An alternative approach to acid–base abnormalities in critically ill patients

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Traditionally, clinical acid–base abnormalities have been interpreted using the pH notation proposed by Sorensen, and the \( \text{PCO}_2 / \text{bicarbonate} \) model of Henderson and Hasselbalch (H–H). However, for some patients in the operating theatre or intensive care unit (ICU), the traditional method is often inadequate to explain the severity and complexity of acid–base disorders as it emphasizes interpretation rather than pathophysiology. In this review, we discuss some of the limitations of the traditional approach and how, using an alternative physical chemical approach, we can improve our understanding of perioperative acid–base balance.

The traditional approach and its limitations

The traditional approach using the pH notation based on the concept of a hydrogen ion exponent was recently reviewed in this journal. One limitation of pH (the log of the reciprocal of the hydrogen ion concentration) is the fact that it is a dimensionless number, the changes of which are not readily translated into changes in hydrogen ion concentration [H\(^+\)]. The H–H equation describes the chemical hydration reaction of carbon dioxide to carbonic acid:

\[
\text{pH} = \text{pK} + \frac{\log \text{HCO}_3^-}{\text{Dissolved CO}_2}\]

When interpreting blood gas results, keep in mind that only \([\text{H}^+]\) and \(\text{PCO}_2\) are measured directly; the bicarbonate concentration is derived by solving the H–H equation. It is important to realize what this equation does, and does not, tell us. The equation allows the classification of disorders by the primary type of acid that is increasing or decreasing. By carefully examining the changes that occur in \(\text{PCO}_2\) and \([\text{HCO}_3^-]\) in relationship to each other, one can identify a highly conserved pattern that can differentiate chronic from acute respiratory derangements and metabolic acidosis from metabolic alkalosis. Table 1 illustrates the direction of changes in [\(\text{HCO}_3^-\)] and \(\text{PaCO}_2\), in response to metabolic and respiratory acid–base disturbances; these rules also allow us to diagnose mixed disorders.

However, the equation does not allow us to quantify the severity of the metabolic derangements in the same way as the respiratory component and it does not tell us about any acids other than carbonic acid.

Base excess

To address the first shortcoming of the H–H equation, that is, the inability to quantify the metabolic component, base excess (BE) methodology has been used. This is defined as the amount of acid or base that must be added to a sample of whole blood in vitro to restore the pH of the sample to 7.40 while the \(\text{PCO}_2\) is held at 5.33 kPa at a given haemoglobin (Hb) concentration. The BE of oxygenated blood with a Hb of 15 g dl\(^{-1}\) at a pH of 7.4 and \(\text{PCO}_2\) of 5.33 kPa is zero. BE is strongly influenced by Hb concentration, which is the main buffer in blood. It was noted that the discrepancy between in vitro and in vivo BE values could be reduced by using a Hb value of 5 g dl\(^{-1}\), an empiric estimate to account for an ‘average’ content of Hb across the entire extracellular fluid space. This was called the standard BE (SBE), which is independent of \(\text{PCO}_2\) and can be used to define the metabolic component of an acid–base disturbance. However, BE does not address the second problem that is associated with the H–H equation, that is, it does not tell us about the mechanisms of metabolic acid–base disturbance.

The anion gap

The anion gap (AG) was introduced to help establish the cause of a metabolic acid–base...
Table 1 Changes in Pₐₐₙₒ and [HCO₃⁻] in response to acute and chronic acid–base disturbances. Δ, change in value; [HCO₃⁻], concentration of bicarbonate

<table>
<thead>
<tr>
<th>Disorder</th>
<th>[HCO₃⁻] vs Pₐₐₙₒ</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute respiratory acidosis</td>
<td>Δ[HCO₃⁻] = 0.2 ΔPₐₐₙₒ</td>
</tr>
<tr>
<td>Chronic respiratory acidosis</td>
<td>Δ[HCO₃⁻] = 0.5 ΔPₐₐₙₒ</td>
</tr>
<tr>
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</tr>
<tr>
<td>Chronic respiratory alkalosis</td>
<td>Δ[HCO₃⁻] = 0.5 ΔPₐₐₙₒ</td>
</tr>
<tr>
<td>Metabolic acidosis</td>
<td>ΔPₐₐₙₒ = 1.3ΔHCO₃⁻</td>
</tr>
<tr>
<td>Metabolic alkalosis</td>
<td>ΔPₐₐₙₒ = 0.75 ΔHCO₃⁻</td>
</tr>
</tbody>
</table>

