Predictive value of serum bicarbonate, arterial base deficit/excess and SAPS III score in critically ill patients

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Abstract. Arterial base deficit/excess (BD/E) is commonly used marker of metabolic acidosis in critically ill patients, but requires an arterial puncture and blood gas analysis. We hypothesized that serum bicarbonate (HCO_3), which can be routinely obtained, strongly correlates with arterial BD/E and provides equivalent predictive information. In addition, we evaluated predictive value of simplified acute physiology score III (SAPS III). Total of 152 critically ill surgical patients were included in retrospective analysis. On admission to intensive care unit sets of simultaneously obtained paired laboratory data, including an arterial blood gas and serum chemistry panel with serum HCO_3 were obtained. Very strong correlation between BD/E and simultaneously measured serum HCO_3 levels was found ($r = 0.857$, $R^2 = 0.732$, $p < 0.01$). The serum HCO_3 level reliably identified a significant metabolic acidosis (AUC = 0.761, $p < 0.05$). BD and SAPS III were good predictors of mortality (AUCs 0.70 and 0.74, respectively). Serum HCO_3 may be used as substitute to detect severe metabolic acidosis. BD and SAPS III score were good predictors of mortality.

Key words: Serum bicarbonate — Base deficit — Critically ill — SAPS III score

Introduction

The association between acidosis and increase in multiple organ dysfunction and mortality for intensive care patients has been long known. To assist in the resuscitation of critically ill patients, clinicians have developed the concept of endpoints of therapy or resuscitation, most importantly in the early stage of critical illness (Rivers et al. 2007). One of the most commonly used endpoints of therapy or resuscitation is arterial base deficit/excess (BD/E). Despite acid-base imbalance being an integral aspect of ongoing pathologic processes in a large number of critically ill patients, the importance of understanding the fundamental principles behind the physiology has been largely ignored. Measurement of the standard bicarbonate and BD/E has been used

for decades as indicators of metabolic acid-base disturbances (Rhodes and Cusack 2000). The standard bicarbonate is the concentration of bicarbonate (HCO_3) in the plasma when the hemoglobin in the whole blood has been fully oxygenated, at a temperature of $37^{\circ}C$ and corrected to arterial partial pressure of CO_2 ($PaCO_2$) of 40 mm Hg (5.33 kPa). These corrections remove the influence of the respiratory component upon measurement. BD/E is directly calculated from the blood gas analyzer from $PaCO_2$, pH and serum HCO_3 values as applied to a standard nomogram and represents the amount of acid or base required to normalize the pH in a liter of blood. Unfortunately, BD/E determination generally requires an arterial puncture and often necessitates multiple arterial punctures or placement of an indwelling arterial catheter. This procedure is painful, invasive, costly and can be associated with complications such as infection, pseudoaneurysm, distal embolization, and, in rare cases, hand or limb loss. Moreover, arterial blood gas measurement is not routinely performed in all intensive care unit (ICU) patients early enough, that fact could result in a failure or delay in the

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diagnosis of significant acidosis. The increased concentrations of plasma hydrogen ions with metabolic acidosis are buffered by a variety of homeostatic mechanisms, including plasma bicarbonates (Kellum 2000). Serum HCO_3 levels have been shown to decrease in a linear fashion with increasing acid load and theoretically should provide information similar to the arterial BD/E (Sterns 2003; Wiederseiner et al. 2004). Also, serum bicarbonate is routinely obtained as a part of chemistry panel on most ICU admissions, it does not require any separate equipment to perform analysis, and does not require arterial puncture or catheterization. We hypothesized that serum HCO_3 strongly correlates with arterial BD/E and provides equivalent predictive information.

In addition, simplified acute physiology score III (SAPS III) (Moreno et al. 2008) on ICU admission and SAPS II (Le Gall et al. 1993), sepsis-related organ failure assessment (SOFA) score (Moreno et al. 1999) and acute physiology and chronic health evaluation score II (APACHE II) (Knaus et al. 1985) at 24 h after ICU admission were calculated and recorded.

