

FAQ concerning the acid-base status of the blood

July 2010



O. Siggaard-Andersen

MD, PhD, Dr. Med. Sci.
Professor of Clinical Biochemistry,
University of Copenhagen
Olaf Poulsens Vej 7,
DK-2920 Charlottenlund,
Denmark

Some of the frequently asked questions are: Should we use BE (base excess) or SID (strong ion difference) as a measure of a metabolic acid-base disturbance? Is there any difference between BB (buffer base) and SID? Should we use SBE (standard base excess), i.e. BE referring to the expanded extracellular fluid or just BE referring to whole blood?

Should BE or SBE refer to fully oxygenated blood or to the actual hemoglobin oxygen saturation? Should we use the UA (undetermined anions, anion gap) rather than BE? What is a metabolic acidosis or alkalosis? Is it simply an abnormal BE value, or is it a pathophysiological process which might cause an abnormal BE value?

My answer to all these questions is: Use the concentration of titratable hydrogen ion in the extended extracellular fluid (at the actual oxygen saturation), $\text{ctH}^+_{\text{Ecf}}$, as the relevant measure of an overall metabolic acidosis or alkalosis, which may be due to several cooperative or counteractive pathophysiological processes. $\text{ctH}^+_{\text{Ecf}}$ and

SBE are numerically equal, with opposite sign, but it is the hydrogen ion, not base which is the relevant quantity.

Since 2002, when I had to retire at the age of 70, I have received many e-mails related to the acid-base status of the blood. In the following I have summarized my answers to some of the frequently asked questions.

Singer and Hastings' buffer base

In 1948 Singer and Hastings introduced buffer base (BB^+) [8], defined as the difference: [sum of fixed cations] minus [sum of fixed anions], a fixed ion being an ion unable to bind or give off a hydrogen ion. Fixed cations were then considered strong bases, fixed anions strong acids; hence the term buffer base.

In blood plasma the most important cations are Na^+ and K^+ . All cations in plasma are fixed cations, except H^+ and NH_4^+ , which appear in imperceptible concentrations compared to the others.

The fixed anions are primarily Cl^- . In chemistry, lactate and several other organic anions would not be considered fixed anions but in the pathophysiological pH range they behave as such.

In plasma the non-fixed anions are primarily bicarbonate, albuminate and phosphate. Globulins contribute very little and OH^- appears in imperceptible concentrations. The non-fixed anions were considered weak acids or buffer acids, being able to buffer, i.e. bind hydrogen ions.

According to the law of electroneutrality the sum of cations matches the sum of anions. Hence BB^+ corresponds to the sum of non-fixed (buffer) anions, but is not so defined.

The rationale of introducing BB^+ was to obtain a quantity which stoichiometrically reflects added or removed strong acid or base. In addition it should be independent of adding or removing carbonic acid, i.e. changing the $p\text{CO}_2$.

For example, adding carbonic acid, by increasing the $p\text{CO}_2$, carbonic acid will give off a hydrogen ion and bicarbonate will increase, but the hydrogen ion is bound by albumin and albuminate will fall the same amount as bicarbonate increases; hence BB^+ remains unchanged. In other words, BB^+ is an ideal measure of a metabolic acid-base disturbance, independent of a respiratory acid-base disturbance.

Singer and Hastings determined buffer base of whole blood and used the change in BB^+ from the normal value, $\text{DBB}^+ = \text{BB}^+ - \text{NBB}^+$, to indicate the severity of a metabolic acid-base disturbance. Being an important buffer, hemoglobin needed to be taken into account.

They realized that the normal value for BB^+ , NBB^+ , varies with the hemoglobin concentration. In other words, a high value for BB^+ due to a high hemoglobin concentration should not be considered an indication of a metabolic alkalosis and should not affect DBB^+ .

Stewart's SID

In 1981 Stewart introduced the strong ion difference, SID, defined as: [sum of strong cations] minus [sum of strong anions] [9]. Since strong ions are the same as fixed ions, Stewart's SID is completely identical with Singer and Hastings' BB^+ .

SID was only defined for plasma. A change in SID, $\text{DSID} = \text{SID} - \text{SID}_{\text{normal}}$, was interpreted as a metabolic acid-base disturbance, but a very major difference from the Singer and Hastings approach was that the normal value ($\text{SID}_{\text{normal}}$) was constant, independent of variations in the albumin concentration.

As a consequence, an increase in SID due to an increased albumin concentration, with a normal pH of 7.40 and a normal $p\text{CO}_2$ of 5.3 kPa (40 mmHg) is interpreted as a metabolic alkalosis (the increased SID) together with a hyperalbuminemic acidosis (the increase in albumin anion concentration).

Any increase in albumin concentration is considered a hyperalbuminemic acidosis, because albumin supposedly is added at zero net charge, i.e. adjusted to the isoionic pH of about 4.9. Such an albumin solution would definitely act as an acid. H^+ would be given off and buffered by bicarbonate and albumin (already present) and pH would fall.