Table 1: Changes in Pₐₐₙₒ and [HCO₃⁻] in response to acute and chronic acid–base disturbances. Δ, change in value; [HCO₃⁻], concentration of bicarbonate.

Alternative approach to acid–base abnormalities

Stewart’s work centres on several basic physico-chemical properties of water-based solutions:

(i) **Dissociation**: the separation of the ionic components of a solute. Strong ions completely dissociate in solution, for example, a solution of sodium chloride. Other substances only partially dissociate, for example, weak acids are in solution in both the anionic dissociated form (A⁻) and the undisassociated form (HA).

(ii) **Electroneutrality**: in aqueous solution, the sum of all the positive charged ions in any compartment must equal the sum of all negative charged ions. Pure water is a neutral solution because the H⁺ and the OH⁻ concentrations are equal. Crucially, the concentration of these ions is determined by a temperature-sensitive dissociation constant.

(iii) **Mass conservation**: whereby the amount a substance remains constant unless it is added, removed, generated, or destroyed.

In aqueous solutions, water provides an inexhaustible source of H⁺ through the dissociation of water; changes in pH are not the result of generation or removal of H⁺ per se, but rather changes in other independent variables. In plasma, Stewart identified three principal mathematically independent determinants that, when imposed on the physical chemical milieu of body fluids, dictate their acid–base status. These variables are: (i) carbon dioxide; (ii) electrolytes (strong ions); and (iii) weak acids.

The partial pressure of CO₂ is determined by the balance between CO₂ production by cellular metabolism (or the titration of HCO₃⁻ by metabolic acids) and the elimination of CO₂ through alveolar ventilation. In plasma, strong cations (mainly Na⁺) outnumber strong anions (mainly Cl⁻); the difference between the sum of measured strong cations and anions is known as the strong ion difference (SID):

$$\text{SID} = [\text{Na}^+ + \text{K}^+ + \text{Ca}^{2+} + \text{Mg}^{2+}] - [\text{Cl}^- + \text{lactate}^-]$$

It is important to note that bicarbonate is not a strong ion. The SID has a powerful electrochemical effect on water dissociation, and hence on H⁺ concentration. In healthy humans, plasma SID is 40–44 mmol litre⁻¹. Metabolic acidosis is produced by a decrease in SID. As SID decreases (i.e. becomes less positive), water dissociates more to maintain electrical neutrality. Hence, there is an increase in free H⁺ concentration and pH decreases. In contrast, metabolic alkalosis occurs as a result of an inappropriately large SID.

The remaining negative charges that balance SID (to maintain electrical neutrality) come from CO₂ and weak acids; hence:

$$\text{SID} - (\text{CO}_2 + \text{A}^-) = 0.$$  

Weak acids are mostly proteins (predominantly albumin) and phosphate. Stewart used the term AIRROR to represent the total concentration of weak ions, that is, AH + A⁻. Hypoalbuminaemia, equivalent to a loss of weak acids from the plasma, has a slightly alkalizing effect and the body adapts by decreasing SID.

The AG can be reduced by the abnormal presence of unmeasured cations (e.g. immunoglobulin G and hypercalcaemia) and after lithium administration.

The alternative approach

In 1983, Peter Stewart, a Canadian physiologist, proposed his quantitative physical chemical approach to acid–base balance. Recently, there has been a resurgence of interest in Stewart’s approach as it helped to clarify the underlying mechanisms of a number of common acid–base problems frequently encountered in critically ill patients.