SAPS III is newly developed score and it was design to empirically test, based on a large multicenter multinational database, whether a modified PIRO (predisposition, insult, response and organ dysfunction) concept could be applied to predict mortality in patients with infection and sepsis and our objective was to determine its predictive value in critically ill patients and to compare this score with SAPS II, SOFA and APACHE II scores.

Materials and Methods

This study was designed as a retrospective analysis to compare the use of serum HCO_3 levels with the standard measure of arterial BD/E in a surgical ICU population. Four hospitals were included; all of them were tertiary care facilities. About one quarter of patients were transferred from other hospitals where they were previously treated but failed to improve, and developed severe complications. The study population included adult (>18 years) patients admitted to the surgical ICU from January 2007 to August 2008. They were admitted by either Emergency Departments or one of the general surgical specialty services with one of the following diagnosis: peritonitis, pancreatitis, pneumonia and all were in ICU longer than 24 h. Reason for the admission of patients with pneumonia in surgical ICU was severe complication of pneumonia (gangrenous lesions) which required thoracic surgical treatment.

Patients who met the foregoing criteria and had at least 1 simultaneously drawn arterial blood gas determination (with BD/E) and serum chemistry panel (with HCO_3) were included. The SAPS III on ICU admission, SAPS II, APACHE II and SOFA score at 24 h after ICU admission

were calculated and recorded. The correlation between HCO_3 and BD/E was assessed by calculation of the Pearson correlation coefficient r and coefficient of determination R^2, and linear regression analysis was used to develop a predictive equation for BD. The predictive ability of HCO_3 and pH of severe metabolic acidosis and predictive ability of BD, base excess, HCO_3, pH and four above mentioned scores of mortality were examined by calculating the area under the receiver operating characteristic curve (AUC). Severe metabolic acidosis is defined as BD greater than –5, for example –6, –7 etc. Linear variables are reported as the mean value ±1 SD and AUC with 95% confidence intervals. All statistical analysis was performed with SPSS 12.0 for Windows (SPSS Inc., Chicago, IL, USA) and statistical significance was set at $p < 0.05$. This study was reviewed and approved with waiver of informed consent by the hospital's institutional review boards.

Results

In this study total of 152 critically ill surgical patients were included. In all of them, on admission to ICU, sets of simultaneously obtained paired laboratory data, including an arterial blood gas and serum chemistry panel with serum HCO_3 were obtained. The patient's demographics are shown in Table 1.

All patients with pneumonia were male, frequency of pancreatitis was 5-fold higher in males, numbers of male and female patients with peritonitis were similar (42 and 39, respectively). Overall ICU mortality rate was 73.7%, but it varied according to diagnosis: peritonitis 81.5%, pancreatitis 67.2% and pneumonia 50%. Mechanical ventilation was most

Table 1. Patient demographics

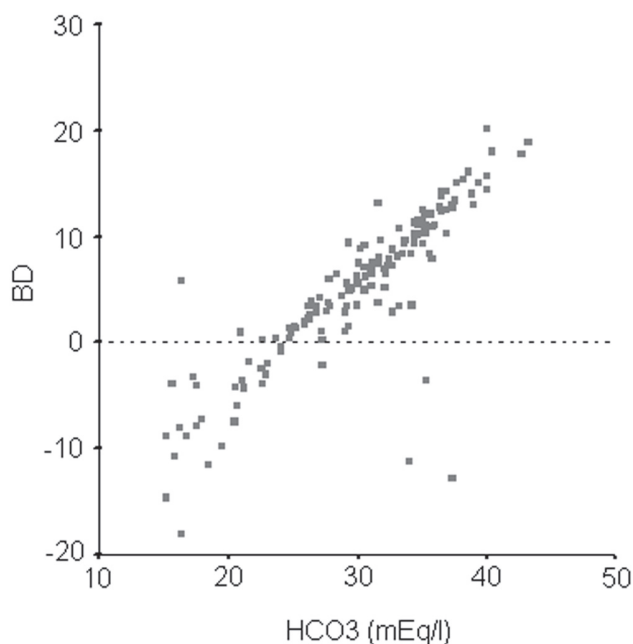| Characteristic	Finding
Patients	152
Age (years)[a]	62.4 ± 13.7
Sex (%) Male Female	103 (67.8) 49 (32.2)
Mechanical ventilation (%)	82 (54)
SAPS II[a]	39.66 ± 11.12
APACHE II[a]	17.19 ± 5.78
SOFA[a]	5.32 ± 3.05
SAPS III[a]	62.34 ± 10.36
Reason for ICU admission (%) Peritonitis Pancreatitis Pneumonia	81 (53.3) 61 (40.1) 10 (6.6)
ICU mortality (%)	112 (73.7)

