Journal of Critical Care 28 (2013) 1048–1054

Contents lists available at ScienceDirect

Journal of Critical Care

journal homepage: www.jccjournal.org

Stewart analysis of apparently normal acid-base state in the critically ill ☆

Miriam Moviat, MD, PhD [a,*], Mark van den Boogaard, PhD [b], Femke Intven, MD [b], Peter van der Voort, MD [c], Hans van der Hoeven, MD, PhD [b], Peter Pickkers, MD, PhD [b]

[a] Department of Intensive Care Medicine, Jeroen Bosch Hospital, 's-Hertogenbosch, the Netherlands
[b] Department of Intensive Care Medicine, Radboud University Nijmegen Medical Centre, Nijmegen, the Netherlands
[c] Department of Intensive Care Medicine, Onze Lieve Vrouwe Gasthuis, Amsterdam, the Netherlands

ARTICLE INFO

Keywords:
Acid-base
Stewart analysis
Critically ill
Hypoalbuminemia
Hyperchloremia
Strong ion gap

ABSTRACT

Purpose: This study aimed to describe Stewart parameters in critically ill patients with an apparently normal acid-base state and to determine the incidence of mixed metabolic acid-base disorders in these patients.
Materials and Methods: We conducted a prospective, observational multicenter study of 312 consecutive Dutch intensive care unit patients with normal pH ($7.35 \leq pH \leq 7.45$) on days 3 to 5. Apparent (SIDa) and effective strong ion difference (SIDe) and strong ion gap (SIG) were calculated from 3 consecutive arterial blood samples. Multivariate linear regression analysis was performed to analyze factors potentially associated with levels of SIDa and SIG.
Results: A total of 137 patients (44%) were identified with an apparently normal acid-base state (normal pH and $-2 <$ base excess < 2 and $35 < PaCO_2 < 45$ mm Hg). In this group, SIDa values were 36.6 ± 3.6 mEq/L, resulting from hyperchloremia (109 ± 4.6 mEq/L, sodium-chloride difference 30.0 ± 3.6 mEq/L); SIDe values were 33.5 ± 2.3 mEq/L, resulting from hypoalbuminemia (24.0 ± 6.2 g/L); and SIG values were 3.1 ± 3.1 mEq/L. During admission, base excess increased secondary to a decrease in SIG levels and, subsequently, an increase in SIDa levels. Levels of SIDa were associated with positive cation load, chloride load, and admission SIDa (multivariate $r^2 = 0.40$, $P < .001$). Levels of SIG were associated with kidney function, sepsis, and SIG levels at intensive care unit admission (multivariate $r^2 = 0.28$, $P < .001$).
Conclusions: Intensive care unit patients with an apparently normal acid-base state have an underlying mixed metabolic acid-base disorder characterized by acidifying effects of a low SIDa (caused by hyperchloremia) and high SIG combined with the alkalinizing effect of hypoalbuminemia.

1. Introduction

Acid-base disorders, predominantly metabolic acidosis, are common in critically ill patients. Their impact on morbidity and mortality, depending on both severity and cause, is substantial [1]. The physicochemical approach first described by Stewart [2] has gained interest in critical care literature because of its superior performance in diagnosing and quantifying complex acid-base disorders in comparison with the conventional Henderson-Hasselbalch approach [3-6]. The Stewart approach takes into account many of the electrochemical disturbances seen in critically ill patients that are not a part of the conventional approach. Essentially, the Stewart approach states that only 3 independent variables determine blood pH: the $PaCO_2$, the net charge balance of all completely dissociated ions (strong ion difference, or SID), and the total amount of weak acids, mainly albumin and phosphate.

The importance of accurately identifying and quantifying all causal factors in acid-base derangements in intensive care unit (ICU) patients is increasingly appreciated [1,4,7,8].

Although normal values of Stewart parameters of healthy subjects are often reported [9-12], values are currently unknown for critically ill patients with normal pH, base excess (BE), and pCO_2. Considering the high incidence of metabolic derangements in critically ill patients, normal values of healthy subjects probably do not apply.

We hypothesize that in ICU patients with normal pH, coexisting metabolic derangements will often be present but go unnoticed when applying the traditional approach. So far, studies largely report only single (mostly admission) values of ICU patients and do not focus on changes in response to institution of therapy and resolution of illness [13]. Serial measurements from the time of admission to the resuscitation and recovery phases will contribute to a better insight into the mechanisms and kinetics of acid-base derangements in the critically ill [8]. Thus, they will better allow for determining the

Abbreviations: BE, base excess; SIDa, apparent strong ion difference; SIDe, effective strong ion difference; SIG, strong ion gap; APACHE-II, Acute Physiology and Chronic Health Evaluation II; SOFA, Sequential Organ Failure Assessment; SD, standard deviation; IQR, interquartile range; RIFLE, Risk, Injury, Failure, Loss, and End-stage Kidney disease; CVVH(D), continuous venovenous hemo(dia)filtration.

☆ Conflicts of interest: None.

* Corresponding author. Tel.: +31 73 5532447, +31 6 47440221.
E-mail addresses: M.Moviat@jbz.nl, mmoviat@me.com (M. Moviat).

0883-9441/$ – see front matter © 2013 Elsevier Inc. All rights reserved.
http://dx.doi.org/10.1016/j.jcrc.2013.06.005

role of etiologic factors such as renal failure, fluid policy, and the presence of sepsis.

The purpose of the current explorative study was 2-fold. First, our objectives were to describe Stewart parameters in critically ill patients without evidence of an acid-base disorder according to the traditional approach and to determine the incidence of subclinical mixed metabolic acid-base abnormalities in these patients. Second, we aimed to explore the kinetics of the Stewart parameters and to determine the influence of several factors such as renal function, fluid management, and the presence of sepsis on the observed metabolic changes in acid-base balance.

