Base excess or buffer base (strong ion difference) as measure of a non-respiratory acid-base disturbance

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Stewart in 1983 (Can J Physiol Pharmacol 1983: 61: 1444) reintroduced plasma buffer base under the name “strong ion difference” (SID). Buffer base was originally introduced by Singer and Hastings in 1948 (Medicine (Baltimore) 1948: 27: 223). Plasma buffer base, which is practically equal to the sum of bicarbonate and albuminate anions, may be increased due to an excess of base or due to an increased albumin concentration. Singer and Hastings did not consider changes in albumin as acid-base disorders and therefore used the base excess, i.e. the actual buffer base minus the buffer base at normal pH and pCO₂, as measure of a non-respiratory acid-base disturbance. Stewart and followers, however, consider changes in albumin concentration to be acid-base disturbances: a patient with normal pH, pCO₂, and base excess but with increased plasma buffer base due to increased plasma albumin concentration get the diagnoses metabolic (strong ion) alkalosis (because plasma buffer base is increased) combined with metabolic hyperalbuminaemic acidosis. Extrapolating to whole blood, anaemia and polycythaemia should represent types of metabolic alkalosis and acidosis, respectively. This reveals that the Stewart approach is absurd and anachronistic in the sense that an increase or decrease in any anion is interpreted as indicating an excess or deficit of a specific acid. In other words: a return to the archaic definitions of acids and bases as being the same as anions and cations.

We conclude that the acid-base status (the hydrogen ion status) of blood and extracellular fluid is described in terms of the arterial pH, the arterial pCO₂, and the extracellular base excess. It is measured with a modern pH-blood gas analyzer. The electrolyte status of the plasma is a description of the most important electrolytes, usually measured in venous blood with a dedicated electrolyte analyzer, i.e. Na⁺, Cl⁻, HCO₃⁻, and K⁺. Albumin anions contribute significantly to the anions, but calculation requires measurement of pH in addition to albumin and is usually irrelevant. The bicarbonate concentration may be used as a screening parameter of a non-respiratory acid-base disturbance when respiratory disturbances are taken into account. A disturbance in the hydrogen ion status automatically involves a disturbance in the electrolyte status, whereas the opposite need not be the case.

Key words: Albumin anion; bicarbonate; blood; chloride; electrolytes; hydrogen ion.

There is general agreement that plasma pH is the target of neutrality regulation of the body fluids and the overall measure of a clinical acid-base disturbance. There is also agreement that the arterial pCO₂ is an independent variable and measure of a respiratory acid-base disturbance. However, there is still discussion about the most relevant measure of a non-respiratory also called metabolic acid-base disturbance, i.e. a change in pH not caused by a change in pCO₂.

Among suggested measures of a non-respiratory acid-base disturbance are: total CO₂, actual bicarbonate, standard bicarbonate, standard pH, buffer base, whole blood base excess, and extracellular base excess. The most

Before year 1923 acids and bases were synonyms for anions and cations. A sodium ion for example, was a base which could be neutralized by acid, chloride ion for example, to form a salt: sodium chloride (12, p. 7-10). In recent parameter, suggested by Stewart in 1981 (1, 2), is SID, acronym for strong ion difference, which is, however, apart from the name, exactly identical with the buffer base suggested by Singer and Hastings in 1948 (3).

Several authors have adopted SID (5-11) and we have been asked why we do not accept this “approach to acid-base which revolutionizes our ability to understand, predict, and control what happens to hydrogen ions in living systems” (2). In the following we will discuss each of the suggested parameters and explain why we prefer the extracellular base excess. But first it seems necessary to rehearse the definitions of acids and bases.

1923-24 Brønsted and Lowry set focus on the hydrogen ion (the protons) (13, 14). The chemical potential of hydrogen ions determines the acidity of a solution. The pH value is directly proportional to the negative value of the chemical
potential. An acid is defined as a substance which is able to give off a hydrogen ion at the given pH, a base a substance which is able to bind a hydrogen ion. A buffer pair is a week acid, which enters equilibrium with its corresponding week base at the given pH. According to these definitions chloride and sodium ions are neither acid nor base but aprotes (without protons).

