ± 16 (n = 18)	51 ± 18 (n = 37)	58 ± 18‡ (n = 34)	55 ± 19 (n = 30)
Home oxygen supplementation, No. (%)§	19 (100)	22 (59.5)	17 (44.7)	24 (70.6)
Home mechanical ventilation, No. (%)§	15 (78.9)	28 (75.7)	16 (42.1)	13 (38.2)

* Group 1: stable respiratory condition and elevated bicarbonate; Group 2: stable respiratory condition and non-elevated bicarbonate; Group 3: unstable respiratory condition and elevated bicarbonate; Group 4: unstable respiratory condition and non-elevated bicarbonate.
† P = .039
‡ P = .025 vs Group 1
§ P = .001 between groups
GOLD = Global Initiative for Chronic Obstructive Lung Disease
FVC = forced vital capacity

prior to the present hospitalization, home oxygen supplementation or mechanical ventilation, cause of admission, and breathing condition at time of blood sampling. An acid-base diagnosis was made for each patient with conventional analysis[23] (Table 1) and physico-chemical analysis.[14] In this approach, the acid-base disorders are classified into 2 categories: respiratory disorders, which are based on the P_{aCO_2} value; and non-respiratory disorders, which are further subgrouped into those pertaining to changes in strong ion difference (low strong ion difference [ie, acidosis] and high strong ion difference [ie, alkalosis]), and to changes in A_{tot} (low A_{tot} [ie, alkalosis] and high A_{tot} [ie, acidosis]).

Statistical Analysis

The normal distribution of the variables was verified with the Q-Q plot. Values are expressed as mean ± SD unless otherwise stated. Normal ranges were established from the values obtained from the 8 healthy volunteers.[17] Abnormal acid-base values were defined as those less than or more than 3 standard deviations from the mean value of the healthy volunteers. As repeat hospital stays during the study period were expected in this setting, repeat admissions to either the ICU or pneumology ward that did not match the exclusion criterion defined above were analyzed as independent events.

Comparison of the groups was made with one-way analysis of variance for quantitative variables, and chi-square test or Fisher's exact probability test for counts and proportions. When overall analysis of variance was significant, we conducted post-hoc pair-wise comparisons with Tukey's honest-significant-difference method, focused on the differences between groups 1 and 2, and groups 3 and 4, to analyze the plasma bicarbonate difference in the stable versus unstable patients; and between groups 1 and 3, and groups 2 and 4, to analyze the condition between patients with elevated versus non-elevated bicarbonate. The correlations between variables were assessed the least-squares regression analysis. Bias was assessed by examining the plots of residuals versus predicted values. Dif-

Table 3. Characteristics for 145 Hospital Admissions

	Group 1* (n = 23) No. (%)	Group 2 (n = 41) No. (%)	Group 3 (n = 44) No. (%)	Group 4 (n = 37) No. (%)
Admissions†				
Pneumology ward	23 (100)	41 (100)	18 (41)	9 (24)
Intensive care unit	0 (0)	0 (0)	26 (59)	28 (76)
Cause of admission†				
Respiratory assessment	23 (100)	41 (100)	0 (0)	0 (0)
Upper airway infection	0 (0)	0 (0)	21 (48)	8 (22)
Lower airway infection	0 (0)	0 (0)	9 (20)	3 (8)
Non-respiratory infection	0 (0)	0 (0)	1 (2)	2 (5)
Left-ventricular failure	0 (0)	0 (0)	4 (9)	6 (16)
Other‡	0 (0)	0 (0)	6 (14)	17 (46)
No cause found for acute respiratory failure	0 (0)	0 (0)	3 (7)	1 (3)
Breathing Condition at Time of Blood Sample				
Spontaneous breathing†	23 (100)	40 (98)	24 (54)	16 (43)
Noninvasive mechanical ventilation†	0 (0)	0 (0)	14 (32)	4 (11)
Invasive mechanical ventilation†	0 (0)	1 (2)§	6 (14)	17 (46)