2. Materials and methods

2.1. Study population

The local medical ethical committee of Arnhem-Nijmegen approved the study and waived the need for informed consent because there was no interference with routine clinical care. This prospective observational study was performed in 3 multidisciplinary ICUs in the Netherlands (Onze Lieve Vrouwe Gasthuis in Amsterdam [n = 112], Radboud University Nijmegen Medical Centre in Nijmegen [n = 130], and Jeroen Bosch Hospital in 's-Hertogenbosch [n = 70]). Patients with a normal pH on day 3, 4, or 5 after ICU admission, defined as $7.35 \leq pH \leq 7.45$, were included. Patients were excluded if they were discharged or died before day 3. Acute Physiology and Chronic Health Evaluation (APACHE-II) data and Simplified Acute Physiology Score (SAPS-II) data were collected for each patient. Furthermore, modified APACHE-II scores were used in which assessment of pH was not included. Clinical data were collected from (electronical) patient charts. Electrolytes, diuretics, and volumes and composition of intravenous fluids, administered 24 hours before normal pH value, were registered because we considered this time frame to be primarily of influence on electrolyte values at the time of normal pH. Urine output was registered 12 hours before normal pH value because this was considered a relevant time frame influencing electrolyte values at the time of normal pH. To compare acid-base variables of critically ill patients with apparent normal acid-base state with healthy subjects, data of a previously reported healthy control group were used (n = 15) [12].

2.2. Measurements

We collected arterial blood samples at 3 consecutive moments: at ICU admission, at the day normal pH was reached (day 3, 4, or 5), and at ICU discharge. If the length of ICU stay exceeded 7 days, the last blood sample was collected on day 7.

pH, partial pressures of oxygen and carbon dioxide (pO_2 and pCO_2), and plasma concentrations of ionized calcium and lactate were measured on a blood-gas analyzer (RapidLab; Bayer Diagnostics, Breda, the Netherlands). Plasma concentrations of sodium, potassium, and chloride were analyzed using an ion-selective electrode on an Aeroset (Abbott Diagnostics, Hoofddorp, the Netherlands) or on a Roche/Hitachi Modular Analytics P800 chemistry analyzer (Roche Diagnostics Nederland BV, Almere, the Netherlands), and plasma concentrations of magnesium, creatinine, urea, phosphate, bilirubin, and albumin were measured on an Aeroset.

2.3. Definitions

In the patients with normal pH on days 3 to 5, we defined a mixed acid-base disorder according to the traditional approach as either abnormal $PaCO_2$ (<35 or >45 mm Hg) or abnormal BE (<−2 or >2 mmol/L) [1,9,14]. Patients were classified into 3 groups, based on the presence or absence of a mixed acid-base disorder at the time of normal pH, using the traditional approach: an apparently "normal acid-base state group" ($-2 < BE < 2$ and $35 \text{ mm Hg} \leq PaCO_2 \leq 45 \text{ mm Hg}$), a "metabolic acidosis group" ($BE < -2$), and a "metabolic alkalosis group" ($BE > 2$). The latter 2 groups were not classified as respiratory alkalosis and acidosis, respectively, because they also contained patients with $PaCO_2$ values within the reference range. Patients with no apparent metabolic abnormalities ($-2 < BE < 2$) at the time of normal pH and an abnormal $PaCO_2$ were classified as "other." This group was only included in the regression analysis (see Statistical Analysis). *Renal failure* was defined according to the Risk, Injury, Failure, Loss, and End-stage Kidney disease (RIFLE) criteria [15] (Injury or Failure). *Total infused cation load* was defined as the net charge of all infused strong positively charged electrolytes (sodium, potassium, magnesium, and calcium) 24 hours before normal pH. *Total infused anion load* was defined as the net charge of all infused chloride 24 hours before normal pH. *Total infused intravenous volume load* was defined as the sum of all intravenously administered fluids 24 hours before normal pH.

2.4. Calculations

Bicarbonate was calculated using the Henderson-Hasselbalch equation ($pH = 6.1 + \log([HCO_3^-]/0.0301\ Pa_{CO_2})$ and the standard BE using the Siggaard-Andersen formulae. The apparent ($SIDa = [Na^+] + [K^+] + [Ca^{2+}] + [Mg^{2+}] - [Cl^-] - [\text{lactate}^-]$) and effective SID ($SIDe = 12.2 \times Pa_{CO_2}/(10^{pH}) + [\text{albumin}] \times (0.123 \times pH - 0.631) + [\text{phosphate}] \times (0.309 \times pH - 0.469)$) and strong ion gap ($SIG = SIDa - SIDe$) were subsequently calculated. The sodium-chloride difference ($[Na^+] - [Cl^-]$) and anion gap ($[Na^+] - [Cl^-] - [HCO_3^-]$) were calculated. All mentioned concentrations are expressed in milliequivalents per liter, except for the concentrations of albumin (g/L), phosphate (mmol/L), and p_{CO_2} (mm Hg).