**ACTUAL BICARBONATE**

Bicarbonate is the most important buffer in a biological system at constant \( pCO_2 \). Therefore, as a first approximation, a pure sodium bicarbonate solution with added salts may serve as a model of the body fluids. In this model, a decrease or increase in bicarbonate concentration directly reflects the amount of added non-carbonic acid or base, while the bicarbonate concentration is independent of changes in \( pCO_2 \). Furthermore, the Henderson-Hasselbalch equation provides a simple relationship among the respiratory parameter, \( pCO_2 \), the non-respiratory parameter, \( cHCO_3^- \), and the overall acidity parameter, pH.

The plasma total \( CO_2 \) concentration, also called \( CO_2 \) content, is only slightly higher than the bicarbonate concentration. It has been much used as a routine measure of a metabolic acid-base disturbance, simply because it was easy to measure with the Van Slyke apparatus (15). The bicarbonate concentration or the \( CO_2 \) content, measured on a modern chemical analyzer, is still fully adequate as a routine screening parameter for metabolic acidosis or alkalosis in patients with normal respiration.

However, a pure bicarbonate solution is too simple as a model of blood and extracellular fluid. Due to non-bicarbonate buffers, especially albumin and haemoglobin, a change in bicarbonate concentration does not reflect the total amount of accumulated non-carbonic acid or base, but more importantly: the bicarbonate concentration is independent of variations in \( pCO_2 \). As \( pCO_2 \) increases, carbonic acid is buffered by non-bicarbonate buffers and the bicarbonate concentration increases. An elevated bicarbonate concentration may therefore erroneously be interpreted as a metabolic alkalosis when respiratory acidosis is the cause. There are reports of this misinterpretation in the literature (16). One approach to solve this problem was to measure the bicarbonate concentration at a standard \( pCO_2 \): standard bicarbonate.

Another approach was to use the sum of bicarbonate and non-bicarbonate buffer anions: buffer base

**STANDARD BICARBONATE**

As early as 1916 Hasselbalch suggested measuring the “reduced” pH after equilibrating the blood with a \( pCO_2 \) of 5.33 kPa (40 Torr). The year after, Van Slyke and Cullen suggested measuring the \( CO_2 \) combining power that is the \( CO_2 \) content after the technician had blown expiratory air into the serum for a while. In 1954 Astrup designed an apparatus with a pH electrode and tonometer for measuring the standard bicarbonate, that is the bicarbonate concentration of the plasma phase of whole blood equilibrated with a \( CO_2-O_2 \) gas mixture of \( pCO_2 \) 5.33 kPa (for references see 12, p. 92-96).

None of these parameters quantitatively express the amount of non-carbonic acid or base accumulated in the blood. However, such a quantitative measure had previously been suggested by Van Slyke in terms of the \( pH \) corrected bicarbonate, which is the bicarbonate concentration of serum or whole blood after equilibrating the sample with different gas mixtures and interpolating to a \( pH \) of 7.40. A change in Van Slyke corrected bicarbonate directly indicates the amount of accumulated non-carbonic acid or base (17).

**BUFFER BASE (STRONG ION DIFFERENCE)**

Singer and Hastings used the second approach to quantify a metabolic acid-base disturbance (3). They employed the old definitions of acids and bases being anions and cations, respectively. Their starting point was the Gamble diagram with the two columns of cations and anions of equal height, illustrating the law of electro-neutrality (18). They defined buffer base as the sum of strong “bases” (aprote or non-buffer cations) minus the sum of strong “acids” (aprote or non-buffer anions). In other words they focus on all other ions than the hydrogen ion. They used the symbol (B⁺).

Today aprote anions and cations are neither acids nor bases. In modern terminology, the concentration of “buffer base” is defined as the sum of the products of substance concentration and charge number of aprote ions (cAI \( \cdot \) zAI). According to the law of electro-neutrality this must equal the negative sum of the products of substance concentration and charge number of buffer ions (cBI \( \cdot \) zBI):

\[
(B⁺) = \Sigma (cAI \cdot zAI) = -\Sigma (cBI \cdot zBI).
\]

Unfortunately the distinction between aprote ions and buffer ions is somewhat arbitrary, depending upon the actual pH interval. A lactate ion is a buffer ion when the pH is around 3.6 but is considered an aprote anion at a pH around 7.4. One of the anion groups of HPO\(_4^{2-}\) is a buffer anion at a pH around 6.8 where the anion H\(_2\)PO\(_4^-\) may be considered an aprote.