* Group 1: stable respiratory condition and elevated bicarbonate; Group 2: stable respiratory condition and non-elevated bicarbonate; Group 3: unstable respiratory condition and elevated bicarbonate; Group 4: unstable respiratory condition and non-elevated bicarbonate.
† $P < .001$ between groups
‡ Other: 4 chronic lung fibrosis exacerbation, 2 cardiac arrest, 2 coma, 2 hemoptysis, 2 postoperative, 2 pneumothorax, 1 pulmonary embolism, 1 pre-renal acute kidney injury, 1 bronchomalacia, 1 bowel occlusion, 1 atelectasis, 1 upper-airway obstruction, 1 bladder retention, 1 thoracic trauma, 1 malignant peritoneal effusion.
§ Long-term home mechanical ventilation via tracheotomy
FVC = forced vital capacity

ferences were considered significant when $P < .05$. The statistical analysis was carried out with statistics software (SPSS 15.0, SPSS, Chicago, Illinois, and R 2.9.0, Foundation for Statistical Computing, Vienna, Austria).

Results

One hundred twenty-eight patients were included (Table 2). Between the 4 groups there were no significant differences in age, sex, cause of chronic respiratory failure, GOLD COPD stage (in patients with COPD), FEV_1, or FVC. The stable patients were using home oxygen supplementation or mechanical ventilation more frequently than the unstable patients (see Table 2). In the ICU patients the SAPS II score was 39 ± 17. Fourteen patients had more than one hospital stay, resulting in 145 admissions among the 128 patients (Table 3). As expected, stable patients were admitted to the pneumology ward only, and the cause of admission and respiratory status at the time of blood sampling differed between the 4 groups (see Table 3).

Table 4 shows the biochemical data on admission. Plasma bicarbonate was significantly higher in Group 1 than in Group 2, and in Group 3 than in Group 4. Therefore, the 4 groups were clearly separated, which was important, given the aim of the study. Plasma bicarbonate and P_{aCO_2} was higher in Group 3 than in Group 1. There were no differences in plasma sodium, potassium, magnesium, and phosphate between the groups. Regardless of the clinical condition, corrected plasma chloride, XA, the strong ion gap, and the corrected anion gap were significantly lower in the elevated plasma bicarbonate groups than in the non-elevated plasma bicarbonate groups, whereas the apparent strong ion difference and the effective strong ion difference were significantly higher. Plasma albumin and A_{tot} were similar between the elevated and non-elevated plasma bicarbonate groups, and were higher in the stable groups than in the unstable groups.

The conventional analysis did not detect any pure acid-base disturbances. In contrast, the Stewart approach provided a figure for the number of distinct alterations in non-respiratory disorders (Table 5). Low effective strong ion difference occurred in 5% of all cases, with no occurrences in the elevated bicarbonate groups. A high effective strong ion difference was observed in 6% of all admissions. Low corrected-chloride-associated high effective strong ion difference was significantly more common in both groups of patients with elevated bicarbonate. Low plasma albumin was significantly more common in the unstable groups than in the stable groups.

The Stewart approach found acid-base abnormalities in 23 hospital admissions with normal standardized base excess (16%), 41 in admissions with non-elevated bicarbon-