2.5. Statistical analysis

Continuous variables were described as the mean ± SD or the median and interquartile range (IQR) for variables with skewed distributions. Except for length of stay on the ICU, all variables were normally distributed, allowing parametric testing. Differences in patient and baseline acid-base characteristics between the 3 groups were tested using χ^2 tests or using analysis of variance (ANOVA) with post hoc Tukey Honestly Significant Difference depending on its measure. Time-dependent changes were analyzed using repeated-measure ANOVA. Acid-base variables at the time of normal pH of the normal acid-base state group were compared with a previously reported healthy control group [12] using unpaired Student *t* test. Differences in acid-base variables and baseline characteristics between the 3 groups (normal acid-base, $BE < -2$ and $BE > 2$) were determined using ANOVA with post hoc Tukey HSD. To analyze factors associated with levels of SIDa and SIG at the time of normal pH, a multivariate linear regression analysis *method enter* was performed in all patients. Variables that, on theoretical grounds, could be associated with levels of SIDa at the time of normal pH (infused cation load, infused anion load, infused intravenous volume load, use of diuretics, and admission SIDa levels) were included in the univariate analysis. Likewise, variables that theoretically could be associated with levels of SIG at the time of normal pH (renal failure [RIFLE categories Injury and Failure], creatinine levels, use of continuous venovenous hemo(dia)filtration [CVVH(D)] 24 hours before normal pH, citrate anticoagulation, presence of sepsis, and SIG levels during ICU admission) were included in the univariate analysis. Variables that were associated with a *P* value less than .15 in the univariate simple linear regression analysis were included for the multivariate analysis. Statistical significance was defined as a $P < .05$, and 2-sided tests of hypotheses were used throughout. All data were analyzed using SPSS version 18.0 (SPSS, Chicago, Ill).

3. Results

3.1. Patients

A total of 433 patients were screened, and 312 patients with a normal pH on days 3 to 5 after ICU admission were included in our study. Baseline clinical and acid-base related data are presented in Table 1. The patients were divided into the 3 predefined groups (see Fig. 1): 137 patients were classified as "normal acid-base state" (normal BE and $Paco_2$), 75 were classified as "metabolic acidosis" (BE < -2), and 74 patients were classified as "metabolic alkalosis" (BE > 2). Twenty-six patients with $-2 <$ BE < 2 but abnormal $Paco_2$ were classified as "other" and were only included in the regression analysis.

Relevant baseline clinical data of these 3 groups are presented in Table 2. Scores of APACHE-II and SAPS-II were significantly higher in the metabolic acidosis group compared with the normal acid-base state and the metabolic alkalosis group (for APACHE-II: $P < .05$ and $P = .03$, respectively; for SAPS-II scores: $P = .003$ and $P = .006$, respectively). In addition, modified APACHE-II scores (excluding pH) were significantly higher in the metabolic acidosis group compared with the metabolic alkalosis group ($P = .04$). Significantly more patients received diuretics in the metabolic alkalosis group compared with the normal acid-base state and metabolic acidosis groups ($P = .02$ and $P = .02$, respectively). There was a significantly lower number of surgical patients in the metabolic alkalosis group compared with the normal acid-base state group and metabolic acidosis group ($P < .001$ and $P = .03$, respectively).

3.2. Stewart parameters in 3 groups with normal pH

3.2.1. Stewart parameters in critically ill patients with normal acid-base state according to the traditional approach

Acid-base parameters at the time of normal pH of the 3 groups and a previously reported healthy control group [12] are presented in Table 3 and illustrated in Fig. 2. In the normal acid-base state group, SIDa values were 36.6 ± 3.7 mEq/L, which is lower than SIDa values previously reported [12] in 15 healthy subjects (41.4 ± 3.7 mEq/L, $P < .001$). These reduced SIDa values resulted from hyperchloremia (chloride levels: 109 ± 4.6 mEq/L, sodium levels: 139 ± 4.2 mEq/L, and sodium-chloride difference: 30.0 ± 3.6 mEq/L), considering the normal mean values of all other components of the SIDa (calcium levels: 2.3 ± 0.2 mEq/L, magnesium levels: 2.0 ± 0.5 mEq/L, and potassium levels: 4.0 ± 0.4 mEq/L). Weak acid values in the normal acid-base state group were also lower compared with healthy subjects, resulting from hypoalbuminemia (albumin levels: 23.8 ± 6.3 g/L), considering the normal mean phosphate levels in the normal acid-base state group. Lastly, SIG values in the normal acid-base state group (3.1 ± 3.2 mEq/L) were higher than levels reported in healthy subjects (1.4 ± 1.8 mEq/L, $P = .04$) [12].

Table 1
Baseline clinical and acid-base–related characteristics of ICU patients with normal pH on day 3, 4, or 5 of admission

	Overall (n = 312)
Age (y), mean ± SD	63.9 ± 14.3
Male sex, n (%)	210 (67.3)
APACHE-II score, mean ± SD	20.5 ± 7.9
SAPS-II score, mean ± SD	46.2 ± 16.9
Mechanical ventilation during study, n (%)	275 (88.1)
Mechanical ventilation at normal pH, n (%)	196 (62.8)
Length of stay (d), median (IQR), range	5 (4-12), 3-223
Mortality, n (%)	58 (18.6)
Sepsis, n (%)	71 (22.8)
Surgical patient, n (%)	123 (39.4)
Admission diagnosis, n (%)	
Cardiovascular	54 (17.3)
Pulmonary	67 (21.5)
Abdominal	12 (3.8)
Neurologic	27 (8.7)
Surgery, elective	69 (22.1)
Surgery, urgent	42 (13.5)
Surgery, trauma	12 (3.8)
Other	29 (9.3)
CVVH(D) 24 h before normal pH, n (%)	42 (13.5)
Citrate anticoagulation, n (%)	30 (9.6)
pH, mean ± SD	7.34 ± 0.1
BE, mean ± SD	−2.9 ± 5.49
pco_2 (mm Hg), mean ± SD	42 ± 12.6
Chloride, mean ± SD	107 ± 6
Sodium-chloride difference, mean ± SD	31.1 ± 5.6
Lactate, median (IQR), range	1.7 (1.1-2.6), 0.4-18.8
Plasma creatinine (μmol/L), median (IQR), range	93 (73-131), 23-796

3.2.2. The etiology of mixed acid-base disorders according to Stewart

3.2.2.1. Apparent SID. Compared with the normal acid-base state group, SIDa levels in the metabolic acidosis group were significantly lower ($P < .001$; acidifying effect), and SIDa levels in the metabolic alkalosis group were significantly higher ($P < .001$; alkalinizing effect). This difference in SIDa levels between the groups was completely explained by the significant differences in chloride levels because the other strong ions that constitute SIDa were not different between groups (data not shown).