But an albumin solution adjusted to pH = 7.4 and infused as sodium albuminate would not act as an acid and pH would remain 7.4. Nevertheless, in the Stewart terminology we would now have a hyperalbuminemic acidosis compensated by a hypernatremic alkalosis.

This terminology may seem logical if any anion is considered an acid and any cation a base. By the same token any increase in blood lactate is considered a lactic acidosis, even when the increase is due to infusion of sodium lactate.

If the concept of SID is adopted for whole blood, the consequence would be that a patient with anemia would have an "anemic alkalosis", and a patient with polycythemia a "hemoglobinemic acidosis".

I am sure Singer and Hastings would have been critical to this interpretation of changes in albumin (or hemoglobin) as being types of acid-base disturbances.

Brønsted's acid-base definitions

I admire Singer and Hastings and their predecessor Donald D. Van Slyke [10]. I have met all of them. Unfortunately they adhered to the old Arrhenius definitions of acids and bases being anions and cations, respectively [1].

Brønsted, in 1923, emphasized that the ion of interest is the hydrogen ion [2]. An acid is a molecule which contains a bound dissociable hydrogen ion. A strong acid gives off all the hydrogen ions in solution (e.g. HCl). A weak acid gives off only part of the bound hydrogen ions (or none at all), depending upon the pH of the solution, and may be called a buffer acid.

A base contains a hydrogen-ion-binding group. A strong base binds hydrogen ions to all available binding groups (e.g. OH⁻), a weak base binds hydrogen ions depending upon the pH. A weak base is also called a buffer base.

In modern terminology buffer base (BB⁻) is defined as the difference: [sum of buffer anions] minus [sum of buffer cations], where the latter, as previously mentioned, is zero in blood plasma.

Hence BB⁻ is the sum of bicarbonate, proteinate (albuminate and hemoglobinate) and phosphate. BB⁻ is numerically identical to BB⁺, albeit defined differently.

Delta buffer base, DBB⁻ is defined as: $DBB^- = BB^- - NBB^-$, where NBB⁻ is the normal value of BB⁻ at pH = 7.40 and $pCO_2 = 5.3$ kPa (40 mmHg), about 42 mmol/L for plasma, depending upon the albumin concentration; 51 mmol/L for whole blood, depending upon both albumin and hemoglobin concentrations. DBB⁻ is also called Base Excess (BE), a negative value indicating a base deficit.

Base excess reflects addition or removal of hydrogen ions except when adding or removing CO₂. Added H⁺ is bound by the buffer anions, and base excess falls in

direct proportion to the added H⁺. But when adding CO₂ (by increasing the pCO_2) bicarbonate increases, and the other buffer anions (albuminate and phosphate) decrease in direct proportion and base excess remains unchanged.

The direct method of measuring excess or deficit of H⁺ is titration. First pCO_2 is adjusted to 5.3 kPa (40 mmHg) and kept at this value by tonometry during the titration.

If pH is less than 7.40, the blood or plasma is titrated to pH = 7.40 with strong base, e.g. NaOH, which is rapidly converted to NaHCO₃ during titration. If pH is initially above 7.40, the titration is performed with HCl.

The excess H⁺ in the first case equals the amount of NaOH required to restore the pH to normal. In the second case the H⁺ deficit equals the amount of HCl. We call the difference between these two the excess (concentration) of titratable hydrogen ion, H⁺ excess for short; a negative value indicating an H⁺ deficit. In actual practice excess H⁺ is calculated from pH, pCO_2 and cHb (perhaps including albumin and phosphate), e.g. using the Van Slyke equation [6, 7].

The H⁺ excess equals the base excess with opposite sign. I now prefer to talk about an H⁺ excess rather than a base excess, because the component of interest, as pointed out by Brønsted, is the hydrogen ion, not the hydrogen-ion-binding group or buffer base. pH is an indicator of the concentration of free hydrogen ions, generally calculated simply as $cH^+ = 10^{9-pH}$ nanomol/L.

The concentration of titratable hydrogen ion, ctH⁺, is a measure of (the change in) the concentration of total, free plus bound, hydrogen ion. An analogy is the concentration of total calcium, i.e. the sum of free (ionized) and bound calcium.

BE is a nice acronym, easy to write, easy to pronounce. The acronym for hydrogen-ion excess, whether HIE or HE, is unfamiliar and will have a hard time to conquer BE. A convenient symbol for the hydrogen-ion excess might be xH (excess hydrogen ion), with some resemblance of pH. However, in the following I will use the symbol ctH⁺.

Referring to plasma, whole blood or the extended extracellular fluid

Singer and Hastings thought that buffer base would remain constant during pure respiratory changes. This is the case when $p\text{CO}_2$ changes in blood in vitro, because the change in bicarbonate is completely balanced by an opposite change in the other buffer anions (primarily albuminate and hemoglobinate).

