Anion gap corrected for albumin, phosphate and lactate is a good predictor of strong ion gap in critically ill patients: a nested cohort study

ABSTRACT

Objective: Corrected anion gap and strong ion gap are commonly used to estimate unmeasured anions. We evaluated the performance of the anion gap corrected for albumin, phosphate and lactate in predicting strong ion gap in a mixed population of critically ill patients. We hypothesized that anion gap corrected for albumin, phosphate and lactate would be a good predictor of strong ion gap, independent of the presence of metabolic acidosis. In addition, we evaluated the impact of strong ion gap at admission on hospital mortality.

Methods: We included 84 critically ill patients. Correlation and agreement between the anion gap corrected for albumin, phosphate and lactate and strong ion gap was evaluated by the Pearson correlation test, linear regression, a Bland-Altman plot and calculating interclass correlation coefficient. Two subgroup analyses were performed: one in patients with base-excess <-2mEq/L (low BE group - IBE) and the other in patients with base-excess >-2mEq/L (high BE group - hBE). A logistic regression was performed to evaluate the association between admission strong ion gap levels and hospital mortality.

Results: There was a very strong correlation and a good agreement between anion gap corrected for albumin, phosphate and lactate and strong ion gap in the general population ($r^2=0.94$; bias 1.40; limits of agreement -0.75 to 3.57). Correlation was also high in the IBE group ($r^2=0.94$) and in the hBE group ($r^2=0.92$). High levels of strong ion gap were present in 66% of the whole population and 42% of the cases in the hBE group. Strong ion gap was not associated with hospital mortality by logistic regression.

Conclusion: Anion gap corrected for albumin, phosphate and lactate and strong ion gap have an excellent correlation. Unmeasured anions are frequently elevated in critically ill patients with normal base-excess. However, there was no association between unmeasured anions and hospital mortality.

Keywords: Acid-base equilibrium/physiology; Critical illness; Blood chemical analysis; Serum albumin/blood; Phosphate/blood; Lactate/blood; Prognosis
AG was calculated as \( \frac{([Na] + [K] - [Cl] - [HCO_3^-])}{(10^{-2} \text{mEq/L} - [\text{hBE} \text{ group}])} \). AGCAPL was calculated as AGCAPL = \((([Na] + [K] - [Cl] - [HCO_3^-]) - (2 \times \text{albumin g/dL} + 0.5 \times \text{phosphate mg/dL}) - \text{[lactate mmol/L]} \)), as previously shown.\(^7\) SIG was defined as the difference between apparent and effective strong ion difference (SIDa and SId\text{e}, respectively). SIDa was calculated as SIDa = \([Na] + [K] + [Mg] + [Ca] - [Cl] - [\text{Lactate}]\). SId\text{e} was calculated as SId\text{e} = 12.2 \times \text{pCO}_2 \times (10^{-0.19}) + 10 \times \text{[albumin]} \times (0.123 \times \text{pH} - 0.631) + [\text{PO}_4^{3-}] \times (0.309 \times \text{pH} - 0.469). Blood gas analysis and lactate measurement were performed using an OMNI analyzer (Roche Diagnostics System, F. Hoffmann, La Roche Ltd, Basel, Switzerland).

Data were tested for normality using the Kolmogorov-Smirnoff or Shapiro-Wilkes test, as appropriate. Continuous normal data were compared using the t-test or analysis of variance. Continuous data that were not normal were compared using the Mann-Whitney test or Kruskal-Wallis test, as appropriate. Fisher’s exact test or Chi-squared tests were used for dichotomous variables.

After confirming the normal distribution of the involved variables, we analyzed the correlation between AGCAPL and SIG using a Pearson correlation test. Agreement was evaluated through a Bland-Altman plot and the measurement of the interclass correlation coefficient (ICC).\(^17\) We also built a linear regression between AGCAPL and SIG and obtained the R\(^2\) of the prediction model. Two subgroup analyses were performed: one in patients with low base excess (BE < -2mEq/L - lBE group) and the other in patients with high base excess (BE > -2mEq/L - hBE group).