Table 4. Biochemical Variables on Admission for 145 Hospital Admissions*

	Group 1* (n = 23) (mean ± SD)	Group 2 (n = 41) (mean ± SD)	Group 3 (n = 44) (mean ± SD)	Group 4 (n = 37) (mean ± SD)	P 1 vs 2	P 1 vs 3	P 2 vs 4	P 3 vs 4
Sodium (mM)	138 ± 3	138 ± 3	138 ± 4	137 ± 4	NS	NS	NS	NS
Potassium (mM)	4.4 ± 0.4	4.3 ± 0.5	4.0 ± 0.5	4.0 ± 0.5	NS	NS	NS	NS
Calcium (mM)	2.24 ± 0.12	2.22 ± 0.10	2.16 ± 0.11	2.08 ± 0.2	NS	NS	< .001	NS
Magnesium (mM)	0.80 ± 0.09	0.77 ± 0.12	0.80 ± 0.14	0.83 ± 0.16	NS	NS	NS	NS
Chloride (mM)	100 ± 4	102 ± 4	99 ± 4	102 ± 4	NS	NS	NS	.003
Phosphate (mM)	1.0 ± 0.2	1.0 ± 0.2	1.0 ± 0.2	1.1 ± 0.4	NS	NS	NS	NS
Total protein (g/L)	75 ± 5	74 ± 6	70 ± 9	65 ± 9	NS	NS	< .001	NS
Albumin (g/L)	35 ± 4	35 ± 5	28 ± 5	28 ± 7	NS	< .001	< .001	NS
pH	7.38 ± 0.02	7.41 ± 0.05	7.37 ± 0.06	7.37 ± 0.08	NS	NS	.02	NS
P_{aCO_2} (mm Hg)	56 ± 5	42 ± 6	65 ± 13	48 ± 11	< .001	.004	NS	< .001
Lactate (mM)	1.1 ± 0.3	1.4 ± 0.6	1.4 ± 0.5	1.6 ± 0.8	NS	NS	NS	NS
Bicarbonate (mM)	33 ± 3	26 ± 3	37 ± 4	27 ± 3	< .001	< .001	NS	< .001
Standardized base excess (mM)	9 ± 3	2 ± 3	12 ± 4	2 ± 3	< .001	< .001	NS	< .001
Albuminate (mM)	10 ± 1	10 ± 1	8 ± 1	8 ± 2	NS	< .001	< .001	NS
Phosphate (mM)	1.8 ± 0.4	1.9 ± 0.3	1.8 ± 0.3	1.9 ± 0.7	NS	NS	NS	NS
Anion gap (mM)	10 ± 3	14 ± 2	6 ± 3	12 ± 3	< .001	< .001	.002	< .001
Anion gap corrected (mM)	11 ± 3	16 ± 3	9 ± 3	15 ± 4	< .001	NS	NS	< .001
Apparent strong ion difference (mM)	48 ± 3	45 ± 2	47 ± 4	43 ± 3	.002	NS	NS	< .001
Effective strong ion difference (mM)	45 ± 3	38 ± 4	46 ± 4	36 ± 4	< .001	NS	NS	< .001
Strong ion gap (mM)	3 ± 3	7 ± 3	1 ± 3	7 ± 4	< .001	.039	NS	< .001
Total nonvolatile weak acids (mM)	12 ± 1	12 ± 1	10 ± 1	10 ± 2	NS	< .001	< .001	NS
Unmeasured anions (mM)	4 ± 3	9 ± 3	2 ± 3	8 ± 4	< .001	NS	NS	< .001
Unmeasured anions corrected (mM)	4 ± 3	9 ± 3	2 ± 3	8 ± 4	< .001	NS	NS	< .001
Chloride corrected (mM)	101 ± 3	103 ± 3	101 ± 3	105 ± 3	.01	NS	NS	< .001

* Group 1: stable respiratory condition and elevated bicarbonate; Group 2: stable respiratory condition and non-elevated bicarbonate; Group 3: unstable respiratory condition and elevated bicarbonate; Group 4: unstable respiratory condition and non-elevated bicarbonate.
NS = not significant; $P > .05$.

ate (28%), and 44 in admissions with normal anion gap (30%) (Table 6).

Significant correlations were found between bicarbonate and standardized base excess, effective strong ion difference and standardized base excess, effective strong ion difference and bicarbonate, and strong ion gap and corrected anion gap between the 4 groups (Fig. 1). The inspection of plots of residuals versus predicted values showed no bias (Fig. 2). No correlations were found between any of the biochemical variables and the GOLD COPD stage nor the pulmonary function test variables.

Discussion

We prospectively enrolled a well defined cohort of patients with chronic respiratory failure and grouped them on the basis of clinical and biological data into groups of baseline condition (Groups 1 and 2) and acute respiratory failure (Groups 3 and 4). The separation of stable and unstable patients, on the one hand, and elevated and non-elevated plasma bicarbonate levels, on the other hand, was successful (see Tables 2–4).

