

## Original article

# Clinical Significance of Strong Ion Gap : between ICU and Hemodialysis Patients with Metabolic Acidosis

Young Sook Lee, M.D.

Department of Internal Medicine, Eulji University Hospital, Daejeon, Korea

Metabolic acidosis is the most frequent acid-base disorder in critically ill patients and dialysis patients. This study is to compare the conventional approach with the physicochemical approach between the intensive care unit (ICU) and hemodialysis (HD) patients. Fifty-seven ICU patients and 33 HD patients were enrolled. All data sets included simultaneous measurements of arterial blood gas with base deficit (BD), serum electrolytes, albumin, lactate, and calculated anion gap observed (AGobs). Physicochemical analysis was used to calculate the albumin and lactate-corrected anion gap (AGcorr), the base deficit corrected for unmeasured anions (BDua), the strong ion difference apparent (SIDa), the strong ion difference effective (SIDE), and the strong ion gap (SIG). The SIDa ( $37.5 \pm 5.3$  vs  $33.9 \pm 9.0$ ,  $p=0.045$ ) and SIG ( $12.3 \pm 5.3$  vs  $8.6 \pm 8.8$ ,  $p=0.043$ ) was significantly higher in the HD group than the ICU group. SIG in the ICU group showed the highest correlation coefficient with AGobs, whereas SIG in the HD group with AGcorr. Concerning the contributions of the three main causes of metabolic acidosis, increased SIG was comparable between the ICU and HD group ( $n=48$ , 90.6% vs  $n=30$ , 93.8%), whereas hyperlactatemia ( $n=9$ , 17.0% vs  $n=0$ , 0%) and hyperchloremia ( $n=20$ , 35.1% vs  $n=2$ , 6.1%) was significantly increased in the ICU group compared with the HD group. Multiple underlying mechanisms are present in most of the ICU patients with metabolic acidosis compared with the HD patients. In conclusion, the physicochemical approach can elucidate the detailed mechanisms of metabolic acidosis in ICU and HD patients compared with conventional measures.

**Key Words :** Acidosis, Intensive care units, Hemodialysis

## Introduction

Acid-base disturbances, especially metabolic acidosis are common in severely injured and critically ill patients. Conventional measures, such as anion gap and base deficit are calculated values that are used to identify the presence and degree of acidosis and to guide corrective therapy. Physicochemical analysis is

an alternative approach based on the principles of electroneutrality and conservation of mass, and may be accurate for defining the presence and type of acidosis and unmeasured anions.

We sought to apply these physicochemical principles to analyze the acid-base status of the intensive care unit (ICU) patients and hemodialysis (HD) patients and compare the results with conventional analysis between the ICU and HD group.

## Materials and Methods

We studied the ICU and HD patients with metabolic acidosis at Eulji University Hospital from the

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Corresponding author : Young Sook Lee, M.D.

Department of Internal Medicine, Eulji University Hospital,  
143-5 Yongdu-dong, Jung-gu, Daejeon, 301-832, Korea

Tel : +82-42-611-3162 Fax : +82-42-611-3853

E-mail : visionjcys@eulji.ac.kr

first of August 2006 to the 31st of August 2006.

The study was approved by the ethical committee of the Eulji University Hospital and written informed consent was obtained from patients and legal representatives.

Patients with metabolic acidosis were identified from the fasting venous and arterial blood samples. The hemodialysis patients with metabolic acidosis were identified from the pre-hemodialysis fasting venous and arterial blood samples.

Serum chemistry, serum electrolyte, and serum magnesium were measured using standard laboratory techniques. Plasma lactate concentrations were determined by an enzymatic method (Cobas, Switzerland) with reference value 0.5–2.2 mmol/L, detection limit 0.2 mmol/L.

Hyperchloremia was defined as serum chloride concentration of  $\geq 110$  mmol/L, and hyperlactatemia as serum lactate concentration of  $>2$  mmol/L.

