Standard Base Excess

T. J. MORGAN
Senior Specialist, Deputy Director,
Adult Intensive Care, Mater Misericordiae Hospitals, South Brisbane, Queensland

Thomas (John) Morgan is an examiner for the Joint Faculty of Intensive Care Medicine, and serves on the editorial board of Critical Care and Resuscitation. Dr Morgan has produced original publications in the areas of acid-base, crystalloid design, tissue oxygenation, haemoglobin-oxygen affinity and evaluation of perioperative risk.

The history of arterial blood gas analysis stretches back over more than forty years. Throughout this time, differences of opinion and entrenched viewpoints have characterized the evaluation of acid-base disturbances. Controversy persists to this day. Most define acidaemia as arterial pH<7.35, and alkalaemia as pH>7.45. Most agree that in isolated respiratory acidosis, PaCO₂ exceeds 45 mmHg, and in isolated respiratory alkalosis, PaCO₂ is less than 35 mmHg. It is also accepted that metabolic (non-respiratory) acid-base abnormalities manifest on blood gas analysis as a disturbed pH/PaCO₂ relationship (Figure 1). The major source of disagreement is how to identify and quantify these metabolic acid-base disturbances. In other words, at any given PaCO₂ and pH, what is the best tool to delineate the separate respiratory and metabolic contributions to the overall acid-base status?

The ideal bedside metabolic acid-base index has the following characteristics:

![Figure 1. PaCO₂/pH relationships in vivo. Illustrated are the normal curve (N) and examples of metabolic acidosis (Acid) and metabolic alkalosis (Alk). The black squares delineate the appropriate PaCO₂ range for each curve.](image-url)
1. Simple and “user friendly”.
2. Independent of PaCO₂ (CO₂-invariant).
3. Stoichiometric in vivo. This means that the index should quantify the amount of strong acid or base (expressed as mmol/l extracellular fluid) which would correct any metabolic acid-base disturbance.

There are three contenders:
2. Strong ion difference (Stewart’s physical chemical approach).

We will discuss each of these in turn. On evaluation it should become evident that standard base excess is closest to the ideal, although all three are merely different ways of describing the same process.¹

**The Boston “rules”**
This is a PaCO₂/[HCO₃⁻] based approach developed by Schwartz, Relman and colleagues at Tufts University.² Three equations were derived using in vivo data from human volunteers and patients (Table 1). These calculate either the appropriate [HCO₃⁻] in primary respiratory disturbances or the appropriate PaCO₂ in primary metabolic disturbances (Table 1). If there is a difference between the actual and the expected [HCO₃⁻] for a given PaCO₂, a metabolic acid-base disturbance is present.

The Boston “rules” require considerable bedside “mental gymnastics”.¹ Mistakes and memory lapses could lead to adverse clinical consequences. It is true that the equations apply throughout the normal “working” range of PaCO₂. This means that there is CO₂-invariance. It is also true that a significant deviation from the expected [HCO₃⁻] for any given PaCO₂ signals a metabolic acid-base perturbation. However, this offset does not quantify the amount of strong acid or base required to correct the metabolic disturbance, even in vitro but most especially in vivo.⁴ In other words, [HCO₃⁻] offsets are not stoichiometric.

Nevertheless, devotees abound. Some have gone as far as removing “base excess” calculations from analyser printouts. This is an over-reaction.

**Strong ion difference**
Peter Stewart’s semi-quantitative analysis using principles of physical chemistry was a major conceptual shift.⁵ In this type of analysis, pH and [HCO₃⁻] are dependent variables determined by three independent variables, which are PaCO₂, strong ion difference ([SID]), and the total concentration of non-volatile weak acid buffer ([ATOT]).

