The Significance of Albumin Corrected Anion Gap in Patients with Cardiopulmonary Arrest

Shuichi Hagiwara, MD,1,3 Kiyohiro Oshima, MD, PhD,1,3 Kazumi Furukawa, MD, PhD,1,3 Takuro Nakamura, MD, PhD,1,3 Yoshio Ohyama, MD, PhD,2,3 and Jun-Ichi Tamura, MD, PhD2,3

Purpose: The reliable parameter, which can be obtained easily and quickly, is necessary to predict the return of spontaneous circulation (ROSC) of patients with cardiopulmonary arrest (CPA) in the emergency situation. In this study, we evaluated the significance of albumin corrected anion gap (ACAG) for the prediction of ROSC in patients with CPA.

Patients and Methods: In 166 patients with CPA between January 2009 and December 2010, 132 patients could be analyzed retrospectively. We compared acute physiology and chronic health evaluation (APACHE) II score, sequential organ failure assessment (SOFA) score, anion gap (AG) and ACAG levels between patients with/without ROSC and evaluated the significance of AG and ACAG to predict ROSC in patients with CPA.

Results: Both AG and ACAG were significantly lower in patients with ROSC than in patients without ROSC. Both AG and ACAG had the relation with APACHE II and SOFA scores, however, coefficients of correlation with APACHE II and SOFA score were higher in ACAG \( (r = 0.506) \) than in AG \( (r = 0.482) \). The sensitivity, specificity, positive predictive value, and negative predictive value of ACAG for the prediction of ROSC in patients with CPA were better than those of AG.

Conclusion: Our study shows that both AG and ACAG have the relation with ROSC and ACAG is better to predict the ROSC following CPR in patients with CPA compared with AG. ACAG can be easily obtained in the emergency situation, and ACAG is a useful parameter to predict ROSC in patients with CPA.

Keywords: cardiopulmonary arrest (CPA), cardiopulmonary resuscitation (CPR), return of spontaneous circulation (ROSC), anion gap, albumin corrected anion gap

Introduction

Despite important advances in prevention, cardiac arrest remains a substantial public health problem and a leading cause of death in many parts of the world.1 When cardiac arrest occurs, prompt and skillful response can make the difference between life and death and between intact survival and debilitation. Cardiopulmonary resuscitation (CPR) is a series of life-saving actions that improve the chance of survival following cardiac arrest.2 Cardiac arrest occurs both in and out of the hospital. Therefore, medical stuffs including physicians, nurses and paramedics make every effort to provide the high quality CPR including basic life support.
Patients and Methods

In 166 patients who were transferred to our hospital by ambulance as cardiopulmonary arrest (CPA) and were provided CPR between January 2009 and December 2010, 132 patients could be analyzed retrospectively. The hospital research ethics board approved the protocol, without the need for informed consent.

Electrocardiographic (ECG) monitor on arrival at our hospital showed one of asystole, pulseless electrical activity (PEA), or ventricular fibrillation (VF)/pulseless ventricular tachycardia (VT) in those patients diagnosed as CPA. The causes of CPA were follows; cardiac disease (including suspicion) in 63, suffocation in 22, respiratory disease in 9, trauma in 7, hypovolemic shock and drowning in 5 respectively, brain disease and carbon monoxide poisoning in 4 respectively, acute aortic dissection and septic shock in 3 respectively, and others in 7. In this period, CPR was performed in conformity with guideline 2005. The patients’ mean age was 69.9 ± 17.8 (ranging 1 to 98) years old and male/female was 84/48.

Arterial blood gas analysis was performed with cobas b 221 (Roche Diagnostics K. K., Tokyo, Japan) and Na⁺, K⁺, Cl⁻ and HCO₃⁻ levels were measured in our laboratory center on arrival at our hospital. Acute physiology and chronic health evaluation (APACHE) II score, sequential organ failure assessment (SOFA) score, AG and ACAG were calculated. AG and ACAG were calculated using following formulae respectively:

\[
\text{AG} \text{ (mmol/L)} = ([\text{Na}^+] + [\text{K}^+]) - ([\text{Cl}^-] + [\text{HCO}_3^-])
\]

\[
\text{ACAG} \text{ (mmol/L)} = [4.4 - \{\text{observed serum albumin (g/dl)}\}] \times 2.5 + \text{AG}
\]

Successful resuscitation was defined as recovery of blood pressure and pulse for more than 1h with or without a continuous catecholamine infusion, and we defined this situation as ‘ROSC(+)’. Patients were divided with the two groups; patients with ROSC {the ROSC(+) group} and without ROSC {the ROSC(−) group}. We performed the comparisons in APACHE II score, SOFA score, AG and ACAG levels on arrival at our hospital between the two groups, and evaluated the significance of ACAG based on the relation of APACHE II score, SOFA score and ROSC in comparison with AG.