Basic principles

Solutions of biological interest share two important characteristics: virtually all are aqueous and most are alkaline ([OH⁻] > [H⁺]).
of the three basic principles coupled with the expression of the three independent variables. Although the equations look simple, they require a computer to solve. These equations were further modified to five equations in what became known as the Fencl–Stewart approach. Keeping in mind that sodium and chloride are the principle components of extracellular SID and albumin is the principal extracellular weak acid, Story and colleagues suggested a simpler equation-based approach to clinical diagnosis of the underlying mechanism of abnormal SBE:

(i) SBE from a blood gas machine;
(ii) sodium–chloride effect on BE = [Na⁺] – [Cl⁻] – 38;
(iii) albumin effect = 0.25 × (42 – [albumin]);
(iv) unmeasured ion effect = SBE – (Na⁺ – Cl⁻ effect) – (albumin effect)

Table 4 provides a clinical example of the simplified Fencl–Stewart approach. It shows an acid–base assessment of a patient after induction of anaesthesia and after 2 h of major gynaecological surgery. Normal saline was used for intraoperative fluid replacement. In this patient, most of the metabolic acidosis can be explained by a decrease in the SID secondary to an increase in plasma chloride. This is partly offset by a decrease in the total weak acid concentration (albumin). Unmeasured ions are unimportant in this acidaemia. These changes follow the infusion of about 6 litres of sodium chloride 0.9%.

Thinking differently about fluids

L.V. fluids mix and equilibrate with extracellular fluid, thus altering the extracellular SID and A TOT. The CO₂TOT of the infused fluid does not affect extracellular SID and A TOT. In other words, it is not the presence of HCO₃⁻ in sodium bicarbonate preparations that reverses a metabolic acidosis; rather it is the high SID (100 mmol litre⁻¹ for 8.4% NaHCO₃) and the absence of A TOT.

Which fluid?

Large-volume normal saline infusion can cause a metabolic acidosis. Although best documented during resuscitation of hypovolaemic patients, acute normovolaemic haemodilution and cardiopulmonary bypass have similar potential. The mechanism is not bicarbonate dilution; bicarbonate is a dependent variable and

Table 2 summarizes the acidifying or alkalinizing effect of Stewart’s independent variables.

Physiological mechanisms controlling strong ion difference

The kidney is the primary organ that changes the relative concentrations of strong cations and anions. Acid handling by the kidney is mediated through chloride balance. Every chloride ion that is filtered, but not reabsorbed, increases SID. Note that H⁺ excretion is irrelevant because water provides an infinite source of H⁺. However, NH₄⁺ is important to systemic acid–base balance because of its co-excretion with Cl⁻. Hepatic generation of ammonium [NH₄⁺] and glutamine are important for systemic acid–base balance and are controlled tightly by mechanisms that are sensitive to plasma pH; hepatic glutaminogenesis is stimulated by base balance and are controlled tightly by mechanisms that are

Stewart’s equations

Stewart set out six independent simultaneous equations describing his approach to acid–base balance (Table 3). They are applications

Table 3 Stewart’s equations. All K-values are known dissociation constants. Pco₂, partial CO₂ tension; SID, strong ion difference

Table 4 Simplified Fencl–Stewart approach
its loss cannot be the cause of acidosis. Instead, chloride administration decreases SID (an independent variable) and produces increased water dissociation and hence, H⁺ concentration (hyperchloraemic metabolic acidoses). The reason why this occurs with normal saline is that although it contains equal amounts of Na⁺ and Cl⁻ (154 mmol litre⁻¹) with a SID of zero, the plasma does not. Infusion of large volumes will have a proportionally greater effect on total body chloride (normal ~100 mmol litre⁻¹) than on total body sodium (normal ~135 mmol litre⁻¹) (Table 5). This effect is not to be confused with dilutional acidoses which results from infusion of hypotonic fluids. Excessive administration of hypotonic, sodium-poor fluids (e.g. 5% dextrose or dextrose–saline solutions), will lead to a decreased SID together with hypotonic, sodium-poor fluids (e.g. 5% dextrose or dextrose–saline solutions), will lead to a decreased SID together with hypo-natraemia (Table 5). Critically ill patients are especially susceptible to these changes because of increased ADH concentrations associated with the stress response.

