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An acid-base disorders analysis with the use of the Stewart approach in patients with sepsis treated in an intensive care unit

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Abstract

Background: Patients with sepsis admitted to the intensive care unit often present with acid-base disorders. As the traditional interpretation might be clinically misleading, an alternative approach described by Stewart may allow one to quantify the individual components of acid-base abnormalities and provide an insight into their pathogenesis. The aim of our study was to compare the traditional and Stewart approaches in the analysis of acid-base disturbance.

Methods: We analyzed arterial blood gases (ABG) taken from 43 ICU septic patients from admission to discharge categorising them according to SBE values. The traditional concept analysis was compared with the physicochemical approach using the Stewart equations.

Results: 990 ABGs were analysed. In the SBE < –2 mEq L^{-1} group, hyperlactatemia was observed in 34.7% ABG, hypoalbuminemia in 100% and SIG acidosis in 42% ABG. Moreover, a Cl/Na ratio > 0.75 was present in 96.9% ABG. In the normal range SBE group, elevated lactates were present in 21.3% ABG, SIG acidosis in 14.9%, elevated Cl/Na ratio in 98.4% and hypoalbuminemia in all 324 ABG. In the metabolic alkalosis group (SBE > +2 mEq L^{-1}), hyperlactatemia was observed in 18.4% ABG, SIG acidosis in 5% ABG, Cl/Na ratio > 0.75 in 88.8%, while 99.1% samples revealed hypoalbuminemia.

Conclusion: The use of the Stewart model may improve our understanding of the underlying pathophysiological mechanism and the true etiology of the derangements of acid-base disorders. Indeed, it proves that patients may suffer from mixed arterial blood gas disorders hidden under normal values of SBE and pH.

Key words: acid-base disorders, Stewart approach, critical care, sepsis

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Patients with severe sepsis or septic shock admitted to the intensive care unit (ICU) present a wide variability of acid-base disorders, with metabolic acidosis being one of the most frequently observed . The presence of metabolic acidosis is connected with greater morbidity and mortality in the ICU [1]. Some of these patients suffer from abnormalities with co-existing metabolic acidosis and alkalosis. Generally, acid-base disorders are analyzed according to the so-called traditional concept, which includes the determination of the standard base excess (SBE), bicarbonate concentration in the plasma (HCO_3^-) and the anion gap (AG). When there is just one simple acid-base disorder present, the traditional concept is sufficient. On the other hand, it provides no detailed knowledge on the source of the problem [2]. The SBE is a calculated figure, derived from PaCO2 and arterial pH, whose calculation assumes normal plasma protein and electrolyte contents [3]. The AG derived from arterial gasometry ignores the role of the main nonbicarbonate buffers in the blood such as plasma proteins and inorganic phosphate. Thus, when electrolyte or protein abnormalities are present, which almost always is a problem in ICU patients, the traditional interpretation might be clinically misleading.

An alternative to this conventional model is the mathematical model based on physicochemical principles described by Stewart [4] and modified by Figge *et al.* [3, 5].

The model proposes that three variables determine pH in plasma by primarily changing the degree of water dissociation into hydrogen and hydroxide ions: the strong ion difference (SID, the difference between fully dissociated anions and cations), the $PaCO_2$, and the total weak acid concentration (consisting mainly of albumin and phosphate). According to Stewart, there may be five main metabolic acid-base derangements, that is: the strong ion gap acidosis (SIG acidosis), caused by the presence of unidentified anions; low SID acidosis (mainly hyperchloremic); high SID alkalosis (mainly hypochloremic and/or hypernatremic); acidosis caused by an increase in weak acid concentration (mainly phosphates); and alkalosis caused by low weak acid concentration (mainly hypoalbuminaemia) [6]. The Stewart method allows the clinician to quantify the individual components of acid-base abnormalities and provides an insight into their pathogenesis. Using physicochemical evaluation, a few studies have shown that the traditional approach often fails to identify acid-base disorders in the population of critically ill patients [6].