### Physicochemical Approach (Stewart Method)

\* Anion gap observed (AGobs) =  $(\text{Na} + \text{K}) - (\text{Cl} + \text{HCO}_3^-)$

\* albumin corrected anion gap (AGalb-corr) = AGobs + 2.5 (4.5 - albumin)

\* albumin and lactate-corrected anion gap (AGcorr) = AGobs + 2.5 (4.5 - albumin) - lactate

\* Base deficit corrected for unmeasured anions (BDua)

: The base-deficit (BD) was calculated as the negative of the standard base-excess reported from the blood gas analyzer (8). Base deficit (BD) was corrected for free water, chloride, and albumin concentration.

:  $\text{BDua} = \text{BD} - (\text{BE}_{\text{fw}} + \text{BE}_{\text{cl}} + \text{BE}_{\text{alb}})$

=  $\text{BD} - 0.3 \times (\text{Na} - 140) - [102 - (\text{Cl} \times 140 / \text{Na})] - 3.4 \times (4.5 - \text{alb})$

\* Strong ion difference apparent (SIDa) is simply the difference between the activity of all abundant cations ( $\text{Na}^+$ ,  $\text{K}^+$ ,  $\text{Mg}^{2+}$ ,  $\text{Ca}^{2+}$ ) and the activity of all abundant anions ( $\text{Cl}^-$ , lactate, urate). Normally this difference is approximately 40 mEq/L.

:  $\text{SIDa} = \text{Na}^+ + \text{K}^+ + \text{Mg}^{2+} + \text{Ca}^{2+} - \text{Cl}^- - \text{lactate} - \text{urate} - [\text{UA}^-]$

(all in mEq/L)

In this equation,  $[\text{UA}^-]$  represents the concentration of the unidentified strong anions (e.g. ketoacids, lactate and exogenous substances etc.). Since urate is typically not an important factor ( $<0.2$  mEq/L), it is usually omitted.

-  $\text{Cl}_{\text{cor}} = \text{Cl}_{\text{measured}} \times (\text{Na}_{\text{normal}} / \text{Na}_{\text{observed}}) = \text{Cl}_{\text{measured}} \times (142 \text{ mEq/L} / \text{Na}_{\text{observed}})$

- In this study, we used  $\text{SIDa} = \text{Na}^+ + \text{K}^+ + \text{Mg}^{2+} + \text{Ca}^{2+} - \text{Cl}^- - \text{lactate}$ , simplified  $\text{SIDa} = \text{Na}^+ + \text{K}^+ - \text{Cl}^- - \text{lactate}$ .

\* Strong ion difference effective (SIDE) is given by the relationship of pH,  $\text{CO}_2$ , phosphate, and protein. Therefore, [SIDE] is a measure of the remaining anions, (ie, normally  $-40$  mEq/L). Serum albumin and inorganic phosphate mainly represented total concentrations of the weak nonvolatile weak acids (Atot).

$\text{SIDE} = \text{HCO}_3^- + \text{Atot}$

=  $\text{HCO}_3^- + \text{albumin} + \text{PO}_4^-$

=  $\text{HCO}_3^- + [\text{alb} \times (0.123 \times \text{pH} - 0.631)] +$

$\text{phos} \times (0.309 \times \text{pH} - 0.469)]$

=  $[1000 \times 2.46 \times 10^{-11} \times \text{pCO}_2 / 10^{-\text{pH}}] +$

$[\text{alb} \times (0.123 \times \text{pH} - 0.631)] +$

$\text{phos} \times (0.309 \times \text{pH} - 0.469)]$

\* Strong ion Gap (SIG) = SIDa - SIDE

Both the BD and SIG become more positive as the concentration of unmeasured- anions increases.

### Statistical analysis

Data were collected from patient charts and the hospital computer system. All statistical analyses were performed using software from SPSS 11.5. Data are presented as mean  $\pm$  SD. Statistical analysis was performed using the student's t-test and chi-square test where appropriate. A p-value  $<0.05$  was considered statistically significant.

