Is there a difference between strong ion gap in healthy volunteers and intensive care unit patients?☆,☆☆,★

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Acid-base equilibrium;
Acid-base imbalance;
Strong ion gap;
Strong ion difference

Abstract
Purpose: Abnormalities of strong ion gap (SIG) are common in critically ill intensive care unit (ICU) patients in conjunction with a high incidence of acid-base abnormalities. However, it is unknown whether abnormalities in SIG are also seen in ICU patients without active acid-base abnormalities. Thus, we conducted this pilot study to examine differences in quantitative acid-base variables between healthy adult volunteers and stable ICU patients with no suspected acid-base abnormalities.

Methods: The study used a prospective observational study of 2 cohorts, 15 healthy adult volunteers and 15 stable adult patients just before ICU discharge who were not receiving renal replacement therapy and had no known active acid-base derangements. We analyzed venous blood for acid-base variables (potential hydrogen in central venous blood [pHCV], partial tension of carbon dioxide in central venous blood [pCVCO2], standard base excess [SBE], lactate, Na+, K+, Cl−, Mg2+, Ca2+, phosphate, and albumin). From these, we calculated strong ion difference (SID) and SIG for both cohorts.

Results: Although mean values for pHCV, pCVCO2, and SBE were within the normal range in both cohorts, 10 (66.7%) of 15 of ICU patients were found to have occult acid-base disorders. The ICU patients also had reduced albumin and SID measurements and significantly greater mean SIG (5.1 ± 2.9 mEq/L) compared to healthy controls (1.4 ± 1.8 mEq/L) (*P = .0002). None of the healthy controls had a SIG higher than 5.0 mEq/L, whereas 7 (46.7%) of 15 of ICU patients had a SIG higher than 5.0 mEq/L. Even among ICU patients with no abnormalities of pHCV, pCVCO2, and SBE, mean SIG was 6.4 (±3.3 mEq/L).

Conclusions: Stable ICU patients have much higher levels of unexplained anions when comparing with healthy controls. Whether this finding represents occult acid-base disorders or simply metabolic differences among the critically ill is uncertain. Further study in larger populations is warranted to establish the significance of high SIG in otherwise stable ICU patients.

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1. Introduction

Acid-base abnormalities are common in intensive care unit (ICU) patients. Traditional methods of evaluating acid-base status can underestimate and even miss complicated acid-base disorders particularly in the setting of hypoalbuminemia [1,2] or in the presence of unmeasured anions [1,3,4]. A quantitative acid-base approach has been applied recently to critically ill patients to better identify occult anions (strong ion gap or SIG) and for risk prediction. Unlike the traditional anion gap, which has a “range” of normal values, the SIG should approach zero—any residual charge representing unmeasured ions [3]. However, a wide range (0-13 mEq/L) for SIG has been reported in the literature [3,5-8]. In the United States, values for SIG in survivors tend to be low and are predictive of survival in critical illness [9-12]. Whereas, in England and Australia, countries that routinely use gelatins for resuscitation, values of SIG have been reported as high as 11 mEq/L in ICU survivors [5] and do not appear to be predictive of outcome [5,13]. Moreover, these high levels of SIG may be seen in the absence of acid-base abnormalities using traditional acid-base measurements (eg, pCO2, standard base excess [SBE], pH).

Analbuminemic (Nagase) rats have been shown to exhibit abnormalities in SIG [14], and hypoalbuminemia is common even among patients being discharged from the ICU when their critical illness has presumably resolved but before complete recovery. However, there were also differences in case mix, demographics, and severity of illness among the subjects enrolled in various studies. Such data are required to understand how clinicians should interpret SIG in critically ill patients.

Although increased SIG has been associated with poor outcome, it is also seen in critically ill patients who survive and may have a “normal response to critical illness.” By studying patients being discharged alive from ICU, we sought to determine if SIG returns to normal or remains increased. Thus, the present report is intended as a pilot study to explore the variation in SIG among the critically ill.