Statistical Analysis

Data are shown as the mean ± standard deviation, and the Mann-Whitney U test or χ² analysis was used to compare variables between the ROSC(+) and the ROSC(−) groups. Linear regression analysis was used for the evaluation of the relationships between ACAG, AG, APACHE II score and SOFA score. Receiver operator characteristic (ROC) curves were used to evaluate the efficacy of AG and ACAG for predicting ROSC in patients with CPA. All statistical analyses were performed using IBM SPSS Statistics 20. Statistical significance was assumed to be present at a p value of less than 0.05.

Results

There were 33 (25%) patients with ROSC. The backgrounds of patients with ROSC were as follows; cardiac disease in 13 (13/63; 21%), suffocation in
Table 1 Comparisons in patients with/without ROSC

<table>
<thead>
<tr>
<th></th>
<th>ROSC(+) (n = 33)</th>
<th>ROSC(−) (n = 99)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y/o)</td>
<td>66 ± 18</td>
<td>71 ± 18</td>
<td>0.150</td>
</tr>
<tr>
<td>Male/female</td>
<td>19/14</td>
<td>65/34</td>
<td>0.531</td>
</tr>
<tr>
<td>The duration between emergency call and arrival at hospital (min.)</td>
<td>26.0 ± 8.4</td>
<td>29.6 ± 13.5</td>
<td>0.136</td>
</tr>
<tr>
<td>APACHE II score</td>
<td>37.2 ± 4.8</td>
<td>44.1 ± 4.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>SOFA score</td>
<td>12.6 ± 1.6</td>
<td>14.0 ± 2.1</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

ROSC: return of spontaneous circulation; APACHE: acute physiology and chronic health evaluation; SOFA: sequential organ failure assessment.

Table 1 shows the comparisons in patients with/without ROSC. There were no significant differences in age and male/female ratio between the two groups. There was also no significant difference in the duration between emergency call and arrival at hospital. Patients in the both groups showed high APACHE II and SOFA scores, nonetheless those scores were significantly higher in the ROSC(−) group than in the ROSC(+) group.

The level of AG were high in the both groups, and AG in the ROSC(−) group was significantly higher than in the ROSC(+) group (Fig. 1A). The level of ACAG had the similar tendency as the level of AG (Fig. 1B).

Figure 2 shows that both AG and ACAG have the correlation to APACHE II score with significance. In addition, the coefficient of correlation with APACHE II score was higher in ACAG than in AG. Both AG and ACAG were also had the relation with SOFA score with significance. However, the coefficient of correlation with SOFA score was lower in AG compared with ACAG (Fig. 3A and 3B).

The sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and predictive accuracy (PA) of AG and ACAG for predicting ROSC in patients with CPA were shown in Table 2. Those values were better in ACAG than in AG. The area under the ROC curve was also better in ACAG (0.871) than in AG (0.850) (Table 2). Those results suggest that both AG and ACAG have the relation with ROSC and ACAG has the relatively high accuracy to predict ROSC in patients with CPA.
**Discussion**

The establishment of the parameters to predict the recovery of ROSC in patients with CPA is important not only for the judgment whether CPR should be continued but also for the medical economic side. In addition, those parameters should be obtained easily and speedy as soon as possible in the emergency situation.

AG is one of parameters showing anion/cation balance. The normal value of AG was 8–16 mmol/L. With the adoption of newer automated systems that more accurately measure serum electrolytes, the normal value of AG had decreased to 3–11 mmol/L. Morris and co-workers also reported that classical range of AG should be interpreted allowing ±2 mmol/L by including four items such as Na⁺, K⁺, Cl⁻ and HCO₃⁻ with inherent measurement errors. AG in plasma is a time-honored diagnostic tool used in the evaluation of metabolic acidosis. However, the observed AG is often unreliable in detecting increased concentrations of these gap anions and Rocktaeschel and his colleague insisted that the AG alone has limitations in critical illness. In particular, hypoaalbuminemia, a common disturbance in hospitalized patients, can mask an increased concentration of gap anions by lowering the value of AG. For example, significant keto acidosis could be missed in a diabetic patient with hypoalbuminemia. Hatherill and his colleagues insisted that ACAG is more appropriate screening tool for the diagnosis of metabolic acidosis in the intensive care unit and ACAG should be calculated to screen for occult tissue anions in children with shock and Morris et al. proposed ACAG-based techniques for bedside use in the critically ill patients. In this study, we paid attention the significance of ACAG for the prediction of ROSC in patients with CPA. As a result, both of AG and ACAG levels in the ROSC (−) group were significantly higher than in the ROSC (+) group. Both AG and ACAG had the relation with APACHE II and SOFA scores, however, coefficients of correlation with APACHE II and SOFA score were higher in ACAG than in AG. The sensitivity, specificity, PPV, NPV, and PA of ACAG for predicting ROSC in patients with CPA were better than those of AG. Those results suggest that both AG and ACAG have the relation with ROSC and ACAG has the relatively high accuracy to predict ROSC in patients with CPA.