The rationale behind buffer base is that accumulation of strong acid or base is reflected stoichiometrically in a decrease respectively increase, whereas changes in \( pCO_2 \) does not affect the buffer base concentration. The rise in bicarbonate concentration associated with a rise in \( pCO_2 \) is
matched by a fall in concentration of other buffer anions

Measurement of buffer base is not easy if it is based on
the equation of definition, which requires separate
measurement of all the aprotic cations and anions. It is
easier to calculate buffer base on the basis of the second
equality, calculating the bicarbonate concentration and
adding the concentration of other buffer ions, e.g.
haemoglobin anion. Singer and Hastings used this
approach and constructed a nomogram which, among other
calculations, allows calculation of plasma and whole blood
buffer base from pH, pCO₂, and haematocrit.

The problem with buffer base is that the normal mean
value, i.e. the value in blood or plasma at a pH of 7.40 and
a pCO₂ of 5.33 kPa, depends on the concentration of
buffers, primarily haemoglobin and albumin. Singer and
Hastings were fully aware of this and recommended to use
delta buffer base \( \Delta \text{BB} \), i.e. the change in buffer base
from the value at pH=7.4 and pCO₂ = 5.33 kPa, as the measure of a metabolic acid-base disturbance (see 12, p.
27).

Stewart, who reintroduced buffer base under the name
“strong ion difference” with the symbol [SID] (1,2), and
his followers Fencl and coworkers from Boston (5-10), do
not use delta buffer base (“delta strong ion difference”) as
measure of a metabolic acid-base disturbance. A decreased
[SID] due to decreased albumin concentration, but with
normal pH and pCO₂, is interpreted as “hypoalbuminaemic
alkalosis” compensated by “strong ion acidosis”. All
anions, including buffer anions, are thought of as having
been added or removed from the plasma as acids. Plasma is
thought of as originating from pure water (or a neutral salt
solution) by addition of pure albumin, which is titrated to
the actual pH at the actual pCO₂ with strong base (strong
cation). Hence [SID] is elevated in the case of
hyperalbuminaemia. This interpretation of an elevated
albumin (or elevated haemoglobin in the case of whole
blood) as indicating a type of metabolic acidosis, and
similarly a decreased albumin or haemoglobin as indicating
a type of metabolic alkalosis, is contrary to all previous
rational thinking. Singer and Hastings would never have
called a decreased whole blood buffer base due to anaemia
a metabolic acidosis with anaemic alkalosis.

BASE EXCESS

The key component in the acid-base status of blood,
plasma, or other body fluids is the hydrogen ion. The
amount of hydrogen ion added to or removed from the
system may be determined by back titration to the original
(reference) pH by adding or removing hydrogen ion (with
CF) when the pH is above or below the reference pH,
respectively.

The two quantities which describe a chemical component
in a physico-chemical system are the chemical potential
such as albumin anions.

(\text{the intensive quantity}) and the stoichiometric amount of
substance of the component (the extensive quantity) \( (19) \).
The former is often expressed as the activity or
concentration of free component in the system. The latter is
generally divided by the volume of the system and
expressed as the stoichiometric concentration or
concentration of total component in the system. Examples
of these two quantities are: pCO₂ and concentration of total
CO₂, pO₂ and concentration of total O₂, concentrations of
free and total calcium ion, concentrations of free and total
thryoxin. In the case of hydrogen ion the intensive quantity
is pH, which is directly proportional to the negative
chemical potential. The stoichiometric concentration is
represented by the concentration of titratable hydrogen ion.

In blood or plasma, where pCO₂ is an independent vari-
able, the concentration of titratable hydrogen ion is deter-
mined by titrating to a pH of 7.4 at a pCO₂ of 5.33 kPa at a
temperature of 37 °C. This quantity with opposite sign is
called the base excess, understanding that a negative value
indicates a base deficit, which is equivalent with a non-
carbonic acid excess (12, p. 12). It is numerically identical
with the \( \Delta \text{BB} \) of Singer and Hastings. In view of the
ambiguity of the words acid and base it might be preferable
to use the name (net) titrimetric (or stoichiometric)
concentration of hydrogen ion or (net) concentration of
titratable hydrogen ion (symbol \( \Delta \text{eH}^+ \), or \( \Delta cH^+ \)).
This would emphasize that the quantity refers to hydrogen ions,
not cations or anions, and indicate that the quantity may be
either positive or negative.