To evaluate the association between admission SIG levels and hospital mortality, we built one logistic regression using hospital mortality as the outcome. Variables associated with a p<0.05 by univariate analysis were included in the analysis.\(^18\) A stepwise regression was performed to identify variables that were independently associated with hospital mortality. The prediction capability of SIG for hospital mortality was also evaluated through the creation of an ROC curve and the calculation of the area under the curve.\(^19\)

All analyses were performed using the R software (www.r-project.org) with the pROC and car packages. Mountain plots were created using MedCalc version 12.7.0 (MedCalc Software, Acacialaan 22, B-8400 Ostend, Belgium). A p<0.05 was considered significant for all analyses.
RESULTS

The general characteristics of the patients who were included in the study are shown in Table 1. Demographic data were similar between patients with metabolic acidosis (lBE) and patients without metabolic acidosis (hBE) at ICU admission. lBE patients had higher illness severity, as evaluated by the total SOFA score (7 [3-9] versus 3.5 [2-6.5]; p<0.01), but similar SAPS3 levels (55 [43.2-68.2] versus 51 [41.7-61.2]; p=0.51). Admission due to sepsis was more common in the lBE than in the hBE group (66% versus 30%; p<0.01). ICU and hospital mortality was similar for both groups. Patients in the lBE group had lower values for pH, BE, bicarbonate, CO₂, SIDa and albumin. The lBE group had higher levels of lactate, AG, AGCAPL and SIG.

There was a very strong correlation between AGCAPL and SIG in the general population (r²=0.94; Figure 1), and the ICC was high (0.93; CI 0.89-0.95). The bias was 1.40, and the limits of agreement were -0.75 to 3.57, as shown in the Bland-Altman plot (Figure 2). The correlation was also high in the lBE group (r²=0.94; ICC = 0.91, CI 0.85-0.95; bias = 1.55; limits of agreement from -0.67 to 3.75) and in the hBE group (r²=0.92; ICC = 0.90, CI 0.82-0.95; bias = 1.22; limits of agreement from -0.85 to 3.3).

Uncorrected AG had a much weaker correlation with SIG in the general population (r²=0.66), lBE group (r²=0.58) and hBE group (r²=0.67). A mountain plot for the difference between uncorrected AG, AGCALP and SIG for each percentile of SIG is shown in figure 3. Values of SIDa, SIDe and SIG for the whole population, lBE group, hBE group and hBE group with high SIG are shown in a violin plot in figure 4.

High levels of SIG (above 6mEq/L) were present in 56 patients (66% of the whole population). In the hBE group, 16 patients (42%) had a SIG above 6mEq/L. The biochemical comparison between patients from the hBE group with high (≥6mEq/L) and low SIG values is shown in Table 2.

Table 1 - Clinical and laboratory features of studied patients

| Features          | All patients (N=84) | Low base-excess (N=48) | High base-excess (N=36) | p value |
|-------------------|---------------------|------------------------|-------------------------|---------|
| Age (years)       | 50.21 (17.40)       | 51.02 (18.70)          | 49.13 (15.64)           | 0.61    |
| Sex, male         | 49 (58)             | 25 (52)                | 20 (55)                 | 0.75    |
| SAPS3             | 52.50 (41.75-64.75) | 55 (43.25-68.25)       | 51 (41.75-61.25)        | 0.01    |
| SOFA at admission | 5 (2-9)             | 7 (3-9)                | 3.5 (2-6.5)             | <0.01   |
| Sepsis            | 43 (51)             | 32 (66)                | 11 (30)                 | <0.01   |
| ICU mortality     | 20 (23)             | 13 (27)                | 7 (19)                  | 0.41    |
| Hospital mortality| 26 (20)             | 18 (37)                | 8 (22)                  | 0.13    |
| pH                | 7.38 (7.33-7.41)    | 7.36 (7.29-7.40)       | 7.40 (7.38-7.41)        | <0.01   |
| BE (mEq/L)        | -2.4 (-4.87-0.75)   | -4.55 (-8.47-3.2)      | -0.3 (-1.12-2.65)       | <0.01   |
| HCO₃⁻ (mEq/L)     | 21.8 (19.24)        | 19.65 (17.45-21.50)    | 24.4 (23.28-27.22)      | <0.01   |
| PCO₂ (mmHg)       | 37.1 (32.45-44)     | 34.15 (29.98-39.78)    | 41 (37.32-46.02)        | <0.01   |
| Na (mEq/L)        | 139 (136-143.2)     | 138 (135.8-143)        | 140 (137-144)           | 0.11    |
| CI (mEq/L)        | 104 (104-108.2)     | 104.5 (101.8-108)      | 104 (100-109)           | 0.88    |
| Mg (mg/dL)        | 1.95 (1.68-2.22)    | 1.97 (1.68-2.13)       | 1.93 (1.68-2.32)        | 0.73    |
| Ca (mg/dL)        | 5 (4-5)             | 4.5 (4-5)              | 5.0 (4.75-5.0)          | 0.01    |
| P (mg/dL)         | 3.4 (2.77-4.95)     | 3.65 (2.67-5.10)       | 3.30 (2.8-4.3)          | 0.57    |
| Albumin (mg/dL)   | 3.0 (2.3-3.5)       | 2.8 (2.1-3.2)          | 3.35 (2.87-3.62)        | <0.01   |
| Lactate (mmol/L)  | 1.56 (1.11-2.48)    | 1.83 (1.27-2.61)       | 1.38 (1.11-1.80)        | 0.03    |
| AG (mEq/L)        | 16.50 (13.92-19.12) | 17.35 (16.05-20.98)    | 15.15 (12.85-16.70)     | <0.01   |
| AGCAPL (mEq/L)    | 6.69 (4.34-9.34)    | 8.68 (6.34-10.52)      | 4.95 (2.69-6.61)        | <0.01   |
| SIG (mEq/L)       | 8.12 (5.79-10.92)   | 9.82 (7.76-12.32)      | 5.82 (3.73-7.41)        | <0.01   |
| SIDa (mEq/L)      | 40.90 (37.13-43.86) | 39.24 (36.37-41.31)    | 43.26 (40.26-45.74)     | 0.01    |
| SIDe (mEq/L)      | 32.09 (28.45-35.90) | 29.11 (26.61-31.18)    | 36.29 (34.10-39.40)     | <0.01   |