One issue addressed in the present study was the contribution of metabolic alkalosis to elevated plasma bicarbonate. In the stable patients with elevated plasma bicarbonate, the apparent strong ion difference and the effective strong ion difference were significantly higher than in the patients with non-elevated plasma bicarbonate. Similar findings were observed in the unstable patients between those with elevated and non-elevated plasma bicarbonate. Furthermore, in the patients with elevated plasma bicarbonate, whether stable or unstable, the apparent strong ion difference and the effective strong ion difference were slightly higher than those expected from an appropriate renal adaptation to chronic hypercapnia.

These findings may indicate the presence of metabolic alkalosis in some chronic-respiratory-failure patients. This rate can be estimated at 12%, as 8 of the 67 patients (stable or unstable) with elevated plasma bicarbonate fell into the non-respiratory-disorder high-effective-strong-ion-difference diagnostic category of the Stewart approach (see Table 5). That proportion is significantly higher than that of the patients (stable or unstable) with non-elevated plasma

Table 5. Diagnostic Categories for Acid-Base Disturbances, According to Stewart's Approach, for 145 Hospital Admissions

	Group 1* (n = 23) No. (%)	Group 2 (n = 41) No. (%)	Group 3 (n = 44) No. (%)	Group 4 (n = 37) No. (%)
Respiratory Disorders				
P_{aCO_2} high†	23 (100)	15 (36)	41 (93)	19 (51)
P_{aCO_2} low	0 (0)	6 (15)	2 (4)	5 (14)
Non-respiratory Disorders				
Effective Strong Ion Difference Low				
Sodium low	0 (0)	1 (2)	0 (0)	0 (0)
Chloride high	0 (0)	1 (2)	0 (0)	1 (3)
Unmeasured anions	0 (0)	2 (5)	0 (0)	2 (5)
Effective Strong Ion Difference High				
Sodium high	0 (0)	0 (0)	1 (2)	0 (0)
Chloride low‡	2 (9)	0 (0)	5 (11)	0 (0)
Non-volatile Weak Acids				
Albuminate high	0 (0)	0 (0)	0 (0)	0 (0)
Phosphate high§	2 (9)	3 (7)	4 (9)	8 (22)
Albuminate low	2 (9)	6 (15)	27 (66)	24 (65)
Phosphate low	2 (9)	1 (2)	2 (4)	4 (11)

* Group 1: stable respiratory condition and elevated bicarbonate; Group 2: stable respiratory condition and non-elevated bicarbonate; Group 3: unstable respiratory condition and elevated bicarbonate; Group 4: unstable respiratory condition and non-elevated bicarbonate.
† $P = .001$ between groups (chi-square test)
‡ $P = .02$
§ $P < .001$ between groups (Fisher's exact test)

Table 6. Diagnostic Categories of Acid-Base Disturbances, According to Stewart's Approach, for 145 Hospital Admissions

	Normal Standardized Base Excess (n = 23) No. (%)	Normal Bicarbonate (n = 41) No. (%)	Normal Anion Gap (n = 44) No. (%)
Respiratory Disorders			
P_{aCO_2} high	23 (100)	15 (36)	41 (93)
P_{aCO_2} low	0 (0)	6 (15)	2 (4)
Non-respiratory Disorders			
Effective Strong Ion Difference Low			
Sodium low	0 (0)	6 (15)	4 (9)
Chloride high	0 (0)	1 (2)	0 (0)
Unmeasured anions	0 (0)	2 (5)	0 (0)
Effective Strong Ion Difference High			
Sodium high	1 (4)	0 (0)	2 (4)
Chloride low	2 (9)	0 (0)	7 (16)
Non-volatile Weak Acids			
Albumin high	0 (0)	0 (0)	0 (0)
Phosphate high	2 (9)	3 (7)	4 (9)
Albumin low	2 (9)	6 (15)	27 (66)
Phosphate low	2 (9)	1 (2)	2 (4)

bicarbonate (none of those 78 patients, $P = .002$ via Fisher's exact test).

