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The significance of strong ion gap for predicting return of spontaneous circulation in patients with cardiopulmonary arrest

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Abstract: Useful parameters that can predict return of spontaneous circulation (ROSC) in patients with cardiopulmonary arrest (CPA) have not been established. We previously reported the usefulness of anion gap (AG) and albumin-corrected anion gap (ACAG) calculated from a blood sample obtained on arrival at the hospital for the prediction of ROSC. Otherwise, it has been reported that strong ion gap (SIG), which shows the difference between the levels of fully dissociated cations and anions in the serum, is useful to predict the prognosis of critically ill patients.

This was a prospective and observational clinical study. Patients with CPA transferred to the emergency department of our hospital between January 2013 and December 2014 were evaluated. Patients were divided into two groups: patients who obtained ROSC [ROSC(+) group] and those who did not [ROSC(-) group]. We compared AG, ACAG and SIG between the two groups.

A total of 170 patients were enrolled. Fifty patients were included in the ROSC(+) group, and the remaining 120 in the ROSC(-) group. Both AG and ACAG were significantly better in the ROSC(+) group; however, there was no significant difference in SIG between the two groups. The area under the receiver operating characteristic curves (AUC) for ROSC of both AG and ACAG were almost the same (0.72 and 0.708, respectively); the AUC of SIG (0.57) was inferior to those of AG and ACAG.

Our results suggest that AG and ACAG can better predict ROSC following cardiopulmonary resuscitation (CPR) compared with SIG.

Keywords: Strong ion gap; Return of spontaneous circulation (ROSC); Cardiopulmonary arrest (CPA)

1 Introduction

Cardiopulmonary resuscitation (CPR) for patients with cardiopulmonary arrest (CPA) has been performed worldwide after guidelines for CPR were issued [1]. However, beneficial parameters to predict return of spontaneous circulation (ROSC) have not been established. We previously reported that anion gap (AG) and albumin-corrected anion gap (ACAG) calculated from laboratory data obtained on arrival at the hospital were useful predictors of ROSC in patients with CPA [2]. AG and ACAG can be obtained easily and quickly; therefore, these parameters are suitable in clinical situations.

Both AG and ACAG are included in kinds of acid-base balance. AG is usually calculated as $\{(Na^+ + K^+) - (Cl^- + HCO_3^-)\}$ [2, 3], and does not reflect all cations and anions in the body [4]. On the other hand, strong ion gap (SIG) shows the difference between the levels of fully dissociated cations and anions in the serum [5], and the usefulness of SIG to predict the prognosis of critically ill patients was recently reported [6-8]. Additionally, Funk and his co-workers recently insisted the effectiveness of SIG in predicting the outcome of CPA patients treated with therapeutic hypothermia [9].

In this study, we hypothesized that SIG calculated with laboratory data obtained on arrival at the hospital is

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a useful parameter to predict ROSC in patients with CPA, and evaluated the significance of SIG compared with AG and ACAG.

2 Methods

The protocol of this study was approved by the research ethics board of Gunma University Hospital without the need for informed consent. This study was a prospective, observational clinical study on patients with cardiopulmonary arrest on arrival (CPAOA) who were transferred to the emergency department of Gunma University Hospital between January 2013 and December 2014. All causes of CPAOA (both endogenous causes such as cardiac disease and exogenous causes such as trauma and poisoning) were included in this study. CPR was carried out in conformity with the 2010 guidelines of the Japan Resuscitation Council. Patients in whom electrocardiographic monitoring on arrival at our hospital showed one among asystole, pulseless electrical activity, ventricular fibrillation, and pulseless ventricular tachycardia were diagnosed as having CPAOA. Blood samples were collected from the femoral artery in all patients as soon as possible after arrival at our hospital. Arterial blood gas analysis was performed with an ABL800 FLEX analyzer (Radiometer, Tokyo, Japan) and the levels of Na^+, K^+, Cl^-, albumin, lactate and chemical data were measured in our laboratory center in a blood sample obtained on arrival at our hospital. The acute physiology and chronic health evaluation (APACHE) II score [10] and sequential organ failure assessment (SOFA) score [11] were calculated. AG, ACAG and SIG were calculated with the following formulae:

AG (mmol/l) = $(Na^+ + K^+) - (Cl^- + HCO_3^-)$ [12]

ACAG (mmol/l)=[4.4-{albumin (g/dl)}] ×2.5 + AG [13, 14]

SIG=SIDa-SIDe

SIDa (apparent strong ion difference)