SAPS3 - Simplified Acute Physiology Score; SOFA - Sepsis Related Organ Failure Assessment; ICU - intensive care unit; BE - base-excess; AG - anion gap; AGCAPL - anion gap corrected for albumin, phosphate and lactate; SIG - strong ion gap; SIDa - apparent strong ion difference; SIDe - effective strong ion difference. p value for high versus low BE groups. The results are expressed as a number (%), mean or median (IQ) ± standard deviation.
The variables included in the mortality prediction model were total SOFA score, SAPS3 score, albumin levels, pH, BE, lactate levels, SIG and diagnosis of sepsis. After stepwise regression, only SAPS3 (OR 1.04; CI 95% 1.01-1.08 per point increase) and albumin levels (OR 0.19; CI 95% 0.07-0.49 per point increase) were associated with hospital mortality. SIG had a poor prediction capability for hospital mortality (AUC 0.61; CI 95% 0.47-0.74).

**DISCUSSION**

Our analysis demonstrates that AGCAPL is highly correlated with SIG in a mixed sample of critically ill patients and that such correlation is independent of the presence of metabolic acidosis. AGCAPL performed much better than uncorrected AG in the general
population and subgroups, as seen by the Pearson correlation and mountain plot results. We have also shown that unmeasured anions are frequently elevated in critically ill patients, even in patients with an apparently normal BE (42% of cases). Additionally, we have shown that SIG is not associated with hospital mortality by logistic regression.

The agreement between corrected anion gap and SIG has been shown in other studies. Moviat et al. have previously evaluated the correlation of albumin- and lactate-corrected anion gap with SIG in acidic BE (-5mEq/L) patients. They concluded that SIG and AG were strongly correlated ($r^2=0.93$), with a small bias, but the interclass coefficient correlation was not reported. We obtained values similar to those from Moviat et al. for the correlation between AG and AGCAPL, suggesting that the addition of the correction for phosphate levels does not improve the correlation between AG and SIG. However, taking agreement into consideration, the bias between SIG and the corrected anion gap was slightly lower in our analysis (1.86 versus 1.40), which may have occurred because phosphate levels were taken into account or due to a difference in samples. Therefore, the only benefit of adding the correction for phosphate in the AG is a small reduction in the bias, which is most likely clinically irrelevant. Martin et al. and Dubin et al. also reported an excellent correlation between albumin-corrected AG and SIG. Finally, Abdulraof Menesi et al. have shown that both the traditional and the physicochemical approaches are similar, even in specific populations, such as patients with kidney graft. Abdulraof Menesi et al. also suggested that the correlation between AG and SIG could be reduced when AG levels were low. In our analysis, we also found a lower slope for the relationship between AGCAPL and SIG in patients with low AGCAPL (<10) compared to those with high AGCAPL (>10) ($r=0.97$ and $r=1.07$, respectively - data not shown). This finding was not the primary endpoint of our study and deserves further evaluation in larger samples.