The debate is still ongoing and there are no conclusions which would suggest using one method over another, which displays the need for studies in this field. Therefore, the aim of our study was to compare the traditional approach and the physicochemical method of the Stewart analysis of acid-base disturbance in a population of ICU septic patients, with a special interest in quantifying the individual components of acid-base disorders.

METHODS

This observational study was conducted in a single, mixed medical and surgical adult ICU with 7 beds in a clinical hospital in Poland. It included 43 septic patients admitted to the ICU between June 2012 and July 2013. Patients were considered eligible for the study if they had a diagnosis of septic shock according to the current definition [7] and had all the necessary laboratory results in order to perform a mathematical analysis according to the Stewart approach. The study was approved by the institutional ethics committee. Because the blood tests and data collected in the study all comprised standard care, informed consent was waived. Demographic, clinical and laboratory data from admission to discharge of the patients were collected and the Acute Physiology and Chronic Health Evaluation II (APACHE) score was calculated. Some of the acid-base status variables were gained from an arterial blood gas analysis, that is: pH, paO_2, $paCO_2$, SBE, HCO_3, lactate and electrolyte concentration. In order, to analyse blood arterial gasometry, a Radiometer abl 90 flex gasometry analyser was used. Based on the SBE, metabolic acidosis was defined as SBE < –2 mEq L^{-1}; normal metabolic acid-base status was defined as SBE between –2 and 2; metabolic alkalosis was defined as SBE > 2 mEq L^{-1}. Some of the variables were calculated. The AG was calculated as follows: $AG = [Na^+] + [K^+] - [HCO3^-] - [Cl^-]$. The anion gap was corrected for the effect of an abnormal albumin concentration using the following formula: AGcorr = AG + + 0.25 × (40 — albumin in g L^{-1}) [8].

A physicochemical analysis was performed using the Stewart equations [4] modified by Figge *et al.* [3, 5] in order to consider the effects of plasma proteins. The Stewart approach takes into account the so-called Strong Ions Difference [SID], which is the difference between fully dissociated ions. This includes SIDa, meaning apparent SID, which was calculated as follows: $SIDa = [Na^+] + [K^+] + [Ca^{2+}] + [Mg^{2+}] - [Cl^-] - [lactate^-]$ (all concentrations in miliequivalents per litre).There is also SIDe, meaning effective SID, which is calculated as follows: $SIDe = 2.46 \times 10^{pH-8} \times paCO_2$ [mm Hg] + $[albumin^-] + [Pi^-]$. $[Albumin^-]$ should be calculated as follows: $[albumin^-] = [albumin] \times (0.123 \times pH - 0.631)$ and inorganic phosphate $[Pi^-]$ (millimolar): $[Pi^-] = [Pi] \times (0.309 \times pH - 0.469)$ [7]. The strong ion gap (SIG) which is the measure of the presence of unidentified anions [UA] was calculated as the difference between apparent SID and effective SID: SIG = SIDa – SIDe, which physiologically should be equal [4, 5]. A positive value was defined as representing the presence of UA, which must be included to account for the measured pH. A chloride to sodium ratio was also calculated, with SID acidosis being diagnosed when the Cl/Na ratio was > 0.75, while SID alkalosis was diagnosed when the Cl/Na ratio was < 0.75 [6]. Hypoalbuminemia was defined as a serum albumin concentration below 35 g L^{-1}. Hyperlactatemia was defined as lactate levels greater than 2 mmol L^{-1}.

Continuous data were presented as a mean with a standard deviation or median (Me) with a lower (Q_1) and upper quartile (Q_3), while ordinal data were presented as a number with a percentage. The results were analyzed statistically with the t-test and Mann-Whitney test (most data did not pass the Shapiro-Wilk normality test). A $P < 0.05$ was considered statistically significant.