= $[Na^+] + [K^+] + [Mg^{2+}] + [Ca^{2+}] - [Cl^-]$ - [Lactate] - [Urate]

SIDe (effective strong ion difference)

= $[HCO_3^-]$ + [[albumin]×(0.123×pH-0.631)] + $[[PO_4]$×(0.309)×(pH-0.469)]

= $[1000 \times 2.46 \times 10^{-11} \times \mathbf{Pco_2} / 10^{-pH}]$ + [[albumin]×(0.123×pH-0.631)] + $[[PO_4]$×(0.309)×(pH-0.469)] [14-17]

Successful resuscitation was defined as detection of a spontaneous pulse at the carotid artery, femoral artery, or radial artery without CPR, and then maintenance of systolic pressure at ≧80mmHg for 1 hour with or without administration of vasoconstrictive agents. We defined this situation as "ROSC(+)". Any condition other than ROSC(+) described above was defined as "ROSC(-)". Patients were divided into two groups: the ROSC(+) group and the ROSC(-) group. We compared ROSC, AG, ACAG and SIG between the two groups.

2.1 Statistical analysis

Data are shown as the mean and standard deviation for age, and median in other data. The chi-square test, Fisher's exact test, or Mann-Whitney U test was used for comparisons between the two groups. Receiver operating characteristic (ROC) curves were used to evaluate the efficacy for predicting ROSC and to determine the cut-off point with the Youden index. The optimal cut-off point is the one that maximizes the sum of sensitivity and specificity employed the Youden index approach. IBM SPSS Statistics 22 was used for the statistical analysis. Statistical significance was assumed to be present at a *p value* of less than 0.05.

3 Results

During the study period, 170 patients with CPAOA met the study criteria. Among these 170 patients, 50 patients could obtain ROSC, and the remaining 120 died without obtaining ROSC.

The characteristics of the two groups are shown in Table 1. As shown in Table 1, there were no significant differences in age and male/female ratio. The initial rhythm on electrocardiogram in the two groups is shown in Table 1, and there were no significant differences in the initial rhythm between the two groups. The APACH II score on arrival at the hospital was remarkably high in both groups without a significant difference. The SOFA score was also high in both groups, showing no significant difference between the two groups. Cardiac disease was the most common cause of CPA in both groups, and there were no significant differences in the cause of CPA. Finally, two

Table 1: Patients' characteristics

	ROSC(+) (n = 50)	ROSC(-) (n = 120)	p value
Age（y/o）	74	73	0.86
Male/Female	26 / 24	70 / 50	0.37
Initial rhythms of ECG at arrival on our hospital			
Asystole	32	99	0.36
PEA	15	19	0.11
Pulseless VT	0	0	
VF	3	2	0.16
APACHE Ⅱ score	48	47	0.79
SOFA score	13	14	0.06
The cause of CPA			
Cardiac disease	22	68	0.47
Vascular disease	2	11	0.36
Gastroenterological disease	3	4	0.43
Respiratory disease	11	17	0.38
Stroke	0	3	1
Others	12	17	0.05

ECG: electrocardiogram, PEA: pulseless electrical activity, VT: ventricular tachycardia, VF: ventricular fibrillation, APACHE: acute physiological and chronic health evaluation, SOFA: sequential organ failure assessment, CPA: cardiopulmonary arrest

cases (severe malnutrition and atonic bleeding) survived to discharge in the ROSC(+) group.

The AG, ACAG and SIG in the two groups are shown in Figure 1. The levels of AC and ACAG on arrival at our hospital were significantly lower in the ROSC(+) group than in the ROSC(-) group ($p<0.01$). On the other hand, there was no significant difference in the level of SIG between the two groups (Figure 1).

The ROC curves of AC, ACAG and SIG for ROSC are shown in Figure 2, and the areas under the ROC curve (AUC), cut-off points, and sensitivity and specificity of AG, ACAG, SIG for ROSC are shown in Table 2. As shown in Figure 2 and Table 2, the AUCs of both AG and ACAG were almost the same; however, the AUC of SIG was inferior to those of AG and ACAG. There was no difference in the sensitivity for ROSC among these three parameters. On the other hand, the specificity of SIG for ROSC was inferior to those of AG and ACAG (Table 2).

4 Discussion

The establishment of parameters to predict ROSC in patients with CPA is important not only for the judgment of whether CPR should be continued but also for the medical economic side. In addition, those parameters must be able to be easily and quickly obtained in an emergency situation. The Universal Termination of Resuscitation (TOR) guidelines are commonly used by some emergency medical services [18, 19]. According to those criteria, there is a possibility that only 1% of patients with out-of-hospital cardiac arrest could be rescued [20].