### Results

Fifty-seven ICU patients and 33 HD patients were enrolled in this study. Patients characteristics, acid-

base and electrolyte data for the study population are presented in Table 1. The ICU patients showed significantly higher pH ( $7.425\pm0.089$  vs  $7.360\pm0.043$ ) with lower  $pCO_2$  ( $33.5\pm6.3$  vs  $38.3\pm4.0$ ) and lower base deficit ( $1.6\pm3.9$  vs  $3.8\pm2.9$ ) compared with the HD patients (Table 1). But, the base deficit corrected for unmeasured anions (Bdua) was comparable between the two groups. The HD patients showed higher BUN, creatinine, cholesterol, glucose, albumin, calcium, phosphorus, uric acid, magnesium, and potassium, except for lower chloride and median hsCRP compared with the ICU patients (Table 1).

Anion gap observed (AGobs), albumin-corrected AG, and albumin and lactate-corrected AG were sig-

nificantly decreased in the ICU group ( $12.6\pm3.3$ ,  $16.0\pm2.9$  and  $14.8\pm3.0$  respectively) compared with the HD group ( $17.7\pm3.8$ ,  $19.4\pm3.3$  and  $18.4\pm3.4$  respectively) ( $p=0.000$ , Fig. 1).

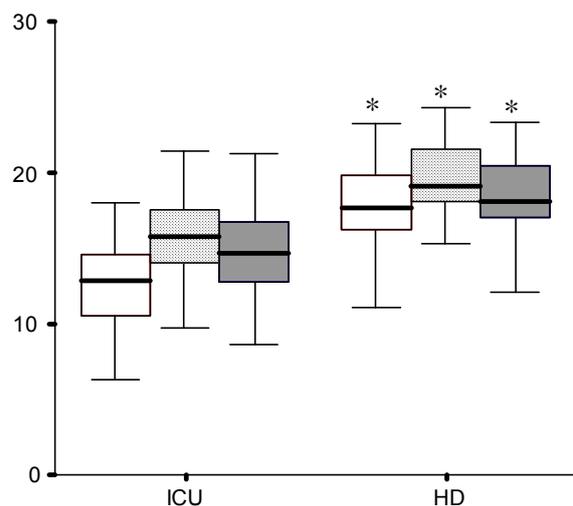
AGobs was significantly correlated with AGalb-corr and AGcorr in both groups, but the correlation coefficients for the ICU group were decreased when the serum lactate levels were used together (AGcorr) (Fig. 2).

The strong ion difference apparent (SIDa) was significantly higher in the HD group than the ICU group ( $37.5\pm5.3$  vs  $33.9\pm9.0$ ,  $p=0.045$ , Fig. 3). On the other hand, the strong ion difference effective (SIDE) was comparable between the ICU and HD group ( $24.7\pm3.5$  vs  $25.2\pm2.9$ ). Therefore, the strong ion gap (SIG) was significantly higher in the HD group than the ICU group ( $12.3\pm5.3$  vs  $8.6\pm8.8$ ,  $p=0.043$ , Fig. 4). SIG in ICU group showed the highest correlation coefficient with AGobs, whereas SIG in HD group with AGcorr (Table 2).

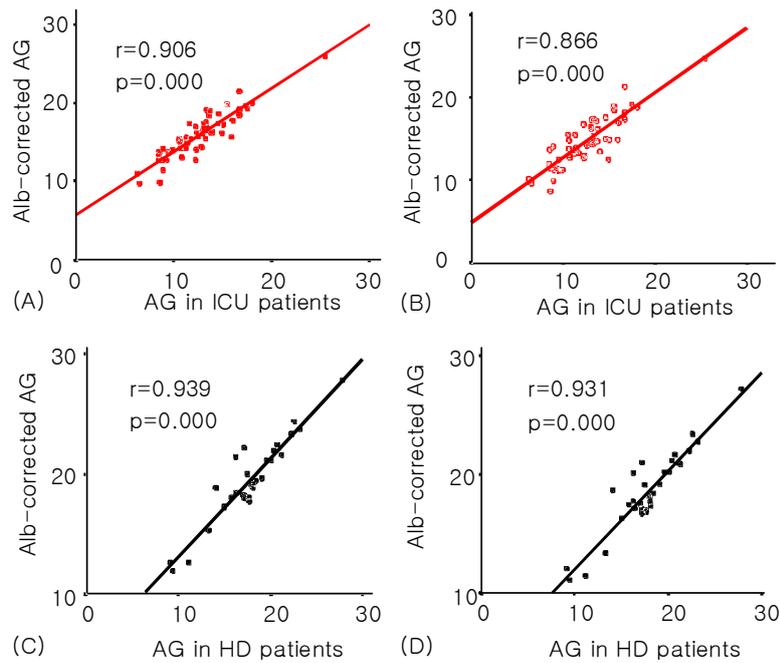
The contributions of the three main causes of metabolic acidosis (hyperchloremia, hyperlactatemia, and increased levels of other unmeasured strong anions) were presented in Table 3. Increased SIG was comparable between the ICU group ( $n=48$ , 90.6%) and the