RESULTS

Forty-three septic patients admitted to the ICU were included in the study. Their demographic and clinical data are presented in Table 1. Moreover, 990 arterial blood gas (ABG) samples were gained from these patients during their ICU stay, with an average of 23 ABGs per patient in order to analyse gas exchange status and acid-base disorders. The arterial blood gases were categorized into three groups according to the traditional approach, with SBE < –2 mEq L^{-1} categorized as metabolic acidosis, SBE in the range –2 – +2 mEq L^{-1} as normal acid-base status and SBE > 2 mEq L^{-1} as metabolic alkalosis. The number of samples which met the criteria of hyperlactatemia, hypoalbuminemia, SIG acidosis and elevated Cl/Na ratio for each of the subgroups is

Table 1. Demographic and clinical data. Presented as medians (Q_1-Q_3) or n (%) as otherwise indicated

Variable	Results
Age (years)	52 (39; 68)
Males	29 (67%)
Average of ABGs per patient [mean]	23
Days in the ICU	14 (8–22)
Survivors	35 (81%)
Medical/Surgical	27 (63%)/16 (37%)
APACHE II score	14 (10–24)
Body mass (kg)	70 (60–84)
Mechanical ventilation at admission	43 (100%)
Vasopressors at admission	43 (100%)
WBC (G L^{-1})	14.7 (10.8–19.4)
Serum creatinine (mg dL^{-1})	0.94 (0.62- 1.69)
CRP (mg dL^{-1})	127.5 (98.6–204.8)

APACHE — Acute Physiology and Chronic Health Evaluation; CRP — C-reactive protein; ICU — intensive care unit; Me — median; Q1 — lower quartile; Q3 — upper quartile

presented in Table 2. Taken all together, hypoalbuminemia was the most frequent disorder related to Stewart important acid-base disorders, and which was present in 99.6% of the analyzed samples. Low SID acidosis revealed by an increased Cl/Na ratio was the most frequent cause of acidosis, and which was present in 93.5% of the samples, while hyperlactatemia was revealed in 22.5% of the analyzed samples. Finally, 153 (15.5%) out of 990 ABG met the criteria of SIG acidosis according to the Stewart approach, proving the presence of unidentified anions.

An analysis of cases with hyperlactatemia > 2 mmol L^{-1} was performed by categorizing the results according to low/ /normal and elevated SBE values (< 2 mmol L^{-1} or > 2 mmol L^{-1}). 225 samples met the criteria of elevated lactate levels. We observed that 88 (39.1%) of arterial blood gases had SBE > 2 mmol L^{-1} despite elevated lactate levels. Patients with SBE > 2 had higher pH and bicarbonate values (7.34 ± 0.15 vs 7.4 ± ± 0.05; 21.38 ± 4.8 vs 28.17 ± 2.1, respectively, with $P < 0.0000001$). The most important parameters of acid-base status analysis for ABG with lactate > 2 mmol L^{-1} are presented in Table 3.

Table 2. Stewart important acid-base disorders in each of the subgroups. Presented as medians (Q_1-Q_3) or n (%)

	SBE < –2 mEq L^{-1}	–2 mEq L^{-1} < SBE < 2 mEq L^{-1}	SBE > 2 mEq L^{-1}
Number of samples	193	324	473
Patients with lactate > 2 mmol L^{-1}	67 (34.7%)	69 (21.3%)	87 (18.4%)
Patients with SIG acidosis	82 (42%)	48 (14.9%)	23 (5%)
Patients with albumins < 35 g L^{-1}	193 (100%)	324 (100%)	469 (99.1%)
Patients with Cl/Na > 0.75	187 (96.9%)	319 (98.4%)	420 (88.8%)
pH	7.35 (7.27–7.40)	7.45 (7.40–7.48)	7.47 (7.44–7.49)
$paCO_2$ (mm Hg)	36.7 (32.4–44.1)	35.5 (32.0–41.0)	39.4 (36.3–43.6)
SIDa (mmol L^{-1})	30.5 (27.1–33.6)	32 (29.6–34.0)	34.3 (32.4–36.2)
SIDe (mmol L^{-1})	29.1 (27.2–31.1)	32.7 (31.3–34.3)	36.6 (34.7–38.8)
Atot (mmol L^{-1})	8.5 (7.4–9.4)	8.3 (7.2–9.3)	8.0 (6.5–9.1)