2. Materials and methods

2.1. Study design

This was a prospective, observational, single-center, cohort study of healthy volunteers and stable ICU patients. After approval from the Investigational Review Board of the University of Pittsburgh (Pa), we enrolled adult (≥18 years) male and female subjects into 2 cohorts. We enrolled 15 volunteers who attested to having no known medical conditions (controls) and 15 “ICU discharged patients” after written informed consent had been obtained according to the instructions of the local ethics committee. Stable ICU patients were defined as patients who had a plan to discharge from ICU and no known or suspected active acid-base derangements using routine arterial blood gas analysis. Exclusion criteria included need for renal replacement therapy, serum creatinine level higher than 1.5 mg/dL (115 mmol/L), arterial pH less than 7.35 or greater than 7.45, SBE greater than ±2 mEq/L, ongoing resuscitation, and vasopressor or inotropic agents still in use. Exclusion criteria for laboratory samples were applied to the most recent values obtained for clinical care not to values obtained for the study.

The ICU samples were in a convenience fashion on “stable” patients waiting to be transferred either to the general ward or to a long-term care facility. No patient received fluid resuscitation within 24 hours of the blood sampling, or were any medications known to affect SIG administered. Patients were either eating by mouth or receiving enteral tube feeding; no patient was receiving parenteral nutrition.

2.2. Measurements and calculations

We calculated the apparent and effective strong ion difference (different strong ion difference [SIDa], effective strong ion difference [SIDe]), SIG, SBE, and the corrected SBE (SBEc) as previously described [15]. In brief,

\[
\text{SIDa} = (\text{Na}^+ + \text{K}^+ + \text{Ca}^{2+} + \text{Mg}^{2+}) - (\text{Cl}^- + \text{lactate}),
\]

(1)

\[
\text{SIDe} = 2.46 \times 10^{-8} \times p_{\text{CV}}^2 / 10^{-pH} + [\text{albumin} \ (\text{g/dL})] \\
\times (0.123 \times p_{\text{CV}} - 0.631) + [\text{phosphate} \ (\text{mg/dL})] \\
\times (0.309 \times p_{\text{CV}} - 0.469),
\]

(2)

\[
\text{SIG} = \text{SIDa} - \text{SIDe},
\]

(3)

\[
\text{SBE} = 0.9287 \times (\text{HCO}_3^- - 24.4 + 14.83 \times p_{\text{CV}} - 7.4),
\]

(4)

and

\[
\text{SBEc} = (\text{HCO}_3^- - 24.4) + [(8.3 \times \text{albumin} \ (\text{g/dL}) \times 0.15) \\
+ (0.29 \times \text{phosphate} \ (\text{mg/dL}) \times 0.322)] \\
\times (p_{\text{CV}} - 7.4).
\]

(5)

All concentrations are in milliequivalent per liter unless otherwise specified. Serum samples were obtained in BD Vacutainer (BD Diagnostic Systems; New Jersey) tubes (Serum Separations Tube). Blood gas samples were collected in a sodium heparin syringe. All samples were analyzed using Vitros 950 (Ortho-Clinical Diagnostics, Raritan, NJ) and ABL 725 (Radiometer, Copenhagen, Denmark). Na+, K+, and Cl− were measured using a direct ion-selective electrode technique, whereas albumin, magnesium, and phosphate were quantitated by standard colorimetric techniques.

2.3. Statistical analyses

Statistical analysis was performed using MedCalc for Windows, version 7.2.0.2 (MedCalc Software, Mariakerke,
Belgium), and significance was assumed for $P < .05$. Comparisons between cohorts were performed by unpaired Student $t$ test comparing sample means for each of the acid-base variables measured. Sample size was calculated a priori to achieve 80% power to detect a 4-mEq difference in SIG and a 4-mEq difference in SID assuming an SD of 4 mEq and $\alpha = .05$.

3. Results

The mean length of stay before the blood sampling was 18 days. Mean values for $p$H$_{CV}$, p$_{CV}$CO$_2$, and SBE were within the normal range in both cohorts. However, 9 (60%) of 15 ICU patients (ICU patient no. 2, 5, 6, 8, 10, 11, 12, 13, and 15) were found to have acid-base disorders defined by abnormal $p$H$_{CV}$ and p$_{CV}$CO$_2$ using traditional criteria [16] (normal values for $p$H$_{CV}$ and p$_{CV}$CO$_2$ were $7.37 \pm 0.03$ and $45 \pm 5$ mm Hg, respectively) (Table 1). The ICU patients had significantly greater mean SIG ($5.1 \pm 2.9$ mEq/L) compared to healthy controls ($1.4 \pm 1.8$ mEq/L) ($P = .0002$). Of note, none of the healthy controls had a SIG greater than 5.0 mEq/L, whereas 7 (46.7%) of 15 of ICU patients had a SIG greater than 5.0 mEq/L. Even among the 5 ICU patients with no abnormalities of $p$H$_{CV}$, p$_{CV}$CO$_2$, or SBE, mean SIG was 6.4 mEq/L ($\pm 3.3$). Additional clinical data for the ICU cohort are shown in Table 1. Finally, we performed a secondary analysis by excluding 4 cases that were diagnosed with liver failure and might have some degree of metabolic derangement. Our results were not significantly different, and ICU patients still had significantly greater mean SIG ($4.3 \pm 2.6$ mEq/L; $P = .002$) compared to healthy controls.