<table>
<thead>
<tr>
<th>Condition</th>
<th>Rule</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute respiratory acidosis.</td>
<td>Expected [HCO₃⁻]=24+(PaCO₂-40)/10</td>
</tr>
<tr>
<td>Chronic respiratory acidosis.</td>
<td>Expected [HCO₃⁻]=24+4×(PaCO₂-40)/10</td>
</tr>
<tr>
<td>Acute respiratory alkalosis.</td>
<td>Expected [HCO₃⁻]=24-2×(40-PaCO₂)/10</td>
</tr>
<tr>
<td>Chronic respiratory alkalosis.</td>
<td>Expected [HCO₃⁻]=24-5×(40-PaCO₂)/10</td>
</tr>
<tr>
<td>Metabolic acidosis.</td>
<td>Expected PaCO₂=1.5 [HCO₃⁻]+8</td>
</tr>
<tr>
<td>Metabolic alkalosis.</td>
<td>Expected PaCO₂=0.9 [HCO₃⁻]+9</td>
</tr>
</tbody>
</table>
What are strong ions and what is [SID]?

Strong ions are those essentially fully ionised under all physiologic acid-base conditions. Quantitatively, any unionised fraction is insignificant. Examples of strong ions include \( \text{Na}^+, \text{K}^+, \text{Ca}^{2+}, \text{Mg}^{2+}, \text{Cl}^- \) and lactate. [SID] is \([\text{strong cations}] - [\text{strong anions}]\). Since this is a difference in charge concentration, [SID] is expressed in mEq/l. In normal plasma, [SID] is approximately 40 mEq/l. To preserve electrical neutrality, the SID “space” is filled passively by the buffer base. The buffer base components of quantitative importance are \( \text{HCO}_3^- \) and “non-volatile buffer anions” (\( \text{A}^- \)). Buffer base therefore = (\( [\text{A}^-] + [\text{HCO}_3^-] \)), and is numerically the same as [SID]. The ions are weak because at physiological pH they combine reversibly with protons to form their conjugate parent molecules as follows:

\[
\text{H}^+ + \text{A}^- \leftrightarrow \text{HA} \\
\text{H}^+ + \text{HCO}_3^- \leftrightarrow \text{H}_2\text{CO}_3 \leftrightarrow \text{CO}_2 + \text{H}_2\text{O}
\]

In fact \( \text{A}^- \) is not a true anion in the strict sense. In plasma, \( \text{A}^- \) is made up primarily of the net negative charge on albumin, (inorganic phosphate also makes a small contribution). In erythrocytes \( \text{A}^- \) is the net negative charge on haemoglobin. Both albumin and haemoglobin have a number of ionisable groups with a range of pK values and charges, so that the net molecular negative charge alters with pH. In Stewart’s terminology this process is described simplistically as \( \text{A}^- \) combining with protons to form the conjugate base HA. We will continue with this convention although it is technically incorrect.

If [SID] is reduced, the buffer base concentration must be reduced by an identical amount, since [SID] is the independent variable setting the buffer base boundaries. The buffer base equilibria therefore shift to the right, reducing \([\text{A}^-]\) and \([\text{HCO}_3^-]\). The \([\text{HCO}_3^-]\) reduction shifts the \( \text{PaCO}_2/\text{pH} \) curve to the left, producing a metabolic acidosis (Figure 1). Similarly an isolated increase in [SID] causes a metabolic alkalosis.

The focus of Stewart and his followers has always been on plasma [SID] rather than whole blood or extracellular [SID], which are harder to quantify. The easiest way to calculate plasma [SID] is as the buffer base concentration (\([\text{HCO}_3^-] + [\text{A}^-]\)), rather than by laborious direct measurement of all strong anions and cations. It can be argued that although [SID] defines, controls and is identical to the buffer base concentration, it is buffer base which determines metabolic acid-base status by setting the relationship between \( \text{PaCO}_2 \) and \([\text{HCO}_3^-]\) and thus that between \( \text{PaCO}_2 \) and pH (Figure 1).

What is \([\text{ATOT}]\)?

Using Stewart’s (over-simplified) terminology, \([\text{ATOT}]\) is \(( [\text{A}^-] + [\text{HA}] ) \). In plasma, \([\text{ATOT}]\) is comprised largely of albumin and inorganic phosphate, and in erythrocytes \([\text{ATOT}]\) consists primarily of haemoglobin. Alterations in \([\text{ATOT}]\) will cause the \([\text{A}^-]\) component of buffer base to vary in parallel. If [SID] is held constant while \([\text{ATOT}]\) is varied, the total buffer base concentration (\([\text{HCO}_3^-] + [\text{A}^-]\)) must remain constant since it is defined and controlled by [SID]. Isolated \([\text{ATOT}]\) reductions therefore reduce \([\text{A}^-]\) and increase \([\text{HCO}_3^-]\), causing a metabolic alkalosis. Conversely isolated \([\text{ATOT}]\) elevations cause a metabolic acidosis.