SBE — standard base excess; SIG — strong ion gap; SIDa — apparent strong ion difference; SIDe — effective strong ion difference; Atot — weak acid concentration; Me — median; Q1 — lower quartile; Q3 — upper quartile

Table 3. Acid-base and electrolyte data for ABG with lactate > 2 mmol L^{-1}. Presented as means ± SD or medians (Q_1-Q_3)

Variable	BE < 2 mEq L^{-1}	BE > 2 mEq L^{-1}	*P* value
Sodium (mmol L^{-1})	136 (133–139)	135.4 (132–138)	0.34
Chloride (mmol L^{-1})	109 (105–111)	106 (102–110)	< 0.001
Phosphate (mmol L^{-1})	1.5 (1.0–1.8)	1 (0.9–1.3)	< 0.001
paCO2 (mm Hg)	40.4 ± 10.3	39.0 ± 6.9	0.36
Albumin (g L^{-1})	18.4 ± 4.5	19.0 ± 5.7	0.38
Urea (mg dL^{-1})	65 (26–83)	25 (15–46)	< 0.001
Lactate (mmol L^{-1})	3.1 (2.2–5.0)	2.4 (2.2–3.4)	< 0.001
Cl/Na	0.80 (0.78–0.81)	0.78 (0.76–0.79)	< 0.001
AGcorr (mmol L^{-1})	14.3 (11.6–17.6)	10.7 (9.0–12.6)	< 0.001
SIG (mmol L^{-1})	2.7 (0.5–5.3)	–0.2 (–1.6–1.7)	< 0.001

Agcorr — anion gap corrected for albumins; Me — median; Q1 — lower quartile; Q3 — upper quartile; BE — base excess; SIG — strong ion gap

DISCUSSION

The performed study revealed that intensive care unit patients may suffer from acid-base disorders despite having normal pH or SBE values. The Stewart approach, in comparison to the traditional equation, allowed one to discover the underlying acid-base derangements and to quantify them enabling appropriate treatment.

Nearly all patients in the analyzed subgroups of patients with BE < −2 mEq L^{-1}, BE between −2 and 2 mEq L^{-1} and BE > 2 mEq L^{-1} suffered from metabolic alkalosis caused by hypoalbuminemia and low SID acidosis caused by a decreased difference between strong ions, mainly sodium and chloride. This second derangement is often referred as hyperchloremic acidosis, as hyperchloremia seems to be a more frequent cause of decreased SID.

Hyperchloremia is a frequent cause of metabolic acidosis in critically ill patients. In children with diabetic ketoacidosis, hyperchloremia is the dominant metabolic component of the acidosis after 12 hours of treatment, comprising 98% of the base deficit and often slowing the recovery of metabolic acidosis in the patient [9]. Infusion of isotonic saline solution, which has equal concentrations of sodium and chloride (154 mmol L^{-1}), results in a reduction of SID, which, in turn, produces an increase in the number of hydrogen ions in order to preserve electrical neutrality [10]. Although studies of ICU patients have failed to detect a significant effect on survival attributable to hyperchloremic acidosis, hyperchloremia has been shown to cause hypotension, renal dysfunction, and increment in plasma cytokine levels [11]. Therefore, our finding that a normal SBE or pH values do not exclude the presence of low SID acidosis (mainly caused by hyperchloremia) may be clinically relevant.