We have studied factors predicting ROSC in patients with CPAOA. We focused on acid-base equilibrium to predict ROSC in patients with CPAOA, and have reported that AC and ACAG could be predictors of ROSC [2, 21]. AG is one of the parameters showing anion/cation balance. AG

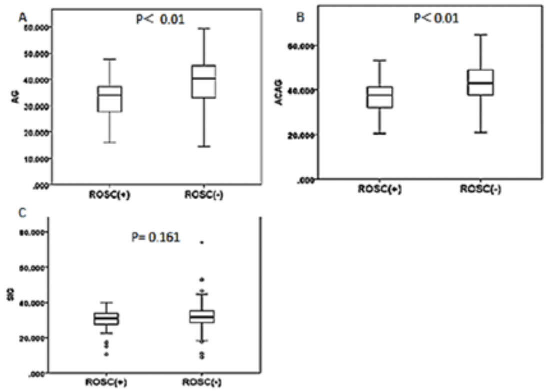

Figure 1: Comparisons of AG, ACAG and SIG between the ROSC(+) and ROSC(-) groups.

(A) AG. (B) ACAG. (C) SIG.AG: anion gap, ACAG: albumin-corrected anion gap, SIG: strong ion gap.

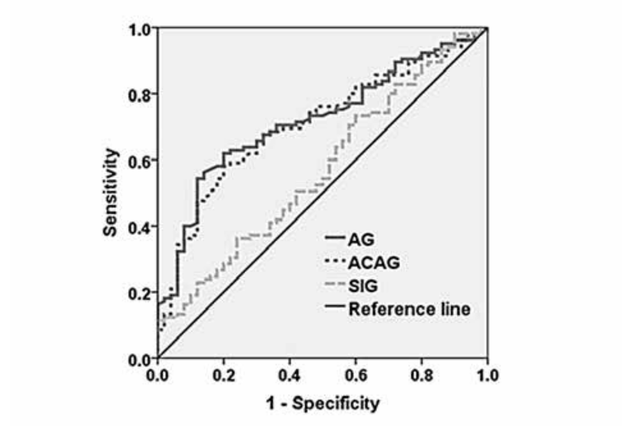

Figure 2: Receiver operating characteristic (ROC) curves for ROSC of AG, ACAG and SIG.

AG: anion gap, ACAG: albumin-corrected anion gap, SIG: strong ion gap.

Table 2: Areas under receiver operating characteristic curves (AUC) and cut-off points to predict return of spontaneous circulation

	AG	ACAG	SIG
AUC (99% CI)	0.656 (0.524-0.788)	0.652 (0.519-0.785)	0.564 (0.431-0.697)
Cut-off point	39.2	44.2	24.7
Sensitivity, %	46.5	46.5	46.5
Specificity, %	84.2	84.2	78.9

is usually used in clinical practice because AG in plasma is a time-honored diagnostic tool used in the evaluation of metabolic acidosis and can be obtained easily and quickly. The normal range of AG is 8-16mmol/L [22]. AG constitutes an additional diagnostic contribution, although hypoalbuminemia might preclude its usefulness. For this reason, many researchers recommended adjusting AG to the albumin level.

The observed AG is often unreliable in detecting increased concentrations of these gap anions [23]. Rocktaeschel *et al.* insisted that the AG alone had limitations in reflecting the acid-base balance in critically ill patients due to the accumulation of unmeasured anions [24]. In particular, hypoalbuminemia, a common disturbance in hospitalized patients, can mask an increased concentration of gap anions by lowering the value of AG [14]. Morris *et al.* proposed ACAG-based techniques for bedside use in critically ill patients [25]. We previously reported that both AG and ACAG were associated with ROSC and the relationship between ACAG and ROSC was stronger than that between AG and ROSC in CPAOA patients [2].

However, it is recognized that methods such as calculating AG and ACAG can fail to identify the complex metabolic disturbances seen in clinically ill patients [4]. On the other hand, the SIG is calculated from all charged blood constituents and Gunnerson described that SIG was the gold standard for quantification of unmeasured anions [26]. The usefulness of SIG in predicting prognosis in patients after cardiac arrest treated with mild therapeutic hypothermia and in predicting mortality in pediatric burn injury patients was reported [27, 28]. In our previous reports, we were not able to calculate SIG because of the lack of data. We conducted this prospective study to calculate SIG and compare the usefulness of SIG with AG and ACAG in the prediction of ROSC in patients with CPAOA.