**Table 1. Patients' Baseline Characteristics**

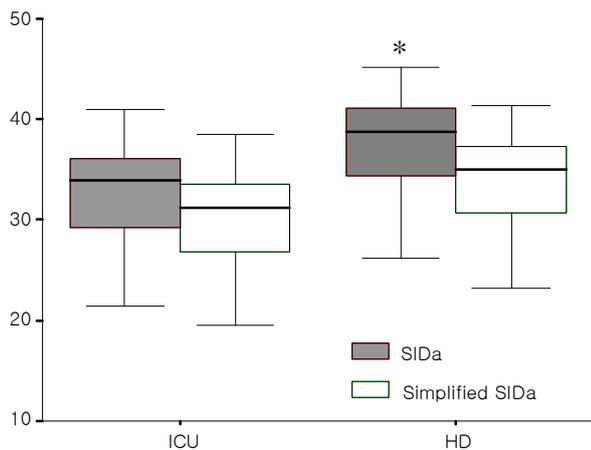
	ICU patients (n=57)	HD patients (n=33)	p-value
pH	$7.425\pm0.089$	$7.360\pm0.043$	0.000
$pCO_2$ (mmHg)	$33.5\pm6.3$	$38.3\pm4.0$	0.000
$pO_2$ (mmHg)	$109.5\pm28.5$	$102.6\pm16.5$	NS
BE (mEq/L)	$-1.6\pm3.9$	$-3.8\pm2.9$	0.008
$HCO_3^-$ (mEq/L)	$22.1\pm3.5$	$21.2\pm2.8$	NS
Base deficit (BD)	$1.6\pm3.9$	$3.8\pm2.9$	0.008
Bdua	$4.03\pm6.64$	$5.81\pm5.57$	NS
Age (yrs)	$62.4\pm17.2$	$55.2\pm11.5$	0.02
Male (%)	34 (59.6%)	17 (51.5%)	NS
Hb (g/dl)	$10.7\pm1.9$	$10.7\pm1.6$	NS
Hct (%)	$30.6\pm5.2$	$31.5\pm4.9$	NS
BUN (mg/dL)	$19.7\pm12.0$	$69.0\pm19.7$	0.000
Creatinine (mg/dL)	$0.9\pm0.4$	$8.4\pm2.8$	0.000
Cholesterol (mg/dL)	$124.4\pm46.8$	$158.3\pm39.5$	0.000
Glucose (mg/dL)	$152.8\pm41.1$	$126.6\pm79.5$	NS (0.085)
Albumin (g/dL)	$3.16\pm0.56$	$3.83\pm0.53$	0.000
Calcium (mg/dL)	$7.41\pm0.65$	$8.45\pm0.72$	0.000
Phosphorus (mg/dL)	$2.93\pm1.01$	$4.98\pm1.72$	0.000
Uric Acid (IU/L)	$3.38\pm1.48$	$7.76\pm1.56$	0.000
Magnesium (mg/dL)	$1.88\pm0.39$	$3.12\pm0.38$	0.000
Sodium (mEq/L)	$139.4\pm8.5$	$136.6\pm4.4$	NS (0.081)
Potassium (mEq/L)	$3.7\pm0.6$	$5.1\pm0.9$	0.000
Chloride (mEq/L)	$108.4\pm8.6$	$102.8\pm5.9$	0.001
Total $CO_2$ (mmol/L)	$22.2\pm4.0$	$20.7\pm3.3$	NS
Mean of Lactate (mg/dL)	$10.8\pm9.0$	$9.0\pm3.3$	NS
Median of Lactate (mg/dL)	10.3	8.55	NS (0.088)
Mean of hsCRP (mg/dL)	$6.33\pm6.59$	$1.47\pm2.77$	0.000
Median of hsCRP (mg/dL)	2.80	0.30	0.000