[a] mean ± SD.

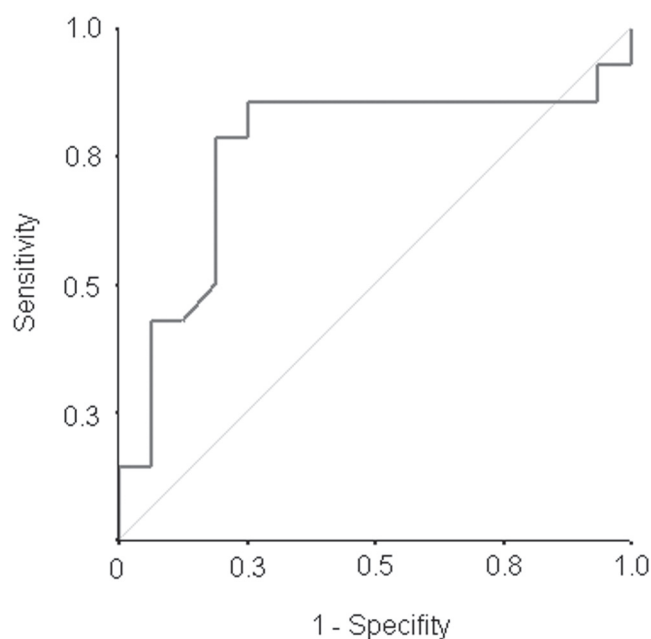**Figure 1.** Scatterplot of the admission BD/E vs. the admission serum HCO_3 level.

Figure 2. Receiver operating characteristic curve for the prediction of significant metabolic acidosis (BD < –5) by serum HCO_3 level.

frequently performed in patients with pneumonia (70%), then in patients with peritonitis (67.9%) and pancreatitis (30%) with statistically highly significant difference (Pearson Chi-square test: 18.379, p <0.01).

Table 2 shows the mean relevant laboratory and score values for study population according to diagnosis on admission. Statistical analysis (ANOVA) showed statistically significant to highly significant difference.

Correlation and regression analysis demonstrated a very strong correlation between the arterial BD/E and simultaneously measured serum HCO_3 levels. Fig. 1 shows the strong linear correlation between the BD/E and serum HCO_3 level drawn at the time of ICU admission with a correlation coefficient r of 0.857 (R^2 = 0.732, p < 0.01).

The regression equation derived from this analysis allows prediction of the arterial BD/E from the serum HCO_3 level by the following formulas: BD = 0.125 – (8.9 × HCO_3) and base excess = 0.885 – (20.296 × HCO_3).

From these equations, two important cutoff points for clinical use would be a serum HCO_3 level of 20.3 mEq/l, which equals a BD/E of 0, and serum HCO_3 level of 17 mEq/l, which equates to a BD of –5.

Assessment of accuracy and reliability of serum HCO_3 level for the identification of significant metabolic acidosis (BD greater than –5) and comparison with other conventional measures of acidosis such as pH was performed. The serum HCO_3 level reliably and accurately identified the presence of a significant metabolic acidosis, with AUC of 0.761 (p < 0.05). Cutoff point of 20 mEq/l had sensitivity of 78.6% and specificity of 75%. Values lower than 20 mEq/l suggested that significant metabolic acidosis is present and *vice versa* (Fig. 2).