In the physical chemical approach, there are thus two determinants of metabolic acid-base status, [SID] and \([\text{ATOT}]\). Both qualify as \( \text{CO}_2 \)-invariant, since they are independent variables. The only way that [SID] can used as a stoichiometric index of metabolic acid-base status is by converting it to SIDex. SIDex is the change in whole
blood [SID] at a given [A_TOT] required to bring the pH to 7.4, while the PaCO_2 is maintained at 40 mmHg. This conversion is really a pointless exercise, since SIDex is virtually identical to base excess (Figure 2). Unlike base excess it cannot be calculated from blood gas analysis alone, which is a major disadvantage.

The strength of the Stewart approach lies mainly in its conceptual insights. For example Stewart's principles can be put to use in the design of crystalloid resuscitation fluids with specific acid-base effects. More direct application to bedside acid-base quantification is impractical.

**Standard base excess**

The evolution of the standard base excess concept was gradual. It began with “standard bicarbonate”, devised by Jørgensen and Astrup. They used tonometry to convert small volumes of blood to fully oxygenated specimens with a PCO_2 of 40 mmHg at 38°C, and then measured the plasma pH. “Standard bicarbonate” concentration could then be determined by substituting the PCO_2 (40 mmHg) and the measured pH value in the Henderson-Hasselbalch equation. CO_2-invariance was thus ensured by physically returning the PCO_2 to 40 mmHg. Any offset of the standard bicarbonate from 24.4 mmol/l signified a metabolic acid-base process.

However, there are two problems with this approach. The first is that [HCO_3-] indices are not stoichiometric. The second is that the in vitro blood tonometry does not replicate the in vivo pH/PaCO_2 relationship.

**The answer to the stoichiometry problem**

Ole Siggaard-Andersen and colleagues solved the stoichiometry problem by introducing a new parameter called base excess (BE). BE can be defined as the concentration of strong acid or base required to return the pH of an in vitro specimen of whole blood to 7.4 while maintaining PCO_2 at 40 mmHg at 37°C by equilibration. If

![Figure 2](image_url). Relationship between whole blood base excess (BE) and whole blood strong ion difference excess (SIDex). There are 271 data points, with [haemoglobin] ranging from 50 to 150 g/l, [albumin] from 10 to 40 g/l, PaCO_2 from 10 to 60 mmHg and pH from 6.9 to 7.6. The line of identity is shown. By inspection, values are almost identical. R^2=0.999.
plasma pH is >7.4 once the PCO₂ has been returned to 40 mMHg, BE is the mmol/l of strong acid which brings the pH to 7.4 (while PCO₂ continues to be maintained at 40 mmHg). BE then has a positive sign. If pH<7.4, BE is quantified by the strong base required (BE then has a negative sign). A negative BE is sometimes referred to as a “base deficit”.

To overcome the need for individual bench top tonometry and acid-base titrations, a series of in vitro experiments was carried out. These recorded the effects on plasma pH of adding known amounts of acid or base to blood maintained by tonometry at various PCO₂ values at 37°C. The experiments were repeated with a wide range of haemoglobin concentrations, which is a way of factoring in the effects of varying [ATOT]. From the data, an “alignment nomogram” was created. With this nomogram it was possible to determine BE from a single measurement of pH, PCO₂ and haemoglobin concentration at 37°C, without tonometry or acid-base titrations. By the late 1960s, blood gas analysers could be programmed with the BE nomogram in the form of look-up tables or equations.