Holland et al[24] reported that metabolic alkalosis contributed to hypercapnic acute respiratory failure in cystic fibrosis and COPD to a greater extent than in the present study. They found that metabolic alkalosis was present in 71% of 14 patients with cystic fibrosis and 22% of 49 COPD patients in exacerbation. An earlier study[1] reported 8 patients with mixed chronic respiratory acidosis and metabolic alkalosis, whose condition improved by managing the metabolic component

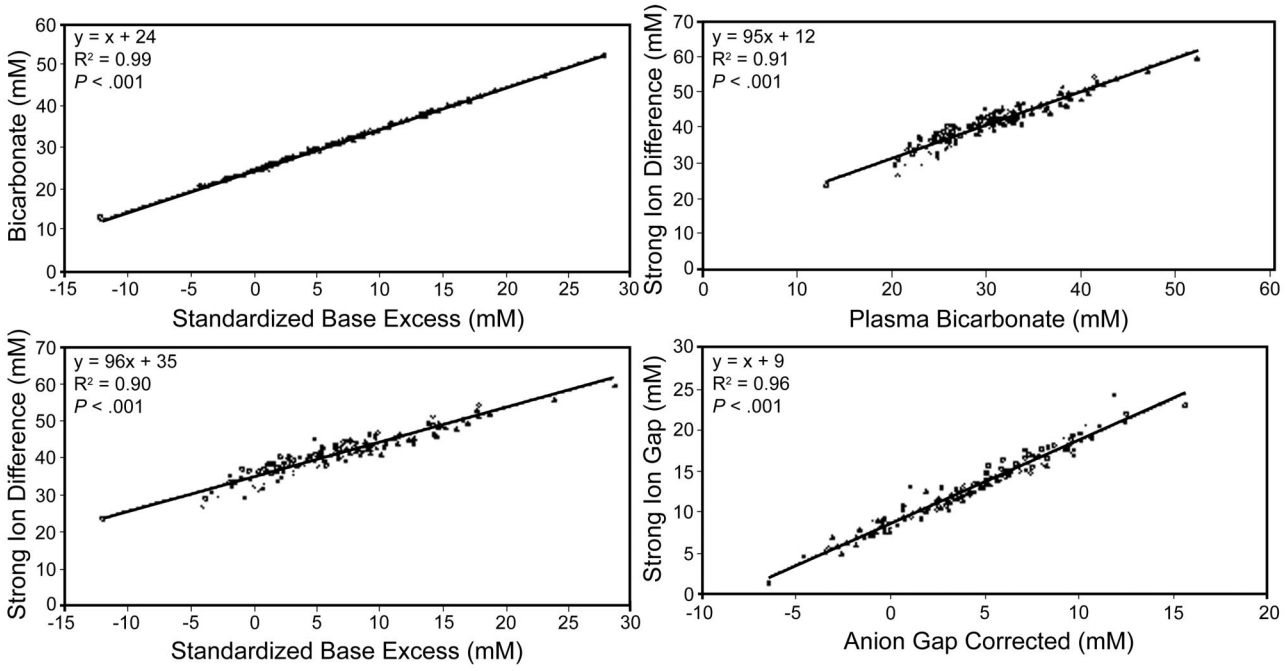

Fig. 1. Relationships of: plasma bicarbonate to standardized base excess; strong ion difference to standardized base excess; strong ion difference to bicarbonate; and strong ion gap to corrected anion gap, in stable patients with elevated (open circles) and non-elevated (open squares) plasma bicarbonate, and in unstable patients with elevated (black triangles) and non-elevated (crosses) plasma bicarbonate. The regression lines are drawn over the whole dataset.