Another important finding was the fact that in every subgroup of patients with BE < −2 mEq L^{-1}, BE between −2 and 2 mEq L^{-1} and BE >2 mEq L^{-1} there were episodes of SIG acidosis. Recently, Noritomi *et al.* [12] found that patients with severe sepsis and septic shock exhibit a complex metabolic acidosis at ICU admission, caused predominantly by hyperchloremia and unmeasured anions (UA) acidosis. The same results were presented by Mallat, with hyperchloraemia and SIG acidosis affecting 70% of analysed septic patients [13]. Despite the awareness of the existence of UA and SIG acidosis, the source and biochemical nature of UA are unclear. These anions may be generated in peripheral tissues during global hypoxic states [14]. In addition, it has been shown that the concentrations of anions normally associated with the Krebs acid cycle are elevated in the plasma of patients with high AG metabolic acidosis [15]. High (preresuscitation) SIG levels at ICU admission are known to be related to the presence of sepsis, as well as renal and hepatic dysfunction, and are also probably a marker of tissue hypoperfusion [16]. Some studies [17, 18] found a clear association between high SIG levels and mortality, whereas one study did not [19]. The prognostic significance of high SIG levels during admission is probably more relevant when preresuscitation values are measured [19]. However, considering its association with unfavourable outcomes 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 an apparently normal acid-base state may have clinical implications

Quite surprising might be the fact that patients with SBE in the reference range, or SBE > 2 mEq L^{-1}, had still a coexistence of metabolic acidosis (in some cases three acidotic derangements), with the net SBE > −2 mEq L^{-1} mainly caused by hypoalbuminemic metabolic alkalosis, and which was the most frequent derangement observed in our study.

Fencl *et al.* [6] has already demonstrated that SBE fails as a measure of metabolic acidosis in critically ill patients. In a study by Mallat *et al.* [13] low SID went unnoticed by changes in SBE because the low SID acidosis was masked by the alkalizing effect of hypoalbuminemia, present in all patients. 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 [1, 19], 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.

The analysis of the acid-base status of ABG samples with elevated lactate levels according to the Stewart method revealed the real reason as to why some of these samples had SBE > 2 mEq L^{-1}. While one may consider that the alkalotic SBE in the presence of increased lactate levels is probably caused by hypoalbuminemia, our study and those of others [20] do not confirm this, with albumin concentrations comparable in both SBE < 2 mEq L^{-1} and SBE > 2 mEq L^{-1} groups. However, we found that patients with SBE > 2 mEq L^{-1} had lower phosphate levels, with phosphate being one of the weak acids with acidotic properties. Another finding was higher urea concentrations and higher SIG values in the SBE < 2 mEq L^{-1} group. Thus, probably the organic acids present in the kidney failure and unidentified anions may be the reason for lower SBE values in those ABG samples.

The limitations of this study include the fact that as the analysed patients at the moment of admission to the ICU had already undergone some amount of fluid resuscitation,

catecholamin infusions and/or antibiotics, either in the operating theatre, emergency department or other ICUs, the APACHE II score or lactate levels probably had relatively low values. Furthermore, as the arterial blood gasometries analysed included samples taken from patients who had stayed in the ICU for more than one week, the electrolyte concentration in the serum and the acid-base disorder interpretation could have been affected by fluid therapy, renal replacement therapy, parenteral nutrition or diuretics administration during the ICU hospitalisation. The fact that all of the patients required mechanical ventilation, which allows one to manipulate minute ventilation and arterial carbon dioxide values, might have affected the metabolic compensation mechanisms. Nevertheless, the aim of the study was to compare two different interpretative models (the traditional and Stewart approaches) analysing the same ABG samples.

In conclusion, we believe that use of the Stewart model may improve our understanding of the underlying pathophysiological mechanisms that lead to important changes in the acid-base balance. It might seem reasonable to include electrolyte, albumin, lactate and phosphate concentrations in the analysis of acid-base disorders in ICU patients. Considering patients with metabolic acidosis according to traditional approach, the Stewart model gives us knowledge about the true etiology of the derangements. Furthermore, the Stewart model proves that despite normal pH and normal or alcalotic SBE values, patients may suffer from mixed arterial blood gas disorders with coexisting metabolic acidosis hidden under those normal values and unrevealed by the traditional approach.

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2. Source of founding — none.

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