Table 2. Mean relevant laboratory and score values for study population according to diagnosis on admission

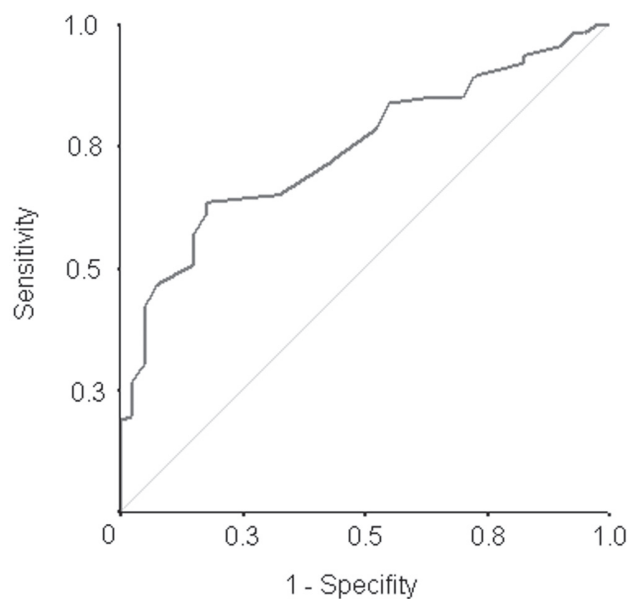|	Peritonitis	Pancreatitis	Pneumonia	p
pH	7.44 ± 0.10	7.46 ± 0.05	7.38 ± 0.06	<0.05
HCO_3 (mEq/l)	30.45 ± 6.64	30.45 ± 5.71	23.63 ± 6.98	<0.01
BD/E	5.11 ± 8.06	6.45 ± 5.98	–0.09 ± 6.85	<0.05
SAPS II	43.56 ± 7.84	33.93 ± 12.86	43.00 ± 7.38	<0.01
APACHE II	20.02 ± 4.93	13.05 ± 4.19	19.50 ± 5.80	<0.01
SOFA	6.00 ± 3.33	4.23 ± 2.41	6.50 ± 2.27	<0.01
SAPS III	64.48 ± 11.68	59.05 ± 7.94	65.10 ± 6.77	<0.01

Figure 3. Receiver operating characteristic curve for outcome prediction by SAPS III.

Various laboratory and score values were then analyzed for their ability to predict mortality. The receiver operating characteristic curves for mortality prediction demonstrated that the arterial BD performed better than base excess, serum HCO_3 and pH. For BD, AUC was 0.70, with sensitivity of 82% (chance of dying: 8 out of 10) and specificity of 63% (chance of survival) for cutoff point of –8.3. In those patients (with BD) AUC for serum HCO_3 was 0.67, with sensitivity of 91% and specificity of 63% for cutoff point of 17 mEq/l. In patients with base excess, AUC for BE was 0.64, with sensitivity of 60% and specificity of 60% for cutoff point of 7.7. In the same group of patients AUC for serum HCO_3 was 0.64, with sensitivity of 60% and specificity of 65% for cutoff point of 32 mEq/l. pH value is not good predictor of outcome, AUC was 0.54.

Nonsurvivors were older, had a higher SAPS II, SAPS III, APACHE II and SOFA scores, pH, HCO_3 and lower BD

Table 3. Comparison of survivors and nonsurvivors

Variable	Survived ($n = 40$)	Died ($n = 112$)	p
Age (years)	55.1 ± 13.1	64.9 ± 13.0	<0.01
pH	7.43 ± 0.12	7.45 ± 0.07	n.s.
HCO_3 (mEq/l)	28.62 ± 6.00	30.49 ± 6.61	n.s.
BD	-11.55 ± 4.02	-9.14 ± 2.39	n.s.
SAPS II	33.50 ± 9.80	41.86 ± 10.76	<0.01
APACHE II	12.88 ± 4.40	18.73 ± 5.44	<0.01
SOFA	3.65 ± 1.54	5.91 ± 3.23	<0.01
SAPS III	55.98 ± 6.69	64.62 ± 10.51	<0.01

at the time of ICU admission compared to survivors (Table 3).