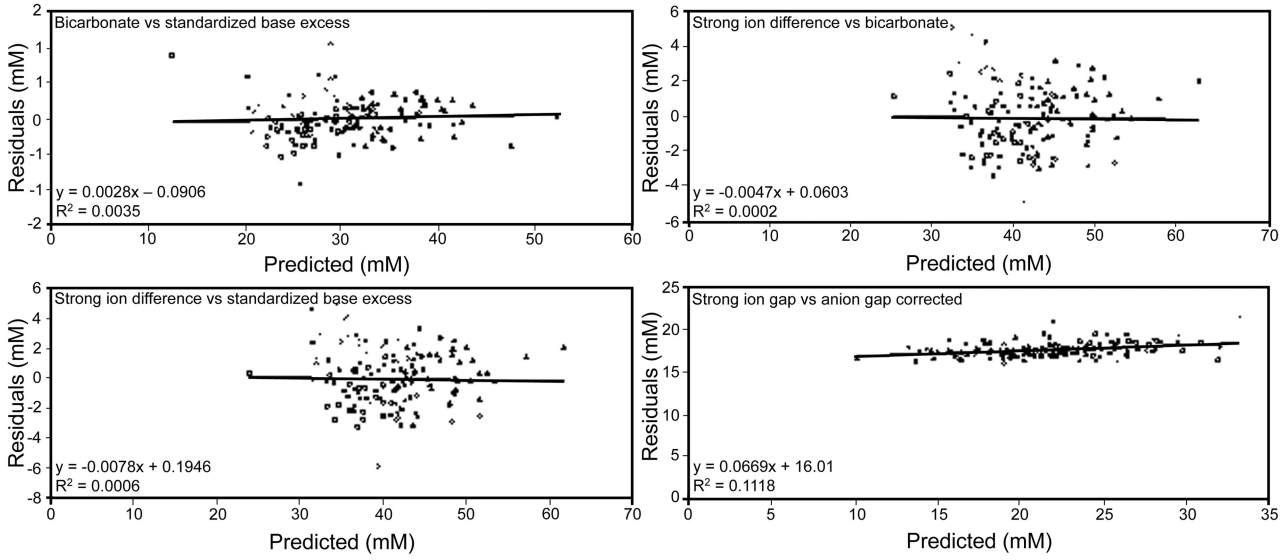

Fig. 2. Plots of residuals to predicted values for the relationships of: plasma bicarbonate to standardized base excess; strong ion difference to standardized base excess; strong ion difference to bicarbonate; and strong ion gap to corrected anion gap, in stable patients with elevated (open circles) and non-elevated (open squares) plasma bicarbonate, and in unstable patients with elevated (black triangles) and non-elevated (crosses) plasma bicarbonate. The regression lines are drawn over the whole dataset.

alone. The Stewart approach would allow for a quicker and more precise assessment of this mixed disorder.

In the present study, an excess of unmeasured anions was found only in patients with non-elevated plasma bicarbonate. The nature of these compounds is unknown. Indeed, plasma lactate levels were non-elevated and the same between groups. Potential candidates are sulfate, urate, hydroxy propionate, hippurate, oxalate, and furan propionate, which accumulate during acute kidney injury.[25] Although this hypothesis might apply to some unsta-

ble patients, there was no evidence for a reduction in glomerular filtration rate in our stable patients. Another source of unmeasured anions is the gelatin used for fluid resuscitation in some areas. That compound was not used in any patients in the present study. Nevertheless, we found that 9% of the (stable or unstable) patients with non-elevated plasma bicarbonate, versus none of those (stable or unstable) patients with elevated plasma bicarbonate ($P = .015$ via Fisher's exact test) fell into the non-respiratory-disorder low-effective-strong-ion-difference diagnostic category of the Stewart approach (see Table 5). This finding reveals an associated metabolic acidosis. In unstable patients, overt sepsis and left-ventricular failure (see Table 3) may explain the presence of metabolic acidosis. However, in stable patients there was no obvious reason for this disturbance. Further investigation should address this issue. Finally, the acidifying effect of hyperphosphatemia should be noted, which was not significantly different between the groups (see Table 5). Although the rate of hyperphosphatemia is not nil, its quantitative contribution to the net balance of the acid-base disorder is negligible.

Hypoalbuminemia was very common in the patients in the present study, so we can confirm that chronic respiratory failure should be added to the long list of conditions in which the alkalinizing effect of hypoalbuminemia must be taken into account. The plasma level of albumin was significantly lower in both groups of unstable patients, compared to their stable counterparts. Hypoalbuminemia-related decrease in non-volatile weak acids was therefore the most prevalent contributing factor in the acid-base disturbances, according to the Stewart approach (see Table 5).