The control cohort had quantitative acid-base variables close to expected values with SIG between 0 and 2 mEq/L ($1.4 \pm 1.8$) and SIDe of 40 mEq/L. Traditional ($p$H$_{CV}$, p$_{CV}$CO$_2$, SBE) acid-base parameters, electrolytes, and albumin levels were all within accepted “normal” ranges.

In addition to differences in SIG, differences between mean acid-base variables are provided in Table 2. The SIDa and SIDe were lower in the ICU cohort; however, both groups had similar traditional acid-base measurements. Significant hypoalbuminemia was present in the ICU cohort. Although the ICU patients were not receiving renal replacement therapy, they did have a higher blood urea nitrogen concentration ($33.9$ mg/dL) and serum creatinine level ($1.2$ mg/dL) as compared to controls ($12.3$ mg/dL and $0.9$ mg/dL, respectively).

4. Discussion

Our results are consistent with previous observations in normal animals [17,18] and values derived from published data in exercising humans [3,19]. Specifically, we found that SIG was near zero in healthy humans ($1.4$ mEq/L $\pm 1.8$). Our results from stable patients just before ICU discharge are generally consistent with other studies in the United States [9-12], as well as those from Holland [8] where SIG was close to 5 mEq/L ($5.1$ mEq/L $\pm 2.9$) but not as high as reported in the studies from England and Australia [5,13,20]. Furthermore, the high SIG of stable ICU patients in our study and previous studies [10-12] was significantly lower than the SIG reported for nonsurvivors. We have previously speculated that the difference may lie with the use of gelatins (an exogenous source of unmeasured ions) [21] in these countries [22]. In this

<table>
<thead>
<tr>
<th>ICU patient</th>
<th>Age (y)</th>
<th>Sex</th>
<th>SIDA (mEq/L)</th>
<th>SIDe (mEq/L)</th>
<th>SIG (mEq/L)</th>
<th>Alb (g/dL)</th>
<th>SBE (mEq/L)</th>
<th>SBEc (mEq/L)</th>
<th>Lactate (mm Hg)</th>
<th>SBE (mm Hg)</th>
<th>pH$_{CV}$ (mm Hg)</th>
<th>ICU type</th>
<th>Diagnosis</th>
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<tbody>
<tr>
<td>1</td>
<td>61</td>
<td>F</td>
<td>39.0</td>
<td>31.4</td>
<td>7.6</td>
<td>2.9</td>
<td>-3.6</td>
<td>-2.4</td>
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<td>44</td>
<td>7.31</td>
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<tr>
<td>2</td>
<td>53</td>
<td>M</td>
<td>33.9</td>
<td>29.7</td>
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<td>7.31</td>
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<td>38.4</td>
<td>4.8</td>
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<td>2.2</td>
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<td>2.0</td>
<td>48</td>
<td>7.37</td>
<td>36</td>
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</tr>
<tr>
<td>4</td>
<td>59</td>
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<td>34.9</td>
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<td>-5.3</td>
<td>-5.1</td>
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<td>34</td>
<td>7.37</td>
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<td>Card surg Card shock</td>
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<td>5</td>
<td>64</td>
<td>M</td>
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<td>27.7</td>
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<td>2.6</td>
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<td>7.39</td>
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<tr>
<td>6</td>
<td>50</td>
<td>M</td>
<td>31.3</td>
<td>24.0</td>
<td>7.3</td>
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<td>-5.8</td>
<td>-6.3</td>
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<td>F</td>
<td>43.1</td>
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<td>57</td>
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<td>0.9</td>
<td>2.8</td>
<td>42</td>
<td>7.39</td>
<td>8</td>
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<tr>
<td>10</td>
<td>36</td>
<td>M</td>
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<td>26.0</td>
<td>8.3</td>
<td>2.6</td>
<td>-9.3</td>
<td>-8.1</td>
<td>1.6</td>
<td>37</td>
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<td>44.6</td>
<td>41.5</td>
<td>3.1</td>
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<td>2.3</td>
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<td>-2.5</td>
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<td>7.29</td>
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<td>-3.6</td>
<td>1.5</td>
<td>48</td>
<td>7.26</td>
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<tr>
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<td>M</td>
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<td>37.5</td>
<td>1.8</td>
<td>2.2</td>
<td>4.0</td>
<td>4.5</td>
<td>1.8</td>
<td>45</td>
<td>7.41</td>
<td>27</td>
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<td>38.8</td>
<td>1.4</td>
<td>2.8</td>
<td>4.2</td>
<td>3.8</td>
<td>1.4</td>
<td>38</td>
<td>7.48</td>
<td>34</td>
<td>Med/surg Trauma</td>
</tr>
<tr>
<td>Mean</td>
<td>54</td>
<td></td>
<td>38.1</td>
<td>33.1</td>
<td>5.1</td>
<td>2.6</td>
<td>-1.3</td>
<td>-0.8</td>
<td>2.3</td>
<td>40</td>
<td>7.38</td>
<td>18</td>
<td></td>
</tr>
</tbody>
</table>