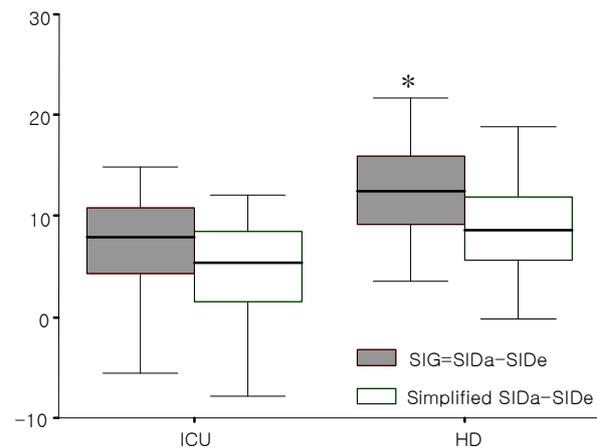
**Fig. 1.** Box and whisker plots for Anion Gap observed (AGobs, white box), albumin-corrected AG (AGalb-corr, dotted box), and albumin and lactate-corrected AG (AGcorr, gray box) between the ICU and HD patient group. \* $p<0.000$  vs. ICU patient group.



**Fig. 2.** Correlation of Anion Gap observed (AGobs) with albumin-corrected AG (AGalb-corr) and albumin and lactate-corrected AG (AGcorr) in the ICU (A, B) and HD (C, D) patient group.



**Fig. 3.** Box and whisker plots for Strong Ion Difference apparent (SIDa, gray box) and simplified SIDa (white box) between the ICU and HD patient group. \* $p=0.045$  vs. ICU patient group.



**Fig. 4.** Box and whisker plots for Strong Ion Gap (SIG=SIDa-SIDe, gray box) and simplified SIDa-SIDe (white box) between the ICU and HD patient group. \* $p=0.043$  vs. ICU patient group.

HD group (n=30, 93.8%). Hyperlactatemia (n=9, 17.0% vs n=0, 0%) and hyperchloremia in the ICU group (n=20, 35.1% vs n=2, 6.1%) showed significantly increased numbers of patients compared with the HD group (Fig. 5).

**Table 2. Correlation Coefficients of SIG Among the Variables ( $p=0.000$ )**

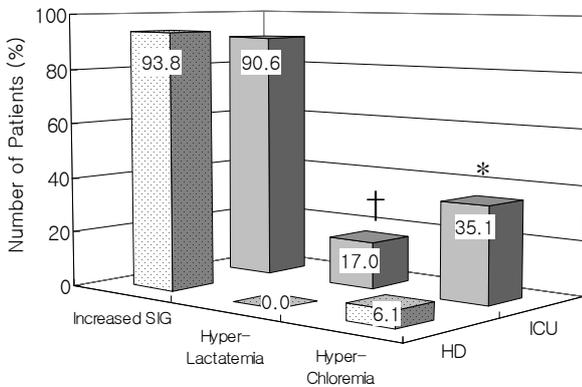
	AGobs	AGalb-corr	AGcorr
SIG in whole patients	0.820	0.774	0.800
SIG in ICU patient group	0.776	0.707	0.700
SIG in HD patient group	0.724	0.725	0.757

AGobs, anion gap observed; AGalb-corr, albumin-corrected AG; AGcorr, albumin and lactate-corrected AG; SIG, strong ion gap

**Table 3. Distribution of the Three Main Underlying Mechanisms of Metabolic Acidosis (chi-square)**

Underlying mechanism	Number of Patients (%)	
	ICU patients (n=57)	HD patients (n=33)
Increased SIG	25 (43.9%)	30 (90.9%)
Increased lactate	1	
Increased chloride	2	
Increased SIG+lactate	5 ( 8.8%)	
Increased SIG+chloride	15 (26.3%)	2 ( 6.1%)
Increased lactate+chloride		
Increased SIG+lactate+chloride	3 ( 5.3%)	

SIG, strong ion gap



**Fig. 5.** Distribution of the three main underlying mechanisms of metabolic acidosis between the ICU and HD patient group. \* $p < 0.01$ , † $p < 0.05$  vs. HD patient group.