An increase in net titratable hydrogen ion reflects
addition of hydrogen ion, whether added from the outside
or generated within the system. For example, oxygenation
of haemoglobin causes an increase in net titratable hydrogen ion because hydrogen ions are liberated from
the so-called oxygen linked buffer groups, an effect, which is
traditionally called the Haldane effect (see 12, p. 71).
Hydrogen ions cannot be added without simultaneously
adding some anion or removing some cation. The Haldane
effect results in addition of hydrogen ions with the
simultaneous disappearance of \( =\text{NH}_2^- \), \( =\text{NH}_3^+ \), or \( -\text{NH}_3^+ \)
ions of the oxygen linked buffer groups.

In actual practise net titratable hydrogen ion is not deter-
ed by titration but rather by calculation as Singer and
Hastings did from pH, pCO₂, and the buffer concentration.
A curve nomogram was constructed for this purpose, later
transformed into an alignment nomogram similar to the
Singer and Hastings nomogram (see 12, p. 51-70). An
equation for calculating net titratable hydrogen of whole
blood was also developed (12, p. 51, Eqn 15), later named
the Van Slyke equation (20, 21) to honour Donald D. Van
Slyke's contributions to our understanding of acid-base
equilibria (although he used the old definitions of acids and
bases as being equivalent to anions and cations). An
updated version of the Van Slyke equation is given in
Table 1.
While base excess is defined as titratable base, titrating to an end point pH of 7.40 at a $p$CO$_2$ of 5.33 kPa, plasma buffer base (SID) may be determined (in principle at least) by titrating to an end point pH equal to the isoionic pH of albumin at a $p$CO$_2$ of zero (12, p. 27). The titration would not include all the phosphate ions, but this would cause a very minor discrepancy. This point of view clearly shows the analogy between base excess and buffer base, but also shows that the end point of titration is much more physiological in the case of base excess than in the case of buffer base.

Table 1. The Van Slyke equation (21) updated. For calculation of the extracellular concentration of net titratable hydrogen ion, $\Delta cH^+$, divide the haemoglobin concentration of the blood by 3: $cHbHb = cHbHb/3$.

$\Delta cH^+ = (1 - cHbHb/cHbHb) \cdot (\Delta cHCO_3^- \cdot p + \beta H^+ \cdot P_{\Delta pH}),$

$cHbHb$ haemoglobin concentration of the blood,

$\Delta cHCO_3^-$ bicarbonate concentration in standard plasma at pH = 7.4 and $p$CO$_2$ = 5.33 kPa,

$\beta H^+$ = $\beta H^+$, an empirical parameter accounting for erythrocyte plasma distributions,

$\beta Hb$ apparent molar buffer capacity of haemoglobin (monomer) in whole blood (11, p. 47),

$\beta Albr$ substance concentration of albumin in plasma, (default value 0.65 mmol/L),

$\beta Glib$ apparent specific buffer capacity of plasma globulins,

$\beta PO_4$ molar buffer capacity of phosphate ion,

$\beta Pr$ apparent specific buffer capacity of total protein in plasma,

$P_{\Delta pH}$ = $PH^+ \cdot PH$. Base excess or deficit, especially when elevated levels of an anion or exchange with a cation. Analysis of the other ions (the electrolyte status) may give some clue to the cause of a base excess or deficit, especially when elevated levels of an organic anion such as lactate or 3-hydroxy-butyrate are found. But an increased blood lactate, for example, does not necessarily indicate lactic acidosis. It could be due to
infusion of sodium lactate as a therapeutic measure in a case of metabolic acidosis due to gastrointestinal loss of sodium bicarbonate. The diagnosis hyperchloraemic acidosis, a relic from the time when chloride was considered an acid, does not reveal anything about the etiology of the acidosis. It could be due to dehydration and loss of sodium bicarbonate. The same applies to hypochloraemic alkalosis and hypernatriaemic alkalosis, which merely indicate an increased base excess associated with decreased chloride or increased sodium, respectively.