Alb indicates albumin; LOS, length of stay before sample; F, female; M, male; Neurosurg, neurosurgery; Med, medical; Surg, surgery; Card surg, cardiovascular surgery.
therapy, a positive correlation between SIG and pHCV, pCVCO2, SBE. However, there were substantial identical mean values for traditional acid-base measurements gelatins[9,10] or where SIG values were obtained before In contrast, studies conducted in countries that do not use some patients with normal pHCV, pCVCO2, and SBE had had abnormal traditional acid-base variables. Furthermore, in countries that use gelatin-based resuscitation fluids[5,13].

Interestingly, previous studies that failed to scenario, SIG is likely to be a mixture of endogenous and exogenous anions. Interestingly, previous studies that failed to find a correlation between SIG and mortality were performed in countries that use gelatin-based resuscitation fluids [5,13]. In contrast, studies conducted in countries that do not use gelatins [9,10] or where SIG values were obtained before therapy [23,24], a positive correlation between SIG and hospital mortality was found.

When we compared both of cohorts, we found almost identical mean values for traditional acid-base measurements (pHCV, pCVCO2, SBE). However, there were substantial acid-base derangements that were not suspected in the ICU cohort (Table 1). Indeed, more than 50% of these patients had abnormal traditional acid-base variables. Furthermore, some patients with normal pHCV, pCVCO2, and SBE had acid-base disorders detected by SIG. For example, the patient number 9 (Table 1) had a SIG of 10.5 mEq/L, yet this same patient had traditional acid-base variables within the “normal” range. Other patients in the ICU cohort had unexpected acid-base abnormalities, traditional and quantitative, that the primary care team did not suspect. Entry criteria specifically limited enrollment to those patients who the primary care team thought were “stable,” meaning no ongoing resuscitative efforts, not receiving renal replacement therapy, and also without any known acid-base derangements from arterial blood gas.

The reduced SID (both SIDa and SIDe) in the ICU cohort was most likely a reflection of the decreased albumin concentration. Albumin contributes to the overall buffer capacity of plasma, and thus, this decrease in albumin would reflect an overall reduction in buffer base. Our finding of hypoalbuminemia is consistent with previous reports [1,7,25]. Thus, if SID were to remain in the normal range (40-42 mEq/L) in the face of hypoalbuminemia, there would be a metabolic alkalosis [6]. It appears instead that SID is “reset” to a lower level to maintain normal pH [7].

As a pilot, our study has also limitations. Our sample size is too small to permit us to establish a true “normal range” for SIG as this would require hundreds (or even thousands) of patients. This elevated SIG may have come from a wide variety of unknown exogenous and endogenous sources in our “stable” ICU cohort [26]. Although the immediate clinical significance of this finding is unclear, a growing body of evidence suggests that it is a marker of decreased survival.

5. Conclusions

Although healthy adults have a SID close to 40 mEq/L and SIG close to 0, stable ICU patients without suspected acid-base abnormalities have significantly higher SIG values and lower SID values. It is unclear whether the increased SIG represents a “resetting of the normal range” or an occult acid-base derangement. By contrast the decreased SID appears to be linked to the decreased buffer base resulting from hypoalbuminemia and as such does not appear to represent an acid-base disorder.