### Discussion

We conducted this study to compare the clinical significance of SIG between adult ICU patients and maintenance HD patients with metabolic acidosis.

Several clinical and biologically relevant findings emerged in this study. First, the conventional AGobs levels showed a decreased correlation coefficient with the AGcorr levels in the ICU group, which suggested that hyperlactatemia was main contributing mechanisms in the ICU group than the HD group.

Second, the HD group showed significantly higher SIDa and SIG levels compared to those in the ICU group. This result may represent unmeasured anions

was the main mechanism of metabolic acidosis in HD patients.

Third, AGobs, AGalb-corr, AGcorr, SIDa and SIG levels were significantly increased in the HD patient group than the ICU patient group in our study. In conventional method by AGobs, the results mean that hyperkalemia and hypochloremia made the higher AGobs metabolic acidosis in the HD group than the ICU group. Using physicochemical method by SIDa and SIG, the results mean that hypermagnesemia and hypercalcemia including hyperkalemia and hypochloremia were included in these mechanisms.

Fourth, concerning the contributions of the three main causes of metabolic acidosis, number of patients with increased positive SIG was comparable between the ICU and HD group, whereas hyperlactatemia and hyperchloremia was significantly increased in the ICU group compared with the HD group. In relation to these etiology, lower SIDa and SIG levels were seen in the ICU group compared to those in the HD group.

Fifth, SIG in ICU group showed the highest correlation coefficient with AGobs, whereas SIG in HD group with AGcorr. These results suggest that selecting different diagnosing tools is needed to understand and explain the metabolic acidosis according to patient population.

Acid-base balance evaluation according to the Henderson-Hasselbalch equation enables us to assess the contribution of respiratory ( $pCO_2$ ) and/or non-respiratory (metabolic,  $HCO_3^-$ ) components to the acid-base balance status. A new approach to acid-base balance 'evaluation according to Stewart-Fencl, which is based on a detailed physicochemical analysis of body fluids, defined three independent variables that enable us to accurately define metabolic disturbances of the acid-base balance. The main physicochemical principle, which must be accomplished in body fluids, is the rule of electroneutrality. There are 3 components in biological fluids which are subject to this principle: a) water, which is only in minor parts dissociated into  $H^+$  and  $OH^-$ , b) 'strong', i.e. com-

pletely dissociated, electrolytes, which therefore do not interact with other substances, and body substances, such as lactate, and c) 'weak', i.e. incompletely dissociated substances<sup>1)</sup>. Therefore 3 independent variables are: One is the SIDa, and the second is total concentrations of the weak non-volatile weak acids (Atot), represented mainly by albumin and inorganic phosphate. Raising Atot while holding SIDa constant causes metabolic acidosis (and vice versa); also, lowering plasma SIDa while holding Atot causes metabolic acidosis (and vice versa)<sup>2)</sup>. Third, respiratory acid-base balance disturbances are assessed according to pCO<sub>2</sub>, in the same way as in a conventional approach<sup>3)</sup>.

To obviate these concerns, the Stewart approach, later modified by Figge, Fencel and Watson, was developed. This approach is based on the principles of electroneutrality and conservation of mass<sup>4)</sup>. Quantitative physicochemical analysis of the results was performed with Stewart's quantitative biophysical methods as modified by Figge et al. to take into account the effects of plasma proteins. This method involves first calculating the SIDa. SIDa is simply the difference between the activity of all abundant cations (Na<sup>+</sup>, K<sup>+</sup>, Mg<sup>2+</sup>, Ca<sup>2+</sup>) and the activity of all abundant anions (Cl<sup>-</sup>, lactate, urate). Normally this difference is approximately 39±1 mEq/L. Values lower than 38 express metabolic acidosis and values over 40 mean metabolic alkalosis<sup>3,5)</sup>. This equation, however, does not take into account the role of weak acids (CO<sub>2</sub>, albumin and phosphate) in the balance of electrical charges in plasma water. This is expressed through the calculation of the SIDe. Therefore, SIDe is a measure of the remaining anions, i.e. normally -40 mEq/L. The formula for SIDe was as determined by Figge et al. This formula quantitatively accounts for the contribution of weak acids to the electrical charge equilibrium in plasma. The relative balance of plasma positive and negative charges drives water association and dissociation by the law of mass action<sup>6)</sup>. Once weak acids are quantitatively taken into