However, BE can also be defined more simply as the offset in buffer base concentration. In other words BE is really (ΔA⁻+Δ[HCO₃⁻]). Plasma BE is thus easy to derive by non-empiric means. All that is required to calculate ΔA⁻ is the pH and a value for the buffering capacity of albumin, and Δ[HCO₃⁻] is simply ([HCO₃⁻]–24.4) mmol/l. For whole blood the non-empiric method is more complicated, since whole blood is plasma mixed with red cells, and haemoglobin is the predominant buffer. In 1977 Siggaard-Andersen published the Van Slyke equation, which enables whole blood BE to be calculated from pH, PaCO₂, and haemoglobin concentration using linking equations for plasma and intra-erythrocytic buffering and Gibbs-Donnan ionic distributions. The Van Slyke equation can be written:

$$BE = ([HCO_3^-] - 24.4 + (2.3 \times [Hb] + 7.7) \times (pH - 7.4)) \times (1 - 0.023 \times [Hb])$$

where [HCO₃⁻] and pH are plasma values and [Hb] is the blood haemoglobin concentration expressed in mmol/l. On publication, Siggaard-Andersen reported close agreement between this equation and its empiric predecessor — the whole blood BE nomogram. Our group has re-evaluated the in vitro accuracy of the Van Slyke equation. We confirmed that it quantifies whole blood metabolic acid-base change with acceptable degrees of precision and minimal bias. We found that the accuracy was maintained at very low haemoglobin concentrations, and was little affected by large simultaneous alterations in PCO₂.

The in vivo versus in vitro equilibration problem

In 1963, Schwarz and Relman pointed out that BE is not CO₂-invariant in vivo. This is because for any specimen of arterial blood the in vitro plasma pH/PaCO₂ equilibration curve differs from the in vivo curve, since in vivo CO₂ equilibration occurs throughout the total extracellular compartment. An isolated in vivo change in PaCO₂ shifts whole blood BE in the opposite direction although no overall extracellular metabolic acid-base alteration has occurred (Figure 3).

This phenomenon is due to ionic shifts between intravascular and interstitial compartments. When PaCO₂ rises, HCO₃⁻ is generated maximally within the erythrocytes, where buffering capacity is greatest due to haemoglobin. It then diffuses down a concentration gradient to the plasma (as occurs in vitro) but continues on into the interstitial fluid. Cl⁻ moves in the opposite direction, with final ionic distributions
determined according to Gibbs-Donnan equilibria and the laws of chemical equilibrium and electroneutrality. Thus the rise in plasma $[\text{HCO}_3^-]$ during hypercapnia will not be as high in vivo as in vitro. Or put in physical chemical terms, when $\text{PCO}_2$ rises in an in vitro specimen of whole blood, erythrocytic [SID] decreases, plasma [SID] increases but whole blood [SID] and thus BE do not change. When $\text{PaCO}_2$ rises in vivo, whole blood [SID] and thus BE decrease, interstitial [SID] increases but extracellular [SID] is unaffected.

The answer to the objection of Schwarz and Relman is remarkably simple. If BE is calculated from the measured plasma pH and $\text{PCO}_2$ as originally described, but at a haemoglobin concentration of 50 g/l (the approximate mean extracellular haemoglobin concentration), total extracellular buffering is emulated successfully. BE calculated in this way is termed standard BE (SBE). “Rules of thumb” equations derived by meta-analysis of published numerical and graphical data now describe the appropriate SBE responses to acute and chronic respiratory acid-base disturbances, and the appropriate $\text{PaCO}_2$ responses to primary disturbances in SBE. They are similar in nature to the Boston rules, and are set out in Table 2. Importantly, the meta-analysis showed that

![Figure 3. Relationship in vivo between BE and PaCO2 for haemoglobin concentrations of 100 g/l and 200 g/l. A change in PaCO2 causes BE to change in the opposite direction. The effect is more marked at higher haemoglobin concentrations. In contrast, standard base excess (SBE) does not change with PaCO2 (see text).](image)

<table>
<thead>
<tr>
<th>Condition</th>
<th>Rule</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute respiratory acidosis and alkalosis</td>
<td>$\Delta \text{SBE} = 0 \times \Delta \text{PaCO}_2$</td>
</tr>
<tr>
<td>Chronic respiratory acidosis and alkalosis</td>
<td>$\Delta \text{SBE} = 0.4 \times \Delta \text{PaCO}_2$</td>
</tr>
<tr>
<td>Metabolic acidosis</td>
<td>$\Delta \text{PaCO}_2 = \Delta \text{SBE}$</td>
</tr>
<tr>
<td>Metabolic alkalosis</td>
<td>$\Delta \text{PaCO}_2 = 0.6 \times \Delta \text{SBE}$</td>
</tr>
</tbody>
</table>
SBE is CO₂-invariant in vivo (see Table 2, Rule 1), confirming that although SBE is only an approximation of total extracellular buffering, it successfully replicates the in vivo situation.