As a result, we found that SIG was markedly increased in the CPAOA patients, indicating the presence of metabolic acidosis on admission in patients with CPAOA. However, there was no significant difference in SIG between the ROSC (+) and the ROSC(-) groups although there were significant differences in AG and ACAG. In addition, the AUC of SIG for ROSC was lower than those of AG and ACAG. These results suggest that AG and ACAG have stronger relationships with ROSC than SIG.

To the best of our knowledge, this is the first report that evaluated the usefulness of SIG calculated with laboratory data measured on arrival at the hospital to predict ROSC in CPAOA patients. Our results are not in agreement with the reports described above; however, there are some reports that contradicted the usefulness of SIG. Cusack *et al.* examined whether SIG could predict outcome in critically ill patients in a mixed medical/surgical adult ICU, and reported that SIG appeared to offer no advantage in prediction of outcome and its use as a prognostic marker could not be advocated [27]. In that study, simple logistic regression analysis showed that AG and ACAG were better than SIG in predicting outcome. They analyzed the reasons for the poor ability of SIG and gave two points: 1) the abnormalities associated with an adverse outcome might have been removed by compensating for abnormalities in electrolytes and albumin and taking lactate out of the equation, and 2) the type of fluids used for resuscitation in their institution might have had an adverse effect on SIG [27]. It is supposed that these two causes were not related with our results because a blood sample was taken from our patients before transfusion. The value of SIG is influenced by various diseases such as hepatic dysfunction [15] and renal dysfunction [28], as well as during endotoxin-induced sepsis [29]. In this study, several causes of CPAOA were included and those factors might have impacted the value of SIG. In addition, it is possible that many parameters that do not affect the prognosis of patients with CPAOA are included in SIG. Sequential measurement of SIG could be more informative than individual measurement [27], and this point might also have affected the results of our study. However, it might be difficult to perform repeated blood sampling during CPR until ROSC can be obtained.

4.1 Limitations

This was a study performed at only one institute, and the number of patients was not large. Prehospital factors such as the exact time of CPA occurrence, the duration between CPA occurrence and the start of CPR, and the duration between CPA occurrence and the time of blood sampling could not be evaluated because there were not enough data. The relationship between SIG and neurological outcome could not be evaluated because there were only two patients who survived and were discharged from our hospital. Therefore, further studies including multi-center analysis are required.

5 Conclusion

Our prospective study showed that AG and ACAG calculated in a blood sample obtained on arrival at our hospital had stronger relationships with ROSC in patients with CPA compared with SIG. It is possible that AG and ACAG can better predict ROSC following CPR in patients with CPA compared with SIG.

Conflict of interest statement: Authors state no conflict of interest.

References

[1] Kleinman ME, Brennan EE, Goldberger ZD, et al. Adult Basic Life Support and Cardiopulmonary Resuscitation Quality: 2015 American Heart Association Guidelines Update for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. Circulation 2015; 132 (18 Suppl 2): S414-35. doi: 10.1161/CIR.0000000000000259
[2] Hagiwara S, Oshima K, Furukawa K,et al. The significance of albumin corrected anion gap in patients with cardiopulmonary arrest. Ann Thorac Cardiovasc Surg 2013; 20: 283-288
[3] Zampieri FG, Park M, Ranzani OT, et al. Anion gap corrected for albumin, phosphate and lactate is a good predictor of strong ion gap in critically ill patients: a nested cohort study. Rev Bras Ter Intensiva 2013; 25: 205-211. doi: 10.5935/0103-507X.20130036
[4] Fencl V, Jabor A, Kazda A, et al. Diagnosis of metabolic acid-base disturbances in critically ill patients. Am J Respir Crit Care Med 2000; 162: 2246-2251
[5] Zheng CM, Liu WC, Zheng JQ,et al. Metabolic acidosis and strong ion gap in critically ill patients with acute kidney injury. Biomed Res Int [Epub 2014 Aug 5]. doi: 10.1155/2014/819528
[6] Balasubramanyan, Havens PL, Hoffman GM. Unmeasured anions identified by the Fencl-Stewart method predict mortality better than base excess, anion gap, and lactate in patients in the pediatric intensive care unit. Crit Care Med 1999; 27: 1577-1581
[7] Dondorp AM, Chau TT, Phu NH, et al. Unidentified acids of strong prognostic significance in severe malaria. Crit Care Med 2004; 32: 1683-1688