account, the SIDa-SIDe should equal 0 (electrical charge neutrality) unless there are unmeasured charges to explain this "ion gap". Such charges are described by the SIG. A positive value for SIG must represent unmeasured anions (sulfate, keto acids, citrate, pyruvate, acetate, gluconate, etc.) exceeding unmeasured cations in the circulation that must be included to account for the measured pH. When the SIG is less than zero, cations exceed anions<sup>1,5-7)</sup>.

Lactate is considered a useful indicator of illness severity and a useful predictor of mortality rate. However, lactate measurements are not immediately and easily available in all ICUs. Therefore, the conventional anion gap (AG) and base excess (BE) have been used to predict lactate levels. However, the AG is considered a poor predictor of hyperlactatemia in the critically ill because of the confounding effects of hypoalbuminemia, the presence of unmeasured anions, the degree of hyperlactatemia targeted for detection, and the multifactorial nature of any acidosis<sup>7)</sup>.

Stewart-Figge methodology has been found to be useful in explaining acid-base changes in various clinical situations, where conventional analysis was deficient. The SIG is not artificially affected by conditions such as alkalosis, hypoalbuminemia, or dehydration. By contrast, these conditions are known to affect the anion gap artificially<sup>5)</sup>. The source of acidosis in a broad range of critical illness remains unknown. Lactic acid accounts for only a fraction of the acidosis seen in these conditions. The curious presence of unidentified anions in the circulation represents a potential mechanism of acidosis. The concepts inherent in the strong ion difference dictate that an addition of anions to the circulation will increase the hydrogen ion concentration either by bringing hydrogen ions with them or by increasing water dissociation<sup>5)</sup>. Therefore, Stewart's approach not only explains fluid induced acid-base phenomena, but also provides a framework for the design of fluids for specific acid-base effects<sup>8-11)</sup>.

Classically, metabolic acidosis is defined as a de-

crease in blood pH secondary to a decrease in the bicarbonate concentration. The decrease in bicarbonate concentration may be secondary to an excess of acids that will consume bicarbonates, reflecting the open character of this buffering system, or to a loss of bicarbonates through the digestive or the renal route<sup>12)</sup>. According to this theory, metabolic acidosis may be secondary to a decrease in the SIDa (increase in  $\text{Cl}^-$ , lactate, or other strong anions) or to an increase in weak acids (mainly hyperphosphatemia). On the other hand, hypoalbuminemia, which is very common in ICU patients, may obscure the presence of strong ions because it has an alkalizing effect. Acidosis resulting from advanced renal insufficiency is called uremic acidosis. Thus the hallmark of uremic acidosis is a diminished GFR. The acidosis of advanced renal failure characteristically presents a high anion gap (normochloremic acidosis) caused by accumulation of sulfate, phosphate, and organic anions. However, the accumulation of these anions per se is not the cause of the acidosis. Metabolic acidosis would not disappear if these anions were removed, for example, by dialysis. Reduction in renal acid excretion and accumulation of uremic anions are both the result of reduced renal function, but not causally related to each other<sup>13)</sup>.

In our study, the mean SIG values were 8.6 mEq/L among ICU patients and 12.3 mEq/L among HD patients. Measurement technology also might be responsible for these differences, as the mean SIG value for critically ill patients reported in the literature can vary from 0 to 13 mEq/L<sup>5, 7, 14, 15)</sup> and its calculation requires the measurement of nine variables.

In conclusion, the physicochemical approach can elucidate the mechanisms of metabolic acidosis in ICU and HD patients compared with conventional measures. Complex acid-base disorders are easier to understand, explain, and rationalize using Stewart's methods compared with the traditional model. Advances in basic chemistry, mathematics, and computer science may yet provide new insight into a complex

acid-base problem.

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