Hartmann’s solution (Table 6) is the best-known commercial ‘balanced’ electrolyte solution. It has a SID lower than plasma but greater than zero, which will drop the plasma SID just enough to counteract the A TOT dilutional alkalosis caused by albumin-free fluid transfusion. Hartmann’s solution contains 29 mmol litre⁻¹ of lactate which is rapidly metabolized in the absence of severe liver dysfunction.

In states of hypovolaemia associated with loss of free water, although the total concentration of ions remains unchanged, SID increases as sodium increases more than chloride. This is the basis of contraction alkalosis. These patients respond to transfusion of normal saline or any fluid with zero SID. Some types of metabolic alkalosis are associated with hypokalaemia and total body potassium deficits. When dealing with these patients, infusing potassium chloride can reverse the alkalosis. This is because most of the infused potassium will end up within the cell, whereas chloride, the strong anion, stays in the extracellular space and so reduces plasma SID.

Colloids are often used in fluid resuscitation of critically ill patients. A recent multicentre randomized trial has shown no difference in outcome at 28 days between ICU patients resuscitated with either normal saline or albumin 4% (the SAFE study), thus lifting the cloud hanging over albumin solutions. The overall tendency of the available colloids (Table 7) is to decrease plasma SID and cause metabolic acidosis, an effect tempered by the lower infusion volumes normally required to resuscitate the patient.

At collection, blood is mixed with a preservative, normally CPD-A, providing citrate ions and small amount of phosphate. The accompanying sodium cation adds approximately 40 mmol litre⁻¹ to the effective SID of the blood unit. For this reason, it is not surprising that large-volume blood transfusion results in metabolic acidosis after citrate has been metabolized. In severe liver dysfunction, the problem becomes metabolic acidosis and hypocalcaemia from the accumulated citrate.

**Strong ion gap**

The strong ion gap (SIG) represents the quantity of unmeasured anions other than lactate. It can be quantified by the difference between the apparent SID (SIDa) and the effective SID (SIDE).

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

\[
\text{SIDE} = \text{CO}_2 + \text{A}^- \quad \text{[because SID = (CO}_2 + \text{A}^-) = 0, to achieve electrical neutrality]}
\]

\[
\text{SIG} = \text{[SID]} - \text{[HCO}_3^-] - \text{[albumin]}
\]

The SIG is normally zero, that is, the net negative charge of CO₂ and weak acids counterbalances the net positive charge of the SID. The SIG is not the same as the AG. The AG is an estimate of the sum of SIG + A⁻. A metabolic acidoses with a raised SIG may occur in diabetic ketoacidosis where the SIG quantitatively reflects plasma ketone concentration. In critically ill patients with metabolic acidoses, the nature of the SIG remains unknown. A recent study reported that pre-resuscitation SIG predicts mortality in injured patients better than blood lactate, pH, or injury severity scores.

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**Table 5 Equivalent reductions in SID by adding 1000 ml water or 1000 ml of normal saline to a 3000 ml sample of mock extracellular space. All concentrations are given in mmol litre⁻¹**

<table>
<thead>
<tr>
<th>ECF</th>
<th>After saline</th>
<th>After water</th>
</tr>
</thead>
<tbody>
<tr>
<td>[Na⁺]</td>
<td>140</td>
<td>142.5</td>
</tr>
<tr>
<td>[Cl⁻]</td>
<td>100</td>
<td>112.5</td>
</tr>
<tr>
<td>[A⁻] + [HCO₃⁻]</td>
<td>40</td>
<td>30</td>
</tr>
<tr>
<td>SID</td>
<td>40</td>
<td>30</td>
</tr>
</tbody>
</table>