The correct diagnosis of the metabolic disturbance is important for clinical management. High lactate levels are related to hypoperfusion, while hyperchloremia may be the result of aggressive resuscitation using chloride-rich solutions. The latter consideration may be particularly important because hyperchloremia has been suggested to be associated with mortality. The association between unmeasured anions and hypoperfusion, however, is less clear. It remains to be determined if SIG levels can be used as a marker of hypoperfusion or if it is appropriate to institute a specific treatment (e.g., fluid loading, inotropes) when unmeasured anions are increased. Nevertheless, unmeasured anions are frequently elevated in critical illness, reportedly elevated in more than 90% of trauma patients when a low cutoff is used, and may be associated with poor prognosis. Patients may present with “occult” metabolic acidosis, i.e., the higher levels of unmeasured anions may be masked by concomitantly reduced albumin levels. In our analysis, 42% (16) of the patients with normal BE had high levels of unmeasured anions. When those patients were compared with the remaining patients in the hBE group with low SIG (20 patients) (Table 2), they had a lower PCO$_2$ and lower SIDs. Therefore, the high SIG levels were compensated for by a reduction in SIDs that was mainly caused by decreased albumin (Table 2) and a reduction in PCO$_2$, highlighting the complex acid-base behavior in critical illness. AGCAPL still had an excellent correlation with SIG in these patients ($r^2=0.95$).

The impact of SIG on mortality is also debated, with some reports showing an association with mortality, while others found no association. Durward et al. showed that SIG was better than lactate as a predictor of mortality after cardiac surgery in children, although no model was built. In trauma patients, Kaplan et al. reported that SIG was a good predictor of mortality and was the strongest factor associated with mortality by logistic regression. On the other hand, Rocktaeschel et al. found that, despite being associated with mortality by multivariate analysis, SIG values had a poor prediction capability for mortality. Recently, Ratanarat et al. also suggested that SIG was higher in non-survivors, although no multivariate model was implemented to reduce confounding variables. In our analysis, SIG values were not associated with in-hospital mortality after logistic regression. In fact, not even BE was associated with mortality in our analysis, contrary to previous research on the subject. The prediction capability of SIG for hospital mortality was also poor (AUC 0.61; 95% CI 0.47-0.74). This finding may be explained by the mix of clinical diagnosis at admission, particular sample features or both.

The best method for the interpretation of acid-base disorders at the bedside remains to be defined. Dubin et al. have shown that the physicochemical approach offers no advantage over the traditional approach with corrected AG; in fact, the physicochemical approach allowed for an additional diagnosis of metabolic acidosis in only 1% of the cases. Martin et al. have shown that the results of the traditional approach (using anion gap) and the physicochemical approach yield different clinical interpretations in up to 28% of trauma patients, while
Kaplan et al. have suggested that a physicochemical approach can improve the accuracy of acid-base disturbances in trauma and, therefore, reduce inappropriate fluid loading due to the suspicion of hyperfusion-induced metabolic acidosis. Boniatti et al. reported a series of 175 patients and evaluated the percentage of cases in which the physicochemical approach would supply different results when compared to the traditional approach. The authors concluded that the physicochemical approach would allow for an additional diagnosis of metabolic disorder (specifically, a decrease in SIDe) in over 33% of the cases. However, several caveats in the methods, such as the use of different thresholds for BE and SID and misinterpretations of the acid-base status, limit the validity of the data. As Dubin et al. have previously stated, both methods will most likely yield similar results if they are properly applied. Although this question has yet to be settled, our findings suggest that AGCAPL is a good surrogate for SIG measurements, with the advantage of being more easily calculated at the bedside.

Our study has several limitations. First, our small sample limits subgroup analysis and reduces external validity. Because this is a single-center study, the bias between SIG and AGCAPL reflects the evaluated population. Despite including a significant range of diagnoses, these results cannot be generalized to other specific populations in different settings. Second, we did not evaluate the impact of any approach on clinical management. Therefore, the impact of the measurement of unmeasured anions at the bedside should be explored in further studies. Third, we only evaluated ICU admission values. Consequently, the impact of acid-base status changes during ICU stay on prognosis was not possible.

CONCLUSION

Unmeasured anions are frequently elevated in critically ill patients. Because there is a strong correlation between anion gap corrected for albumin, phosphate and lactate and strong ion gap in patients with both normal and low base-excess, anion gap corrected for albumin, phosphate and lactate may be used as a surrogate for strong ion gap at the bedside. Strong ion gap values at admission are not associated with in-hospital mortality.

Authors’ contributions

FG Zampieri, LM Cruz Neto, HP Souza, FP Silva designed the study and conducted data collection. FG Zampieri, OT Ranzani, M Park and AT Maciel performed statistical analysis. FG Zampieri and M Park wrote the manuscript. All authors reviewed the manuscript in its final form.
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