The strong ion gap (SIG) quantifies unmeasured anions in the blood, based on Stewart’s acid-base model as modified by Figge and Fencl and is calculated according to the following formula:

\[ \text{SIG} = [\text{SID}]a - [\text{SID}]e \]

\[ [\text{SID}]a \text{ (apparent strong ion difference)} = [\text{Na}^+] + [\text{K}^+] + [\text{Mg}^{++}] + [\text{Ca}^{++}] - \text{[Cl}^{-}] - [\text{lactate}] - [\text{urate}] \]

\[ [\text{SID}]e \text{ (effective strong ion difference)} = 1, 000 \times 2.46E - 11 \times \text{PO}_{4}^{3-}^{2-}/(10^{-pH}) + [\text{albumin}] \times (0.123 \times \text{pH} - 0.631) + [\text{PO}_4^{3-}] \times (0.309 \times \text{pH} - 0.469) \]

In comparison to the traditional AG, the SIG is calculated from all charged blood constituents and Gurnerson described that SIG was the gold standard for the quantification of unmeasured anions. An elevated SIG is associated with increased mortality in critically ill infants, in patients with severe malaria and in patients with major vascular injury. In addition, it has been recently reported the usefulness of SIG in patients after cardiac arrest treated with mild therapeutic hypothermia. On the other hand, Cusack and coworkers insisted that SIG appeared to offer no advantage in prediction of outcome of critically ill patients and SIG could not be advocated as a prognostic marker comparing with traditional indices such as AG, base excess and pH. We thought that SIG was not suitable to use in the emergent situation because the formula of SIG included factors which could not be measured quickly and calculation of SIG was complicated as described above. Additionally, Mallet and co-workers showed a good correlation between SIG and AG in patients with septic shock. Those were other reasons why we paid attention the significance of AG and ACAG in patients with CPA.

It has been reported that meaningful neurological recovery cannot be reliably predicted from physical findings during the first 24 h after cardiac arrest. In contrast, the study by Adrie and colleagues had proposed the out-of-hospital cardiac arrest (OHCA) score for patients with postcardiac arrest. OHCA score, which incorporated initial rhythm, no-flow and low-flow intervals, and admission levels of serum creatinine and lactate, was developed to predict death or poor neurological outcome after OHCA in France, and could predict survival with minimal neurological impairment of patients with OHCA at ICU admission.
Table 2  Sensitivity, specificity, positive predictive value, negative predictive value and predictive accuracy of AG and ACAG to predict ROSC in patients with CPA

<table>
<thead>
<tr>
<th></th>
<th>Sensitivity (%) (95% CI)</th>
<th>Specificity (%) (95% CI)</th>
<th>PPV(%) (95% CI)</th>
<th>NPV(%) (95% CI)</th>
<th>PA(%) (95% CI)</th>
<th>AUC</th>
</tr>
</thead>
<tbody>
<tr>
<td>AG</td>
<td>0.816 (0.782–0.839)</td>
<td>0.688 (0.652–0.726)</td>
<td>0.490 (0.435–0.527)</td>
<td>0.910 (0.892–0.923)</td>
<td>0.722 (0.689–0.754)</td>
<td>0.850</td>
</tr>
<tr>
<td>ACAG</td>
<td>0.862 (0.799–0.851)</td>
<td>0.750 (0.710–0.769)</td>
<td>0.559 (0.508–0.578)</td>
<td>0.937 (0.906–0.944)</td>
<td>0.780 (0.738–0.793)</td>
<td>0.871</td>
</tr>
</tbody>
</table>

AG: anion gap; ACAG: albumin-corrected anion gap; ROSC: return of spontaneous circulation; CPA: cardiopulmonary arrest; CI: confidence interval; PPV: positive predictive value; NPV: negative predictive value; PA: predictive accuracy; AUC: area under curve

Hunziker et al. also insisted that this score had a high positive predictive value and performed well in identifying high risk patients for poor outcomes in the United States.\(^{30}\) However, this scoring system has not been widespread because of the following reasons:

1. this score limits the ability to generalize to other countries,\(^{30}\)
2. complicated to calculate,
3. difficulty to obtain factors for this score if there is no by-stander.

**Limitations**

In this study, patients were not divided into subgroups based on the CPA wave pattern showing ECG monitoring such as asystole, PEA or VF/pulseless VT because we would like to evaluate whether ACAG was the useful parameter as a predictor for ROSC in all kinds of CPA pattern. By the same reason, patients were not divided based on the background resulting in CPA.

Our study did not evaluate whether the level of lactate participated in ROSC because we could not obtain enough data of lactate. We did not evaluate the relation with ACAG and neurological prognosis in this study because there were few patients with good neurological function. Further studies including neurological and long-term prognosis should be performed with multi-centers.

**Conclusion**

Our study shows both AG and ACAG have the relation with ROSC in patients with CPA. The higher AG and ACAG become, the lower the probability that patients with CPA can get ROSC. In addition, ACAG is better to predict the ROSC following CPR in patients with CPA compared with AG. ACAG can be easily obtained in the emergency situation, and ACAG is a useful parameter to predict ROSC in patients with CPA.

**Disclosure Statement**

All authors have no conflict of interest.

**References**