**Table 6 Constituents of Hartmann’s solution and normal saline. All concentrations are given in mmol litre⁻¹**

<table>
<thead>
<tr>
<th></th>
<th>Hartmann’s</th>
<th>Normal saline</th>
</tr>
</thead>
<tbody>
<tr>
<td>[Na⁺]</td>
<td>129</td>
<td>154</td>
</tr>
<tr>
<td>[Cl⁻]</td>
<td>109</td>
<td>154</td>
</tr>
<tr>
<td>[K⁺]</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>[Ca²⁺]</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>[L-lactate]</td>
<td>29</td>
<td>0</td>
</tr>
<tr>
<td>Effective SID</td>
<td>27</td>
<td>0</td>
</tr>
</tbody>
</table>

**Table 7 A comparison of different colloids. Electrolyte concentrations are given in mmol litre⁻¹**

<table>
<thead>
<tr>
<th>4% albumin</th>
<th>Haemaccel</th>
<th>Gelofusine</th>
<th>Pentastarch</th>
</tr>
</thead>
<tbody>
<tr>
<td>[Albumin]</td>
<td>40 g litre⁻¹</td>
<td>35 g litre⁻¹</td>
<td>40 g litre⁻¹</td>
</tr>
<tr>
<td>[Gelatin-succinylated]</td>
<td>40 g litre⁻¹</td>
<td>154</td>
<td>154</td>
</tr>
<tr>
<td>[Gelatin–urea-linked]</td>
<td>40 g litre⁻¹</td>
<td>120</td>
<td>154</td>
</tr>
<tr>
<td>[Starch]</td>
<td>140</td>
<td>145</td>
<td>154</td>
</tr>
<tr>
<td>[K⁺]</td>
<td>128</td>
<td>145</td>
<td>154</td>
</tr>
<tr>
<td>[Ca²⁺]</td>
<td>5.1</td>
<td>12.5</td>
<td>0</td>
</tr>
<tr>
<td>Effective SID</td>
<td>12</td>
<td>17.6</td>
<td>34</td>
</tr>
</tbody>
</table>
Chloride to sodium ratio

The chloride to sodium (Cl⁻:Na⁺) ratio (normal range 0.75–0.79) serves as a simple substitute to quantify the role of hyperchloraemia in acid–base disturbances. A high Cl⁻:Na⁺ ratio (>0.79) has an acidifying effect. Patients with metabolic acidosis and high ratio may have hyperchloraemia as the cause of acidosis. A normal Cl⁻:Na⁺ and metabolic acidosis indicate a mixed acidosis, that is, hyperchloraemia and raised SIG. A low Cl⁻:Na⁺ ratio (<0.75), in the face of metabolic acidosis, suggests a raised SIG. As the ions of the SIG are negatively charged, other plasma anions (e.g. chloride and albumin) must fall to maintain electroneutrality if the cations (K⁺ and Na⁺) remain constant. Clinically, both the Cl⁻:Na⁺ ratio and serum albumin will be low in the presence of tissue acids.

In metabolic alkalosis, the Cl⁻:Na⁺ ratio is usually low. This is most likely due to a decrease in chloride, rather than an increase in bicarbonate concentration. For example, furosemide causes greater renal loss of Cl⁻ than Na⁺, leading to a low Cl⁻:Na⁺ ratio, increased SID, and metabolic alkalosis.

Lactic acidosis and hyperlactataemia

Critically ill patients may develop lactic acidosis from hypovolaemic shock and hypoperfusion. Lactate generated from hypoperfusion decreases SID and promotes proton production. This is in contrast to lactate from Hartmann’s solution, which is readily metabolized, leaving behind sodium to increase SID. Lactic acidosis has long been used as an outcome predictor. Yet, in order to avoid inappropriate therapy, it is important to differentiate lactic acidemia from hyperlactataemia (normal pH and elevated lactate concentration) which is not infrequent in critically ill patients with increased intermediary metabolism, or from administration during renal replacement therapy. Hyperlactataemia is not necessarily associated with adverse outcomes.

References


Further reading

The following web site contains a simple explanation of Stewart’s approach together with a downloadable Excel-based macro to run on any PDA: http://www.ccm.upmc.edu/education/resources/phorum.html

Please see multiple choice questions 1–4