As originally reported by Fencl et al, in unselected ICU patients,[14] a substantial number of patients with standardized base excess, plasma bicarbonate, or anion gap in the normal range actually have respiratory and non-respiratory disorders according to the Stewart approach. Moreover, the conventional approach did not detect any pure acid-base disorders. Recently, Martinu et al[26] investigated 14 COPD patients and 4 patients with cystic fibrosis with chronic respiratory acidosis for the acid-base prediction rules by drawing linear regression analysis between plasma bicarbonate and P_{aCO_2}. They found that the intercept and slope of the relationship were 5.23 mM/mm Hg and 0.51 mM/mm Hg, respectively ($R^2 = 0.92$, $P < .001$). We carried out the same analysis for the stable patients in the present study and found that in those with elevated plasma bicarbonate the values were 9.9 mM/mm Hg and 0.42 mM/mm Hg ($R^2 = 0.55$, $P < .01$), and in those with non-elevated plasma bicarbonate the values were 8.4 mM/mm Hg and 0.42 mM/mm Hg ($R^2 = 0.60$, $P < .01$). Interestingly, the slopes in these studies were very close. However, both the differences in intercept (twice as high in the present study) and R^2 suggest that patients were not selected in the same way. In any case, both investigations showed that the simple prediction rules, based on experimental data,[27] may not be clinically valid.

Limitations

First, the number of patients was quite low. The threshold of 30 subjects per group, which was the minimum required for relevant statistical analysis, was reached in all groups except Group 1. This was because it is uncommon that a stable patient has elevated plasma bicarbonate (according to our normal values). Second, patients were not followed up over time. Third, the baseline and acute-respiratory-failure patients were not the same, so strictly speaking there was no control, which limits the conclusions we can draw from comparisons between the groups.

Conclusions

In patients with chronic respiratory failure, in stable or unstable respiratory condition:

- The acid-base balance disturbance pattern is complex.
- Metabolic alkalosis is present in some patients with elevated hypercapnia.
- Metabolic acidosis is a contributing factor for some patients with non-elevated plasma bicarbonate.
- Hypoalbuminemia is very common and severe in unstable patients.
- The diagnostic performance of the Stewart approach was better than the conventional approach, even when corrected anion gap was taken into account.

Whether the Stewart approach can have a positive impact on the management and outcomes of chronic-respiratory-failure patients remains to be seen.

REFERENCES

1. Bear R, Goldstein M, Phillipson E, Ho M, Hammeke M, Feldman R, et al. Effect of metabolic alkalosis on respiratory function in patients with chronic obstructive lung disease. Can Med Assoc J 1977;117(8): 900-903.
2. Laaban JP, Grateau G, Psychoyos I, Laromiguiere M, Vuong TK, Rochemaure J. Hypophosphatemia induced by mechanical ventilation in patients with chronic obstructive pulmonary disease. Crit Care Med 1989;17(11):1115-1120.
3. Laaban JP, Marsal L, Waked M, Vuong TK, Rochemaure J. Seizures related to severe hypophosphataemia induced by mechanical ventilation. Intensive Care Med 1990;16(2):135-136.
4. Pontoriero G, Locatelli F, Ritz E. Calcium, phosphate and magnesium balance in patients with acute illness. In: Ronco C, Bellomo R, editors. Critical care nephrology. Dordrecht, The Netherlands: Kluwer Academic; 1998:211-223.
5. Mauri S, Pedroli G, Rudeberg A, Laux-End R, Monotti R, Bianchetti MG. Acute metabolic alkalosis in cystic fibrosis: prospective study and review of the literature. Miner Electrolyte Metab 1997;23(1):33-37.