Clinical application of standard base excess
In most laboratories, the reference range for SBE is approximately –3 mmol/l to +3 mmol/l. Before applying the SBE rules, primary acid-base disturbances should be detected first by inspection of the pH and PaCO₂ (Table 3). A primary process is one that if unopposed will shift the pH out of the normal range, and can be either respiratory (PaCO₂) or metabolic. There can be one, two or less commonly more than two primary processes operating at once. A primary metabolic process should stimulate immediate respiratory compensation, and a primary respiratory process normally results in metabolic compensation by renal [HCO₃⁻] adjustment within hours. However compensation rarely returns the pH to normal except in the case of chronic respiratory alkalosis. With this exception, it can be stated that if only one of either PaCO₂ or pH is normal, two primary processes must be operating simultaneously.

<table>
<thead>
<tr>
<th>PaCO₂</th>
<th>pH</th>
<th>Primary processes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>Normal</td>
<td>None</td>
</tr>
<tr>
<td>Normal</td>
<td>High</td>
<td>Metabolic alkalosis, Respiratory alkalosis</td>
</tr>
<tr>
<td>Normal</td>
<td>Low</td>
<td>Metabolic acidosis, Respiratory acidosis</td>
</tr>
<tr>
<td>High</td>
<td>Normal</td>
<td>Respiratory acidosis, Metabolic alkalosis</td>
</tr>
<tr>
<td>High</td>
<td>High</td>
<td>Metabolic acidosis</td>
</tr>
<tr>
<td>High</td>
<td>Low</td>
<td>Respiratory acidosis</td>
</tr>
<tr>
<td>Low</td>
<td>Normal</td>
<td>Chronic respiratory alkalosis</td>
</tr>
<tr>
<td>Low</td>
<td>High</td>
<td>Respiratory acidosis</td>
</tr>
<tr>
<td>Low</td>
<td>Low</td>
<td>Metabolic acidosis</td>
</tr>
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</table>

After scanning for primary processes, SBE can then be combined with the PaCO₂/SBE rules in Table 2 to quantify:
1. The in vivo metabolic component of any acid-base disturbance.
2. The appropriateness of the metabolic response to any respiratory acid-base derangement.
3. The appropriateness of the respiratory response to any metabolic acid-base derangement.

For example, if the pH, PaCO₂ and SBE are all elevated, the primary process is a metabolic alkalosis. The next step is to quantify the severity of the metabolic alkalosis by determining the elevation of SBE above the normal range. It then remains to decide whether the accompanying respiratory acidosis is purely compensatory. If so, the PaCO₂ should be within a few mmHg of (40+0.6×ΔSBE) mmHg. If this is not so, there are two primary acid-base disturbances (metabolic and respiratory).

Concealed metabolic acidosis
It is important to understand that a normal SBE can conceal complex metabolic acid-base disturbances. The example given by Schlichtig and colleagues concerns a patient with chronic lung disease and a compensated respiratory acidosis who develops
septic shock and lactic acidosis.\textsuperscript{1} In this case SBE and [SID], originally elevated by the compensatory metabolic alkalosis, are reduced acutely to normal by an increased concentration of lactate (a strong anion). The normal SBE and elevated PaCO\textsubscript{2} give the appearance on blood gas analysis of a simple acute respiratory acidosis. Here the truth can only be revealed by attention to history and examination, supplemented by the anion gap (which is likely to be elevated) and a measured plasma lactate.

**In vivo evaluation of SBE**

In virtually all published in vivo studies, it is BE rather than SBE which has been evaluated. The difference between BE and SBE is usually quite small.