3.2.2.2. Weak acids. The concentrations of the weak acids albumin were not significantly different, and phosphate levels were only marginally different between groups.

3.2.2.3. Strong ion gap. Strong ion gap levels were significantly lower (alkalinizing effect) in the metabolic alkalosis group compared with the metabolic acidosis group ($P < .001$) and normal acid-base group, respectively ($P = .03$). The SIG levels of the normal acid-base group tended to be lower ($P = .057$) compared with the metabolic acidosis group.

3.2.2.4. $Paco_2$. In the metabolic acidosis group, pco_2 levels were significantly lower (alkalinizing effect) compared with the normal acid-base state group and the metabolic alkalosis group (both $P < .001$). Furthermore, pco_2 levels were significantly higher in the metabolic alkalosis group (acidifying effect) compared with the normal acid-base state group ($P < .001$).

3.3. Kinetics of Stewart parameters in patients with normal acid-base state according to the traditional approach

The kinetics of Stewart parameters in patients with normal acid-base state according to the traditional approach during the first week of admission before and after normalization of pH on 3 consecutive moments are presented in Table 4.

3.3.1. Before normalization of pH

The significant rise in pH was associated with an increase in BE. This increase in BE ($P = .0001$) was accompanied by a significant decrease in SIG levels ($P = .0001$) and a marginal but statistically significant decrease in phosphate levels ($P = .008$; Table 4).

3.3.2. After normalization of pH

pH increased further after normalization, associated with a significant increase in BE, because the slightly increasing pco_2 level accounts for a acidifying effect. This further increase in BE was accompanied by an increase in SIDa levels (responsible for an alkalinizing effect). This increase in SIDa levels was almost completely caused by a significant decrease in serum chloride levels (from 109 ± 4.6 to 107 ± 3.9 mmol/L, $P < .001$), as well as a slight decrease in lactate levels (from 1.6 ± 0.8 to 1.5 ± 0.8 mmol/L, $P = .045$) and an increase in calcium levels (from 1.1 ± 0.1 to 1.2 ± 0.1 mmol/L, $P =$

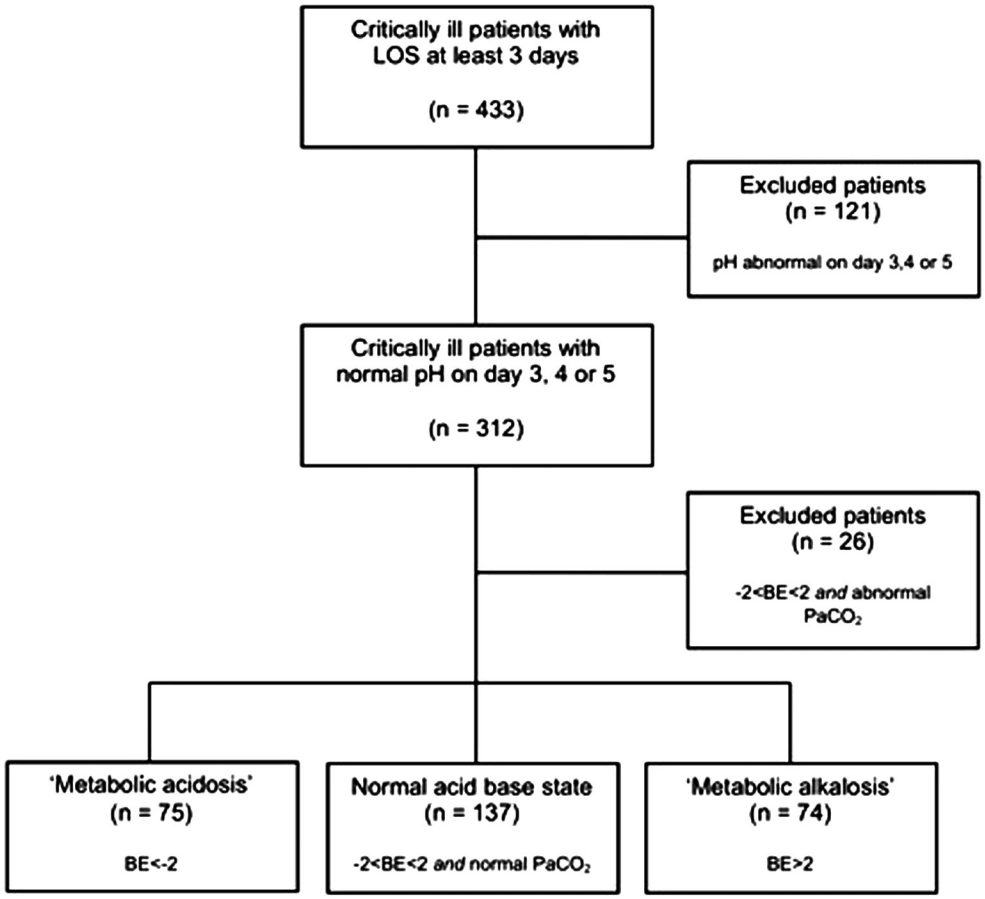

Fig. 1. Flowchart of patient groups. Base excess is expressed in millimoles per liter. $PaCO_2$ indicates arterial CO_2 tension.

.008 in the normal acid-base state group). Levels of the weak acid albumin did not significantly change over time, and levels of phosphate only increased marginally (Table 4).

3.4. Covariates that modulate acid-base balance

3.4.1. Factors associated with SIDa

Total infused cation load, total infused chloride load, total infused volume load, diuretic use, and admission SIDa levels were univariately associated ($P < .15$) with SIDa levels during normal pH. Subsequently, multivariate regression analysis showed that SIDa during normal pH remained significantly and independently associated with cation load, chloride load, and admission SIDa. The adjusted r^2 of the model was 0.40 (standard error of estimate, 3.51; $P < .001$). Regression coefficients are outlined in Table 5.