The receiver operating characteristic curves for mortality prediction demonstrated that the all four scores performed well as predictors of outcome ($p < 0.01$). For SAPS II, AUC was 0.71, with sensitivity of 66% and specificity of 63.5% for cutoff point of 36.5. For APACHE II, AUC was 0.79, with sensitivity of 85% and specificity of 63% for cutoff point of 13.5. For SOFA, AUC was 0.72, with sensitivity of 60% and specificity of 73% for cutoff point of 4.5. For SAPS III, AUC 0.74, with sensitivity of 61% and specificity of 83% for cutoff point of 60 (Fig. 3).

Discussion

Systemic arterial pH is maintained between 7.35 and 7.45 by extracellular and intracellular chemical buffering together with respiratory and renal regulatory mechanisms. The control of $PaCO_2$ by central nervous system and respiratory system and the control of the plasma bicarbonate by the kidneys stabilize the arterial pH by excretion or retention of acid or alkali. The metabolic and respiratory components that regulate systemic pH are described by the Henderson-Hasselbalch equation. Under most circumstances, CO_2 production and excretion are matched, and the usual steady-state $PaCO_2$ is maintained at 40 mm Hg. The development of metabolic acidosis is a common occurrence during critical illness (DuBose 2005). Early and accurate identification and correction of significant metabolic acidosis are particularly relevant to patients in the surgical ICU. But arterial blood gas sampling carries all the risks associated with arterial puncture. Contraindications to this procedure are numerous: cellulites or the infections over the radial artery, absence of palpable radial artery pulse, various coagulopathies, history of arterial spasms following previous punctures, severe peripheral vascular disease, arterial graft (Rodriguez Montalban et al. 2000; Crawford 2004; Wallach 2004). Particular attention should be paid to negative results of an Allen test (collateral circulation test), indicating that only one artery supplies the hand. In that case, another extremity as the site for arterial puncture should be selected. The substitution of an easily measured value from a venous sample, such as the serum HCO_3, would overcome most of these drawbacks if it provided clinical information equivalent to the arterial BD/E.

There are only several published studies examining the utility of using the serum HCO_3 to provide information equivalent to arterial BD/E in the ICU. The most important two studies were performed by Martin (in surgical ICU) and FitzSullivan (in trauma ICU) with co-workers (FitzSullivan et al. 2005; Martin et al. 2005). Martin found that serum HCO_3 levels showed significant correlation with arterial

BD levels both at admission ($r = 0.85$, $R^2 = 0.72$, $p < 0.01$) and throughout the ICU stay ($r = 0.88$, $R^2 = 0.77$, $p < 0.01$). He concluded that serum HCO_3 reliably predicted the presence of significant metabolic acidosis (BD greater than –5) with an AUC of 0.93 at admission ($p < 0.01$), outperforming pH, anion gap and lactate and that admission serum HCO_3 level predicted ICU mortality as accurately as the admission arterial BD (AUCs of 0.68 and 0.70, respectively) and more accurately than either admission pH or anion gap. Our study showed similar findings. We found strong linear correlation between the BD/E and serum HCO_3 level at ICU admission ($r = 0.857$, $R^2 = 0.732$, $p < 0.01$). Also, in our study serum HCO_3 level reliably and accurately identified the presence of significant metabolic acidosis (BD greater than –5) with an AUC of 0.761 at admission ($p < 0.05$), outperforming pH. FitzSullivan presented similar results in trauma patients: serum HCO_3 showed a significant linear correlation with BD ($r = 0.80$, $p < 0.01$) on admission, and reliably predicted the presence of significant metabolic acidoses, with an AUC of 0.96 ($p < 0.01$). Unlike Martin's and FitzSullivan´s study, in our investigation difference in BD and serum HCO_3 levels between survivors and nonsurvivors did not reach statistical significance. Eachempati with co-workers (2003) also performed the study in which correlation of serum bicarbonate with BD in a cohort of surgical ICU patients was evaluated. They found strong linear inverse correlation between two measures ($r = 0.91$, $R^2 = 0.83$, $p < 0.01$).