**Some animal studies**

In 1991, Davis and colleagues bled 16 pigs to 40\% of their blood volumes over 30 minutes, waited a further 30 minutes, then resuscitated the animals with crystalloid and blood.\textsuperscript{18} With the onset of hypovolemia, mean arterial pressure and mixed venous oxygen saturations decreased promptly and arterio-venous oxygen extraction increased, but all began to improve from compensatory homeostasis before resuscitation was commenced. BE decreased just as promptly, but improvement was delayed until volume replacement. The authors commented that BE was more reflective of the true volume deficit in compensated hypovolemic shock. In a related study, BE correlated significantly with arterial lactate concentrations (R=0.81).\textsuperscript{19}

Another report in 1991 came from Dunham and colleagues, who subjected 63 dogs to haemorrhagic shock titrated to predetermined oxygen debts.\textsuperscript{20} Baseline oxygen consumption was measured prior to controlled bleeding over one hour to oxygen debts ranging from 60 ml/kg to 120 ml/kg. At 60 minutes there was no statistically significant difference in shed blood volumes among the groups, and neither blood pressure nor cardiac output discriminated well between the degrees of oxygen debt. However plasma lactate and whole blood BE were both highly significant discriminators of oxygen debt, with BE having the highest explained variability. The fall in BE prior to resuscitation was almost twice the rise in plasma lactate, perhaps reflecting additional dysoxic metabolites.

**Some clinical studies**

In a retrospective analysis, it was possible using the admission BE to stratify 209 patients with blunt or penetrating trauma into groups with very similar initial mean arterial pressures, trauma scores, blood and total fluid requirements.\textsuperscript{21} A decreasing BE was associated with ongoing hemorrhage in 65\% of cases. Another retrospective review of 3223 blunt trauma patients revealed the admission BE as the single most important predictor of the need for laparotomy (odds ratio 6.2).\textsuperscript{22} The less successful predictors were admission hypotension (odds ratio 5.1), chest injury (odds ratio 4.8), pelvic fracture (odds ratio 3.3) and pre-hospital hypotension (odds ratio 3.1). The authors recommended that in cases of blunt abdominal trauma an admission BE of \(<–6.0\ \text{mmol/l} \) should be considered an indication for diagnostic peritoneal lavage or abdominal CT. In burns, the admission BE predicts resuscitation volume requirements, and when \(\leq–6.0\ \text{mmol/l} \) it portends a greatly increased mortality rate (9\% versus 72\%, \(P<0.001\)).\textsuperscript{23}

Siegel and colleagues studied admission data from 185 consecutive patients with hepatic trauma.\textsuperscript{24} By linear logistic modeling, BE predicted death as successfully as the
24 hour blood transfusion requirement, and better than arterial lactate, the Glasgow Coma Score and the Injury Severity Score. A predictive model incorporating BE and the Glasgow Coma Score was then tested successfully against 323 additional patients with pelvic fracture as their index injury. In one recent study of general medical/surgical intensive care patients, the admission BE was strongly linked with mortality. By combining the admission BE with the admission plasma lactate concentration, it was possible to predict mortality with a sensitivity of 80.3% and a specificity of 58.7%. Failure to improve BE significantly over 24 hours in this population was an adverse prognostic factor. In shocked trauma patients, failure to increase BE to >–6 mmol/l in the first 24 hours predicted an increased frequency of acute respiratory distress syndrome, multiple organ failure and death. There are other similar studies.

In summary, SBE is a simple, user-friendly CO₂-invariant index of extracellular metabolic acid-base status. BE itself is stoichiometric on in vitro evaluation in whole blood. From studies in shock, trauma and in ICU patients in general, BE appears to have clinical meaning. It can be a guide to the overall severity of shock and trauma, and is closely related to oxygen debt in experimental hemorrhagic shock. It tracks elevated plasma lactate concentrations, and at times adds information to lactate analysis. BE may have some utility as a guide to resuscitation or even surgical intervention. Importantly, SBE and the Copenhagen approach are quite consistent with the physical chemical analysis of acid-base status, and complement rather than antagonize the Stewart approach.

References