Table 2
Baseline clinical characteristics of 3 groups with normal pH at day 3, 4, or 5 according to BE

	Normal acid-base state (n = 137)	BE < −2 (n = 75)	BE > 2 (n = 74)
APACHE-II score, mean ± SD	20.1 ± 7.6	22.8 ± 8.0[a]	19.4 ± 8.1[b]
APACHE-II score adjusted for admission pH, mean ± SD	19.3 ± 7.1	21.6 ± 7.8	18.5 ± 7.9[b]
SAPS-II score, mean ± SD	44.3 ± 15.7	52.4 ± 16.2[a]	43.9 ± 18.9[b]
Mortality, n (%)	29 (21.2)	12 (16.2)	15 (20.8)
Sepsis, n (%)	29 (21.2)	22 (29.3)	15 (20.3)
Surgical patient, n (%)	67 (48.9)	29 (38.7)	16 (21.6)[b,b]
Renal failure during normal pH, n (%)	59 (43.1)	31 (41.3)	24 (32.4)
Diuretics 24 h before normal pH, n (%)	42 (30.7)	22 (28.2)	37 (50.0)[b,b]
CVVH(D) 24 h before normal pH, n (%)	24 (17.5)	6 (8)	9 (12.2)
Citrate anticoagulation, n (%)	18 (13.1)	3 (4)[a]	6 (8.1)

Exact *P* values are mentioned in the Results section.
[a] Statistically significantly different ($P < .05$) compared with normal BE.
[b] Statistically significantly different ($P < .05$) compared with BE < −2.

3.4.2. Factors associated with SIG

Renal failure during normal pH, creatinine levels during normal pH, use of CVVH(D) 24 hours before normal pH, use of citrate anticoagulation, SIG levels during admission, and sepsis were univariately associated ($P < .15$) with SIG during normal pH. After multivariate analysis, SIG during normal pH remained significantly and independently associated with creatinine during normal pH, sepsis, and SIG levels at ICU admission. The adjusted r^2 of the model is 0.28 (standard error of estimate, 2.78; $P < .001$). Regression coefficients are outlined in Table 6.

4. Discussion

The main findings of this study are 3-fold. First, we described values of Stewart parameters in critically ill patients with an apparently normal acid-base state and determined the incidence of subclinical acid-base abnormalities. Second, exploring the kinetics of the acid-base parameters during the first week of ICU admission, we found that the increase in pH is largely a result of metabolic changes. Third, we identified several factors that were independently related to SIDa levels and SIG levels during normal pH.

Table 3
Acid-base parameters of 3 groups during normal pH at day 3, 4, or 5 ($t = 2$) according to BE compared with a previously reported healthy control group[a]

	Normal acid-base state(n = 137)	Control (n = 15)	BE < −2 (n = 75)	BE > 2 (n = 74)
pH, mean ± SD	7.41 ± 0.03	7.38 ± 0.09[b]	7.39 ± 0.03[b]	7.42 ± 0.03[c]
$Paco_2$ (mm Hg), mean ± SD	39 ± 3	45 ± 9.3[b]	34 ± 4[b]	47 ± 6[b,c]
BE, mean ± SD	0.1 ± 1.1	0.1 ± 2.7	−4.1 ± 1.5[b]	4.9 ± 2.2[b,c]
Anion gap (mmol/L)[d], mean ± SD	8.6 ± 5.3		9.1 ± 5.7	7.9 ± 6.2
SIDa (mEq/L), mean ± SD	36.6 ± 3.7	41.4 ± 3.7[b]	33.2 ± 3.5[b]	41.2 ± 3.8[b,c]
Sodium (mmol/L), mean ± SD	139 ± 4.2	139 ± 1.8	140 ± 6.1	140 ± 4.2
Chloride (mmol/L), mean ± SD	109 ± 4.6	103 ± 2.8[b]	113 ± 6.0[b]	106 ± 4.7[b,c]
Sodium-chloride difference, mean ± SD	30.0 ± 3.6		26.3 ± 3.0[b]	34.2 ± 4.0[b,c]
Potassium (mmol/L), mean ± SD	4.0 ± 0.4	4.0 ± 0.2	4.1 ± 0.5	4.1 ± 0.5
Calcium (mEq/L), mean ± SD	2.3 ± 0.2	2.5 ± 0.1[b]	2.3 ± 0.3	2.3 ± 0.2
Magnesium (mEq/L), mean ± SD	2.0 ± 0.5	1.5 ± 0.1[b]	2.1 ± 0.6	2.0 ± 0.4
Lactate (mmol/L), median (IQR)	1.5 (1.2-1.9)	1.8 ± 0.5	1.6 (1.2-2.0)	1.3 (1.0-1.7)
Albumin (g/L), mean ± SD	23.8 ± 6.3	45 ± 5[b]	23.0 ± 5.6	24.8 ± 6.5
Phosphate (mmol/L), mean ± SD	1.0 ± 0.3		1.1 ± 0.4	1.0 ± 0.3[c]
SIDe(mEq/L), mean ± SD	33.4 ± 2.3	40 ± 3.8[b]	28.8 ± 2.7[b]	39.3 ± 3.3[b,c]
SIG (mEq/L), mean ± SD	3.1 ± 3.2	1.4 ± 1.8[b]	4.3 ± 3.5	1.8 ± 2.9[b,c]

[a] Data from Gunnerson et al [12].
[b] Statistically significantly different ($P < .05$) compared with normal BE.
[c] Statistically significantly different ($P < .05$) compared with BE < −2.
[d] Anion gap (mmol/L): $([Na^+] - [Cl^-] - [HCO_3^-])$.