6. Pedroli G, Liechti-Gallati S, Mauri S, Birrer P, Kraemer R, Foletti-Jaggi C, et al. Chronic metabolic alkalosis: not uncommon in young children with severe cystic fibrosis. Am J Nephrol 1995;15(3):245-250.
7. Meert KL, Clark J, Sarnaik AP. Metabolic acidosis as an underlying mechanism of respiratory distress in children with severe acute asthma. Pediatr Crit Care Med 2007;8(6):519-523.
8. King TE, Cherniack RM, Schwarz MI. Idiopathic pulmonary fibrosis and other interstitial lung diseases of unknown etiology. In: Murray JF, Nadel JA, editors. Textbook of respiratory medicine. Philadelphia: WB Saunders; 1998:1827-1849.
9. Siggaard-Andersen O. The acid-base status of the blood. Copenhagen: Munksgaard; 1974.
10. Schlichtig R, Grogono AW, Severinghaus JW. Human P_{aCO_2} and standard base excess compensation for acid-base imbalance. Crit Care Med 1998;26(7):1173-1179.
11. Emmett M, Narins RG. Clinical use of anion gap. Medicine (Baltimore) 1977;56(1):38-54.
12. Figge J, Jabor A, Kazda A, Fencl V. Anion gap and hypoproteinemia. Crit Care Med 1998;26(11):1807-1810.
13. Stewart PA. Modern quantitative acide-base chemistry. Can J Physiol Pharmacol 1983;61(12):1444-1461.
14. Fencl V, Jabor A, Kazda A, Figge J. Diagnosis of metabolic acid-base disturbances in critically ill patients. Am J Respir Crit Care Med 2000;162(6):2246-2251.
15. Dubin A, Menises MM, Masevicius MD, Moseinco MC, Kutscherauer DO, Ventrice E, et al. Comparison of three different methods of evaluation of metabolic acid-base disorders. Crit Care Med 2007; 35(5):1264-1270.
16. Boniatti MM, Cardoso PR, Castilho RK, Vieira SR. Acid-base disorders evaluation in critically ill patients: we can improve our diagnostic ability. Intensive Care Med 2009;35(8):1377-1382.
17. Guérin C, Bayle F, Poggi B, Germain-Pastenne M, Nesme P, Bourdin G, et al. Quantitative analysis of acid-base disorders in patients with acute on chronic respiratory failure and acute respiratory distress syndrome. Open Clin Chem J 2008;1:27-37. DOI: 10.2174/1874241600801010027.
18. Sharshar T, Chevret S, Bourdain F, Raphael JC, Syndrome FCGo-PEiG-B. Early predictors of mechanical ventilation in Guillain-Barré syndrome. Crit Care Med 2003;31(1):278-283.
19. Siggaard-Andersen O, Wimberly PD, Fogh-Andersen N, Gothgen IH. Measured and derived quantities with modern pH and blood gas equipment: calculation algorithms with 54 equations. Scand J Clin Lab Invest 1988;48(S189):7-15.
20. Wooten EW. Calculation of physiological acid-base parameters in multicompartment systems with application to human blood. J Appl Physiol 2003;95(6):2333-2344.
21. Kellum JA, Kramer DJ, Pinsky MR. Strong ion gap: a methology for exploring unexplained anions. J Crit Care 1995;10(2):51-55.
22. Le Gall JR, Lemeshow S, Saulnier F. A new Simplified Acute Physiology Score (SAPS II) based on a European/North American multicenter study. JAMA 1993;270(24):2957-2963.
23. Kellum JA. Determinants of blood pH in health and disease. Crit Care 2000;4(1):6-14.
24. Holland AE, Wilson JW, Kotsimbos TC, Naughton MJ. Metabolic alkalosis contributes to acute hypercapnic respiratory failure in adult cystic fibrosis. Chest 2003;124(2):490-493.
25. Rocktaeschel J, Morimatsu H, Uchino S, Goldsmith D, Poustie S, Story D, et al. Acid-base status of critically ill patients with acute renal failure: analysis based on Stewart-Figge methodology. Crit Care 2003;7(4):R60.
26. Martinu T, Menzies D, Dial S. Re-evaluation of acid-base prediction rules in patients with chronic respiratory acidosis. Can Respir J 2003;10(6):311-315.
27. Goldstein MB, Gennari FJ, Schwartz WB. The influence of graded degrees of chronic hypercapnia on the acute carbon dioxide titration curve. J Clin Invest 1971;50(1):208-216.