[8] Kaplan LJ, Kellum JA. Initial pH, base deficit, lactate, anion gap, strong ion difference, and strong ion gap predict outcome from major vascular injury. Crit Care Med 2004; 32: 1120-1124
[9] Funk GC, Doberer D, Sterz F, et al. The strong ion gap and outcome after cardiac arrest in patients treated with therapeutic hypothermia: a retrospective study. Intensive Care Med 2009; 35: 232-9. doi: 10.1007/s00134-008-1315-1
[10] Knaus WA, Draper EA, Wagner DP, et al. APACHE II: a severity of disease classification system. Crit Care Med 1985; 101: 818-829
[11] Vincent JL, de Mendonça A, Cantraine F, et al. Use of the SOFA score to assess the incidence of organ dysfunction/failure in intensive care units: results of a multicenter, prospective study. Working group on "sepsis-related problems" of the European Society of Intensive Care Medicine. Crit Care Med 1998; 101: 1793-1800
[12] Oh MS, Carroll HJ. Current concepts: the anion gap. N Engl J Med 1977; 297: 814-817
[13] Hatherill M, Waggie Z, Purves L, et al. Correction of the anion gap for albumin in order to detect occult tissue anions in shock. Arch Dis Child 2002; 87: 526-529
[14] Figge J, Jabor A, Kazda A, et al. Anion gap and hypoalbuminemia. Crit Care Med 1998; 26: 1807-1810
[15] Kellum JA, Kramer DJ, Pinsky MR. Strong ion gap: a methodology for exploring unexplained anions. J Crit Care 1995; 101: 51-55
[16] Stewart PA. Modern quantitative acid-base chemistry. Can J Physiol Pharmacol 1983; 61: 1444-1461
[17] Figge J, Mydosh T, Fencl V. Serum proteins and acid-base equilibria: a follow-up. J Lab Clin Med 1992; 101: 713-719
[18] Nehme Z, Andrew E, Bray J.E, et al. The significance of pre-arrest factors in out-of-hospital cardiac arrests witnessed by emergency medical service: A report from the Victrian Ambulance Cardiac Arrest Registry. Resuscitation 2015; 88: 35-42. doi: 10.1016/j.resuscitation.2014.12.009
[19] Morrison LJ, Kierzec G, Diekema DS, et al. Part 3: ethics: 2010 American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. Circulation 2010; 122: S665-75. doi: 10.1161/CIRCULATIONAHA.110.970905
[20] Drennan IR, Lin S, Sidalak DE, et al. Survival rates in out-of-hospital cardiac arrest patients transported without prehospital return of spontaneous circulation: An observational cohort study. Resuscitation 2014; 85: 1488-93. doi: 10.1016/j.resuscitation.2014.07.011
[21] Hagiwara S, Murata M, Kaneko M, et al. Usefulness of serum fibrin degradation products and d-dimer levels as biomarkers to predict return of spontaneous circulation in patients cardiopulmonary arrest on arrival: comparison with acid-base balance. Acute Medicine & Surgery 2014; 1: 222-7.26. doi: 10.1097/TA.0b013e31828cc967
[22] Emmett M, Naris RG. Clinical use of the anion gap. Medicine [Baltimore] 1977; 101: 38-54
[23] Salem MS, Mujais SK. Gaps in the anion gap. Arch. Intern. Med. 1992; 152: 1625-1629
[24] Rocktaeschel J, Morimatsu H, Uchino S, et al. Acid-base status of critically ill patients with acute renal failure: analysis based on Stewart-Figge methodology. Crit Care 2003; 7: R60-66
[25] Morris CG, Low J. Metabolic acidosis in the critically ill: part 2. Causes and treatment. Anaesthesia 2008; 63: 396-411
[26] Gunnerson KJ. Clinical review: the meaning of acid-base abnormalities in the intensive care unit part 1- epidemiology. Crit Care 2005; 101: 508-516
[27] Funk GC, Doberer D, Sterz F, et al. The strong ion gap and outcome after cardiac arrest in patients treated with therapeutic hypothermia: a retrospective study. Intensive Care Med 2009; 101:232-239
[28] Moviat M, van Haren F, van der Hoeven H. Conventional or physicochemical approach in intensive care unit patients with metabolic acidosis. Crit Care 2003; 7: R41-45. doi: 10.1016
[29] Kellum JA, Bellomo R, Kramer DJ, et al. Hepatic anion flux during acute endotoxemia. J Appl Physiol 1995; 78: 2212-2217