4.1. Stewart parameters in patients with apparently normal acid-base state

Approximately 50% of our studied ICU patients with normal pH had an underlying mixed acid-base disorder according to criteria traditionally used (either abnormal BE and/or pco_2). However, even critically ill patients with an apparently normal acid-base state according to the conventional criteria (pH and both BE and pCO_2 within the reference range) have an underlying mixed acid-base disorder that emerged using the Stewart approach. Compared with data reported from healthy subjects [9-12], this metabolic disorder is characterized by a combination of a low SIDa (caused by hyperchloremia, reflected by the decreased Na-Cl difference), high SIG (both acidifying effects), and a low level of the weak acid albumin (alkalinizing effect). Apparently, traditional methods of assessing acid-base status fail to diagnose complicated acid-base disorders in critically ill patients. As far as we know, our study is the first to report a detailed quantitative analysis of a large group of critically ill patients with an apparently normal acid-base status. Moreover, considering this large group of studied patients and recognizing that the critically ill patient with normal pH, BE, and $Paco_2$ is metabolically different from a healthy person does not prove but may suggest that low SIDa, high SIG, and low albumin levels could be regarded as an adaptive phenomenon during critical illness. Nevertheless, this seems unlikely because hypoalbuminemia (an alkalinizing factor) is considered to be an inevitable event in critically illness and not a regulated variable for acid-base purposes. Accordingly, increased SIG levels are probably a result of organ dysfunction and the underlying disease or its therapy. However, the low SIDa values may (at least partially) reflect an appropriate renal response. Recently, several chloride carriers in the proximal tubules and distal nephron are identified that underline the role of chloride in renal acid-base regulation [16]. In this view, our results illustrate that in case of hypoalbuminemia, SID may be reset to a lower level to maintain a normal pH, as previously suggested [12,17].

4.2. Kinetics of Stewart parameters

Exploring the dynamics of acid-base parameters during the first week of ICU admission, we found that levels of SIDa return to levels almost comparable with healthy subjects. In addition, after normalization of pH, SIG levels remained higher than levels reported for healthy subjects, and hypoalbuminemia persisted. This is in accordance with the recent study of Gunnerson et al [12], who reported the data of 15 stable ICU patients just before ICU discharge. Thus, the main

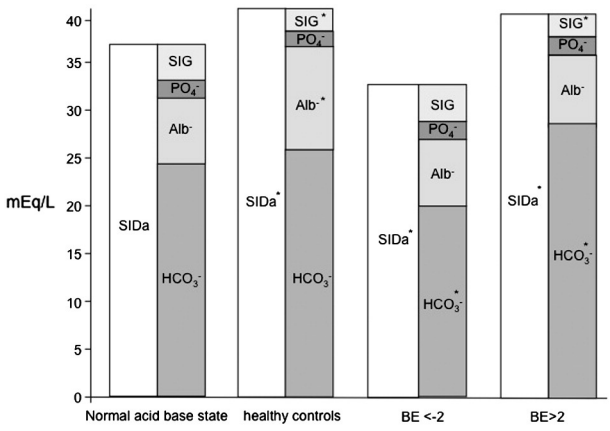

Fig. 2. Acid-base parameters at the time of normal pH, all expressed in milliequivalents per liter, in the normal acid-base state group (normal BE and $PaCO_2$, n = 137), healthy control group (n = 15, data from Gunnerson et al [12]), metabolic acidosis group (BE < −2, n = 75), and metabolic alkalosis group (BE > 2, n = 74). *Statistically significant difference (all $P < .001$, except SIG levels BE > 2 group vs normal BE group: $P = .03$).

Table 4
dynamics of acid-base parameters during the first week of ICU admission of patients with normal acid-base state according to the traditional approach (n = 137) at day 3, 4, or 5 ($t = 2$)

	$t = 1$ (day 1)	$t = 2$ (day 3, 4, or 5)	$t = 3$ discharge/ day 7
pH, mean ± SD	7.35 ± 0.09	7.41 ± 0.03[a]	7.43 ± 0.05[a,b]
$Paco_2$ (mm Hg), mean ± SD	40 ± 9	39 ± 3	41 ± 6[b]
BE, mean ± SD	−3.4 ± 4.6	0.1 ± 1.1[a]	2.3 ± 3.0[a,b]
Sodium (mmol/L), mean ± SD	138 ± 5	139 ± 4[a]	140 ± 5[a]
Chloride (mmol/L), mean ± SD	107 ± 5	109 ± 5[a]	107 ± 4[b]
Sodium-chloride difference, mean ± SD	30.5 ± 4.7	30.0 ± 3.6	32.4 ± 4.3[a,b]
Lactate (mmol/L), median (IQR)	1.5 (1.2-2.6)	1.5 (1.2-1.9)[a]	1.3 (1.0-1.7)[a]
SIDa (mEq/L), mean ± SD	36 .1 ± 5.2	36.6 ± 3.7	39.3 ± 4.5[a,b]
Albumin (g/L), mean ± SD	24.2 ± 6.9	23.8 ± 6.3	24.1 ± 6.0
Phosphate (mmol/L), mean ± SD	1.2 ± 0.5	1.0 ± 0.3[a]	1.1 ± 0.3[b]
SIDe (mEq/L), mean ± SD	30.7 ± 4.6	33.4 ± 2.3[a]	35.8 ± 3.5[a,b]
SIG (mEq/L), mean ± SD	5.3 ± 4.7	3.1 ± 3.2[a]	3.4 ± 3.6[a]

[a] Statistically significant change ($P < .05$) compared with $t = 1$.
[b] Statistically significant change $P < .05$) compared with $t = 2$.