Table 2  Acid-base parameters of adult ICU patients without apparent acid-base abnormalities and healthy adult volunteers (control)

<table>
<thead>
<tr>
<th>Acid-base parameter</th>
<th>ICU patients (n = 15)</th>
<th>Control (n = 15)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>SIDa (mEq/L)</td>
<td>38.1 (±4.4)</td>
<td>41.4 (±3.7)</td>
<td>.036</td>
</tr>
<tr>
<td>SId (mEq/L)</td>
<td>33.1 (±5.6)</td>
<td>40 (±3.8)</td>
<td>.0005</td>
</tr>
<tr>
<td>SIG (mEq/L)</td>
<td>5.1 (±2.9)</td>
<td>1.4 (±1.8)</td>
<td>.0002</td>
</tr>
<tr>
<td>Albumin (g/dL)</td>
<td>2.6 (±0.6)</td>
<td>4.5 (±0.5)</td>
<td>.0001</td>
</tr>
<tr>
<td>pCVCO2 (mm Hg)</td>
<td>40 (±6.1)</td>
<td>45 (±9.3)</td>
<td>.08</td>
</tr>
<tr>
<td>SBE (mEq/L)</td>
<td>−1.3 (±5.4)</td>
<td>0.1 (±2.7)</td>
<td>.36</td>
</tr>
<tr>
<td>SBEc (mEq/L)</td>
<td>−0.8 (±5.0)</td>
<td>0.8 (±3.1)</td>
<td>.29</td>
</tr>
<tr>
<td>pHCV</td>
<td>7.38 (±0.09)</td>
<td>7.37 (±0.04)</td>
<td>.61</td>
</tr>
<tr>
<td>Lactate (mEq/L)</td>
<td>2.33 (±1.2)</td>
<td>1.77 (±0.5)</td>
<td>.11</td>
</tr>
<tr>
<td>Na+ (mEq/L)</td>
<td>136.7 (±5.7)</td>
<td>138.9 (±1.8)</td>
<td>.17</td>
</tr>
<tr>
<td>K+ (mEq/L)</td>
<td>4.2 (±0.6)</td>
<td>4.0 (±0.2)</td>
<td>.48</td>
</tr>
<tr>
<td>Mg2+ (mEq/L)</td>
<td>1.8 (±0.3)</td>
<td>1.5 (±0.1)</td>
<td>.003</td>
</tr>
<tr>
<td>iCa2+ (mEq/L)</td>
<td>2.4 (±0.3)</td>
<td>2.5 (±0.08)</td>
<td>.07</td>
</tr>
<tr>
<td>iCa2+ (mmol/L)</td>
<td>1.2 (±1.0)</td>
<td>1.25 (±0.04)</td>
<td>.07</td>
</tr>
<tr>
<td>Cl− (mEq/L)</td>
<td>103.8 (±8.0)</td>
<td>103.2 (±2.8)</td>
<td>.53</td>
</tr>
<tr>
<td>PO4− (mg/dL)</td>
<td>3.6 (±0.8)</td>
<td>4.0 (±0.4)</td>
<td>.15</td>
</tr>
<tr>
<td>BUN (mg/dL)</td>
<td>33.9 (±20.2)</td>
<td>12.3 (±3.8)</td>
<td>.0005</td>
</tr>
<tr>
<td>Cr (mg/dL)</td>
<td>1.2 (±0.4)</td>
<td>0.9 (±0.2)</td>
<td>.006</td>
</tr>
</tbody>
</table>

There are significant differences in the values of albumin, SIDa, SId, and SIG in the ICU patients compared with healthy controls, despite otherwise normal acid-base parameters (pHCV, pCVCO2, SBE). There are also significant differences in magnesium, blood urea nitrogen, and creatinine level. Mean values are reported with their respective SD. Data are compared by unpaired t test, unequal variance assumed. BUN indicates blood urea nitrogen; Cr, creatinine.

References

[5] Cusack RJ, Rhodes A, Lochhead P, et al. The strong ion gap does not reflect an overall reduction in buffer base. Our finding of hypoalbuminemia is consistent with previous reports [1,7,25]. Thus, if SID were to remain in the normal range (40-42 mEq/L) in the face of hypoalbuminemia, there would be a metabolic alkalosis [6]. It appears instead that SID is “reset” to a lower level to maintain normal pH [7].