Jabor and Kazda in their application of the Stewart approach (11, present volume) describe a set of equations, to classify metabolic acid-base disturbances on the basis of concomitant changes in other electrolytes. They diagnose hyperchloraemic acidosis, hypochloraemic alkalosis, hyperphosphataemic acidosis, hypophosphataemic alkalosis, and hyperalbuminaemic acidosis and hypoalbuminaemic alkalosis, and acidosis and alkalosis “caused by” increases or decreases in undetermined anions. They emphasize that in patients with a normal extracellular base excess many hidden acid-base disorders may be present. In our terminology we would say that many hidden water and electrolyte disorders may be present. Three examples suffice to illustrate the unfamiliar and inept terminology resulting from the Stewart approach:

1) A patient has normal pH, pCO$_2$, and extracellular base excess. Plasma sodium is 149 mmol/l, chloride 110 mmol/L, albumin 0.9 mmol/L. Plasma buffer base (SID) is 45 mmol/L (normal 40 mmol/l). Potassium, calcium, magnesium, and phosphate are normal. In our terminology the patient has a normal acid-base status but a marked hyperalbuminaemia and a moderate hypernatraemia. In the Stewart terminology the elevated plasma buffer base indicates a metabolic alkalosis and classifying the disturbance according to Jabor and Kazda the patient has hypochloraemic (!) alkalosis combined with hyperalbuminaemic acidosis.

2) A patient has normal pH, pCO$_2$, and extracellular base excess with normal plasma sodium, potassium, calcium, magnesium, and phosphate, but slightly increased chloride (111 mmol/l) and decreased albumin (0.38 mmol/L). Plasma buffer base (SID) is 34 mmol/L. In our terminology the patient has a normal acid-base status with slight hyperchloraemia and hypoalbuminaemia. In Jabor and Kazda’s terminology the patient has hyperchloraemic acidosis and hypoalbuminaemic alkalosis. This example clearly shows that they use the terms acidosis and alkalosis to refer to changes in the concentration of anions (in casu chloride and albuminate) not to refer to added or removed hydrogen ion.

3) A patient has pH=7.00, pCO$_2=16.5$ kPa, and extracellular base excess = 0.0 mmol/L. The plasma base excess is 3.0 mmol/L, plasma buffer base (SID) is 43 mmol/L. Plasma sodium, potassium, calcium, magnesium, phosphate are normal, but chloride is slightly decreased to 102 mmol/l. Plasma albumin is normal, but the concentration of plasma albumin anion is decreased to 9.0 mmol/L due to the low pH. In our terminology the patient has a pure respiratory acidosis with no metabolic component. In the Stewart terminology the patient has a slight metabolic alkalosis (reduced plasma buffer base), and in the Jabor/Kazda terminology the patient has a slight hypoalbuminaemic and hypochloraemic alkalosis. This example illustrates that plasma buffer base (SID) does not remain constant in a pure respiratory acid-base disturbance in vivo, and it also reveals some inconsistency between the original Stewart terminology and the terminology suggested by Jabor and Kazda since Stewart would not have diagnosed the hypoalbuminaemic alkalosis.

CONCLUSION

The Stewart approach was proclaimed a revolutionary new approach and it was stated that “many current models for ion movements through membranes will require modification on the basis of this quantitative analysis” (2). Several publications on SID were praised in editorials in the respective journals (4, 30) and we do acknowledge that the study by Figge, Mydosh, and Fencl on the isoionic pH and buffer value of human albumin (9) has provided valuable reference data.

We have shown, however, that the approach is anachronistic and the terminology misleading, confusing anions and cations with acids and bases. The acid-base status of blood and extracellular fluid is equivalent to the hydrogen ion status, not equivalent to the electrolyte status of the plasma. Due to the electro-neutrality principle changes in the hydrogen ion status automatically involve changes in the electrolyte status but the opposite need not be the case. The three relevant acid-base quantities are the arterial pH, the arterial pCO$_2$, and the extracellular base excess. Determination requires an arterial blood sample and a modern pH-blood gas analyzer. Total CO$_2$ (bicarbonate) measured in venous plasma using an electrolyte analyzer or multi-purpose chemical analyzer may be used as screening parameter in patients without respiratory disorders. All other parameters suggested as measures of a metabolic acid-base disturbance are obsolete.

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REFERENCES