Table 5
Univariate and multivariate analyses of factors associated with SIDa levels at normal pH

	Univariate analysis			Multivariate analysis		
	B	95% CI	*P*	*B*	95% CI	*P*
Cation load (mEq/L)	0.251	0.135 to 0.345	<.001	0.232	0.142 to 0.321	<.001
Chloride load (mEq/L)	−0.006	−0.008 to −0.004	<.001	−0.005	−0.008 to −0.002	.001
IV volume (mL)	−0.001	−0.001 to −0.001	<.001			
Diuretic use	2.081	1.038 to 3.123	<.001			
Admission SIDa (mEq/L)	0.414	0.342 to 0.485	<.001	0.344	0.273 to 0.415	<.001

CI indicates confidence interval; IV, intravenous.

contributors to a change in acid-base status in critically ill patients are, first, a decrease (but not complete normalization) of SIG levels and, second, an increase (but not normalization) of SIDa levels. The contribution of the respiratory component appears to be only minor. The decrease in SIG levels before normalization of pH may likely be related to (partial) recovery of organ function or for example institution of renal replacement therapy. High (preresuscitation) SIG levels at ICU admission are known to be related to the presence of sepsis and renal and hepatic dysfunction and are probably a marker of tissue hypoperfusion as well [18-21]. Some studies [22-25] found a clear association between high SIG levels and mortality, whereas another study did not [26]. The prognostic significance of high SIG levels during admission is probably more relevant when preresuscitation values are measured [4,24,26]. The increase of SIDa levels after normalization of pH in our study is almost completely explained by a decrease in chloride levels and might be related to further recovery of organ function. For example, the ability to excrete excess chloride in urine is directly related to renal function [27]. Furthermore, large amounts of intravenous unbalanced fluids are unlikely to be administered in a more stable phase of disease. Unfortunately, we did not collect data of fluid input and output after normalization of pH to support this possibility.

4.3. Covariates that modulate acid-base balance

Using multivariate linear regression analysis, performed in all patients with normal pH (n = 312), we showed that the low SIDa levels during normal pH were independently related to admission SIDa levels, low cation loading, and high chloride loading 24 hours before normal pH. Because these factors account for only 40% of the observed SIDa levels during normal pH, other factors not accounted for in the analysis apparently also play a role. Potential candidates are infused (unbalanced) fluids during the resuscitation phase and, for example, diuretics prescribed during the first 2 days of admission, anion flux from the intracellular and interstitial (changing Gibbs-Donnan equilibrium) compartment, and as mentioned above, presumably increased renal chloride retention as an adaptive response to the alkalinizing factor hypoalbuminemia. Adverse effects of hyperchloremia on organ function, specifically renal function and outcome in critically ill patients are increasingly reported in recent studies [28,29]. Therefore, our finding that a normal blood gas result does not exclude hyperchloremia may be clinically relevant.

Strong ion gap levels in the patients with normal pH were independently related to creatinine levels, the presence of sepsis, and SIG levels during admission. Again, other factors not accounted for in our analysis likely play an important role. First, the calculated values of SIG levels may be overestimated because no Ka values of weak acids have been validated for the critically ill, possibly influencing SIDe [30]. Second, although SIG levels during normal pH decreased compared with their admission values, they are still elevated compared with healthy subjects. Persistent occult tissue hypoperfusion or hepatic dysfunction may account for this. In general, the nature of the increased SIG in ICU patients is currently largely unknown and likely multifactorial [31]. Because this was an explorative study, the prognostic significance of high SIG levels during normal pH remains speculative. However, considering its association with unfavorable outcome and specific disease states if measured during admission, it is reasonable to assume that increased SIG levels are a marker of tissue damage. Therefore, the possibility of increased SIG levels in patients with apparently normal acid-base state may have clinical implications.

Table 6
Univariate and multivariate analyses of factors associated with SIG levels at normal pH

	Univariate analysis			Multivariate analysis		
	B	95% CI	*P*	*B*	95% CI	*P*
Renal failure	1.248	0.500-1.996	.001			
Creatinine (μmol/L)	0.014	0.01-0.018	<.001	0.009	0.005-0.014	<.001
CVVH(D)	1.628	0.567-2.689	.003			
Citrate anticoagulation	1.727	0.496-2.957	.006			
Sepsis	2.417	1.568-3.266	<.001	1.391	0.584-2.198	.001
Admission SIG (mEq/L)	0.28	0.210-0.350	<.001	0.210	0.138-0.281	<.001

CI indicates confidence interval.

5. Conclusions

This is the first study describing Stewart acid-base parameters in an ICU population with no apparent acid-base abnormalities. We demonstrated that in our studied ICU patients with normal pH, pCO_2, and BE, an underlying mixed metabolic acid-base disorder is present. Low SIDa (mainly caused by hyperchloremia) and high SIG levels nullify the alkalinizing effect of hypoalbuminemia. Whether this should be interpreted as an adaptive response or as a complex mixed acid-base disorder remains speculative. In addition, we showed that high chloride load, low cation load, and low admission SIDa were independently related to these low SIDa levels. Creatinine levels, the presence of sepsis at admission, and admission SIG levels were independently related to high SIG levels during normal pH.

Acknowledgments

The authors wish to thank Tijn Bouw (research nurse in Radboud University Nijmegen Medical Centre in Nijmegen, the Netherlands) and Saskia Rijkenberg (clinical researcher in Onze Lieve Vrouwe Gasthuis in Amsterdam, the Netherlands) for their help with the data collection.

References

[1] Gunnerson KJ, Saul M, He S, Kellum JA. Lactate versus non-lactate metabolic acidosis: a retrospective outcome evaluation of critically ill patients. Crit Care 2006;10:R22.
[2] Stewart PA. Modern quantitative acid-base chemistry. Can J Physiol Pharmacol 1983;61:1444–61.
[3] 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;162:2246–51.