But, critically ill patients might present complex acid-base disorders, even when the pH, $PaCO_2$, HCO_3 and BD/E levels are normal. Lactic acidosis is primarily suspected because of presence of metabolic acidosis. Nevertheless, serum HCO_3 and BD/E levels might be normal despite the presence of hyperlactatemia, as a result of simultaneous alkalinizing processes that normalize the BD/E. Three widely accepted methods are used to analyze and classify acid-base disorders, yielding mutually compatible results. The approaches differ only in assessment of the metabolic component (i.e., all three treat $PaCO_2$ as an independent variable): 1. HCO_3 concentration; 2. standard base excess; 3. strong ion difference (SID). All three yield virtually identical results when used to quantify the acid-base status of a given blood sample. There are three mathematically independent determinants of blood pH. First, there is the difference between the sum of the concentrations of strong cations (e.g., Na^+ and K^+) and the sum of the concentrations of strong anions (e.g. Cl^-, lactate); this difference is called the SID. Second, the total weak acid buffers concentration (A_{tot}), which is mostly composed of the concentrations of albumin and phosphate and third is $PaCO_2$. Only these three variables can independently affect blood pH (Stewart 1993). Concentrations of H^+ and HCO_3^- are dependent variables, being functions of SID, A_{tot} and $PaCO_2$. Changes in plasma H^+ concentrations occur as a result of changes in the dissociation of water and

A_{tot} brought about by the electrochemical forces produced by changes in SID and $PaCO_2$. The standard base excess is mathematically equivalent to the change in SID required to restore pH to 7.4 given a $PaCO_2$ of 40 mm Hg and the prevailing A_{tot}. Thus, a standard base excess of –10 mEq/l means that the SID is 10 mEq/l less than the SID that is associated with a pH of 7.4 when $PaCO_2$ is 40 mm Hg (Kellum 2005). Fencl and colleagues (2000) showed that in 152 critically ill patients, Stewart's (1983) approach could detect metabolic acidosis in some patients with normal HCO_3 and BD/E level. In those patients, the metabolic acidosis with a low SID was counterbalanced by alkalinizing processes. Low SID was undetected through changes in BD/E because the low SID acidosis was masked by the alkalinizing effect of hypoalbuminemia present in all patients. This study also showed that the traditional analysis frequently failed to identify severe metabolic acidosis. But, concept of "primary hypoproteinemic alkalosis" in hypoalbuminemic ICU patients with positive BE and elevated HCO_3 levels were recently challenged (Dubin et al. 2007). Tuhay and colleagues (2008) found that 20% of the critically ill patients with severe hyperlactatemia showed normal pH, HCO_3, BD/E and SID levels because of the simultaneous presence of hypochloremic metabolic alkalosis. Nevertheless, the presence of metabolic acidosis in critical patients has prognostic implications. Gunnerson and colleagues (2006) demonstrated that patients with metabolic acidosis (BD greater than –2) had a higher mortality rate than those without this disorder: 45% versus 25%. Some authors stated that the relationship between the bicarbonate and BD/E is only valid if the pH is held constant, that is the case when patients have preserved at least some of the compensatory mechanisms to correct acid-base disorders (Lujan and Howard 2006). In our study, pH changed very little, there was not even significant difference in pH between survivors and nonsurvivors.

SAPS III score performed well as predictor of outcome (AUC 0.74), slightly better than SAPS II (AUC 0.70) and SOFA (AUC 0.72), but slightly worse than APACHE (AUC 0.79). So, SAPS III could be used by physicians to stratify patients at ICU admission or shortly thereafter, contributing to a better selection of treatment regimen according to the risk of death. Mortality rates in our patients were somewhat higher than expected in critically ill patients. We believe that the main reason for this difference is the fact that about one quarter of patients were transferred from other hospitals where they were previously treated but failed to improve, and developed severe complications. That means that precious time for their optimal treatment was lost, so in spite of all our efforts, mortality rate was high.

In conclusion, in our study serum HCO_3 may be used as substitute to detect severe metabolic acidosis because there is a strong linear correlation with arterial BD/E. But, it has

to be done with a caution because critically ill patients might present complex acid-base disorders, even when the pH, $PaCO_2$, HCO_3 and BD/E levels are normal.

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