[4] Kaplan LJ, Kellum JA. Initial ph, base deficit, lactate, anion gap, strong ion difference, and strong ion gap predict outcome from major vascular injury. Crit Care Med 2004;32:1120–4.
[5] Dubin A, Menises MM, Masevicius FD, Moseinco MC, Kutscherauer DO, Ventrice E, et al. Comparison of three different methods of evaluation of metabolic acid-base disorders. Crit Care Med 2007;35:1264–70.
[6] Kaplan L. Acid-base balance analysis: a little off target. Crit Care Med 2007;35: 1418–9.
[7] Moviat M, van Haren F, van der Hoeven H. Conventional or physicochemical approach in intensive care unit patients with metabolic acidosis. Crit Care 2003;7: R41–5.
[8] Martin M, Murray J, Berne T, Demetriades D, Belzberg H. Diagnosis of acid-base derangements and mortality prediction in the trauma intensive care unit: the physiochemical approach. J Trauma 2005;58:238–43.
[9] Park M, Taniguchi LU, Noritomi. DT, Liborio AB, Maciel AT, Cruz-Neto LM. Clinical utility of standard base excess in the diagnosis and interpretation of metabolic acidosis in critically ill patients. Braz J Med Biol Res 2008;41:241–9.
[10] Masevicius FD, Tuhay G, Pein MC, Ventrice E, Dubin A. Alterations in urinary strong ion difference in critically ill patients with metabolic acidosis: a prospective observational study. Crit Care Resusc 2010;12:248–54.
[11] Gunnerson KJ, Kellum JA. Acid-base and electrolyte analysis in critically ill patients: are we ready for the new millennium? Curr Opin Crit Care 2003;9: 468–73.
[12] Gunnerson KJ, Srisawat N, Kellum JA. Is there a difference between strong ion gap in healthy volunteers and intensive care unit patients? J Crit Care 2010;25: 520–4.
[13] Tuhay G, Pein MC, Masevicius FD, Kutscherauer DO, Dubin A. Severe hyperlactatemia with normal base excess: a quantitative analysis using conventional and stewart approaches. Crit Care 2008;12:R66.
[14] Gunnerson KJ. Clinical review: the meaning of acid-base abnormalities in the intensive care unit part I—epidemiology. Crit Care 2005;9:508–16.
[15] Bellomo R, Ronco C, Kellum JA, Mehta RL, Palevsky P. Acute renal failure—definition, outcome measures, animal models, fluid therapy and information technology needs: the second international consensus conference of the Acute Dialysis Quality Initiative (adqi) group. Crit Care 2004;8:R204–12.
[16] Yunos NM, Bellomo R, Story D, Kellum J. Bench-to-bedside review: chloride in critical illness. Crit Care 2010;14:226.
[17] Wilkes P. Hypoproteinemia, strong-ion difference, and acid-base status in critically ill patients. J Appl Physiol 1998;84:1740–8.
[18] Kellum JA, Bellomo R, Kramer DJ, Pinsky MR. Hepatic anion flux during acute endotoxemia. J Appl Physiol 1995;78:2212–7.
[19] Makino J, Uchino S, Morimatsu H, Bellomo R. A quantitative analysis of the acidosis of cardiac arrest: a prospective observational study. Crit Care 2005;9:R357–62.
[20] Kellum JA, Kramer DJ, Pinsky MR. Strong ion gap: a methodology for exploring unexplained anions. J Crit Care 1995;10:51–5.
[21] Moviat M, Terpstra AM, Ruitenbeek W, Kluijtmans LA, Pickkers P, van der Hoeven JG. Contribution of various metabolites to the “unmeasured” anions in critically ill patients with metabolic acidosis. Crit Care Med 2008;36:752–8.
[22] Dondorp AM, Chau TT, Phu NH, Mai NT, Loc PP, Chuong LV, et al. Unidentified acids of strong prognostic significance in severe malaria. Crit Care Med 2004;32: 1683–8.
[23] Durward A, Tibby SM, Skellett S, Austin C, Anderson D, Murdoch IA. The strong ion gap predicts mortality in children following cardiopulmonary bypass surgery. Pediatr Crit Care Med 2005;6:281–5.
[24] Balasubramanyan N, Havens PL, Hoffman GM. Unmeasured anions identified by the fencl-stewart method predict mortality better than base excess, anion gap, and lactate in patients in the pediatric intensive care unit. Crit Care Med 1999;27: 1577–81.
[25] Antonini B, Piva S, Paltenghi M, Candiani A, Latronico N. The early phase of critical illness is a progressive acidic state due to unmeasured anions. Eur J Anaesthesiol 2008;25:566–71.
[26] Rocktaeschel J, Morimatsu H, Uchino S, Bellomo R. Unmeasured anions in critically ill patients: can they predict mortality? Crit Care Med 2003;31:2131–6.
[27] Moviat M, Terpstra AM, van der Hoeven JG, Pickkers P. Impaired renal function is associated with greater urinary strong ion differences in critically ill patients with metabolic acidosis. J Crit Care 2012;27:255–60.
[28] Chowdhury AH, Cox EF, Francis ST, Lobo DN. A randomized, controlled, double-blind crossover study on the effects of 2-l infusions of 0.9% saline and plasma-lyte(r) 148 on renal blood flow velocity and renal cortical tissue perfusion in healthy volunteers. Ann Surg 2012;256:18–24.
[29] Boniatti MM, Cardoso PR, Castilho RK, Vieira SR. Is hyperchloremia associated with mortality in critically ill patients? A prospective cohort study. J Crit Care 2011;26: 175–9.
[30] Constable PD, Stämpfli H. Advances in estimating [Atot] and K_A. In: Kellum JA, Elbers PWG, editors. Stewart's textbook of acid-base (ed 2). Amsterdam: the Netherlands; 2009. p. 233–46.
[31] Moviat MA, Pickkers P, Ruitenbeek W, van der Hoeven JG. The nature of unmeasured anions in critically ill patients. Crit Care 2008;12:416.