However, in vivo, buffer base does not remain constant. It was shown in 1934 by Shaw and Messer that with a rise in $p\text{CO}_2$, pH falls more and bicarbonate rises less than in blood in vitro [4]. This means that ctH^+ of whole blood rises.

The explanation is a redistribution of H^+ between the poorly buffered interstitial fluid and the well-buffered blood. H^+ moves from the interstitial fluid into the blood plasma and further into the red cells, where it is buffered by hemoglobin. Whether it is H^+ moving in one direction, or HCO_3^- moving in the opposite, is immaterial; the result is the same.

If we want a quantity which is independent of $p\text{CO}_2$ changes in vivo, we need to use a model of the extended extracellular fluid, i.e. extracellular fluid including the blood cells. We can create such a model assuming that the red cells are distributed throughout the extended extracellular fluid.

The hemoglobin concentration of this model equals the hemoglobin concentration of the blood times the ratio of the volume of blood divided by the volume of the extended extracellular fluid. We assume that this ratio normally is around one third, but in the newborn the interstitial fluid volume is larger and the ratio may be closer to one fourth.

It is essential to refer to the extended extracellular fluid, especially in the newborn, where we may encounter very high $p\text{CO}_2$ values and large variations in hemoglobin concentration. In other words, neonatologists should definitely use BE_{Ecf} or better $\text{ctH}^+_{\text{Ecf}}$.

Referring to the actual hemoglobin oxygen saturation or fully oxygenated blood

Blood base excess originally in 1960 referred to fully oxygenated blood for the reason that it was determined for blood oxygenated in vitro, i.e. blood in equilibrium with a gas mixture of 94.4 % O_2 and 5.6 % CO_2 .

Later, in 1964, it was redefined to refer to the actual hemoglobin oxygen saturation [5].

The reason is that if the blood is fully oxygenated in vivo, the result is different from the result in vitro. When hemoglobin is oxygenated, hydrogen ion is liberated corresponding to about 0.3 mmol per mmol of oxygen being bound.

Thus, if the oxygen saturation is 50 % and the initial pH is 7.40 with a $p\text{CO}_2$ of 5.3 kPa (40 mmHg) and the hemoglobin concentration 10 mmol/L, then ctH^+ for fully in vitro oxygenated blood would be 1.5 mmol/L. But if the hemoglobin is oxygenated in vivo, then the 1.5 mmol of hydrogen ion would be distributed in the whole extracellular fluid and the rise in ctH^+ would be only 0.5 mmol/L.

It is difficult to explain that oxygenating the hemoglobin in vivo causes a fall in ctH^+ (referring to fully in vitro oxygenated blood) from 1.5 to 0.5, since H^+ was released in the process.

If ctH^+ refers to the actual oxygen saturation, it is easier to explain that oxygenation resulted in a rise from zero to 0.5 mmol/L, since some H^+ was released and distributed throughout the extended extracellular fluid.

This is the reason why ctH^+ of the extended extracellular fluid should refer to the actual hemoglobin concentration, not fully oxygenated blood.

Metabolic acidosis and alkalosis

The question whether metabolic acidosis and alkalosis should refer to the acid-base status of the blood or to the pathophysiological process was thoroughly discussed at a meeting in New York in 1965 [3].

Although complete consensus was not achieved (I think I was one of the dissidents), the majority shared the opinion that the terms should refer to the underlying pathophysiological processes of input or output of acid or base rather than merely indicating changes in the blood.

The laboratory diagnoses should be: Acidemia and alkalemia for low and high pH, respectively, hyper- and hypocapnia for high and low $p\text{CO}_2$, respectively, hyperbasemia and hypobasemia for high or low bicarbonate or base excess. No special name was suggested for an excess or deficit of titratable hydrogen ion.

Nevertheless, if we find a positive hydrogen-ion excess (> 3 mmol/L), the patient must have some type of unspecified metabolic acidosis. Therefore it cannot be wrong to call a hydrogen-ion excess a metabolic acidosis and a hydrogen-ion deficit a metabolic alkalosis.

If ctH^+ is normal and $p\text{CO}_2$ is normal, we can say that the blood acid-base status is normal but we cannot say that there is no metabolic acid-base disturbance, because there could be a mixed metabolic acidosis and alkalosis.

When we have calculated a hydrogen-ion excess or deficit on the basis of a blood gas analysis, it is relevant to ask which anion accompanied the hydrogen ion (or which cation was exchanged for it), trying to explain the underlying pathophysiological process.

For example, a patient with loss of HCl from vomiting and simultaneous loss of NaHCO_3 from diarrhea, with low plasma chloride and sodium but normal hydrogen-ion excess, would be described as a patient with mixed "hydrochloric acid losing alkalosis" and "sodium bicarbonate losing acidosis". The term "diarrheal acidosis" was also suggested.

The terms hypochloremic alkalosis and hyponatremic acidosis are misnomers because it would be odd to have a hypochloremic alkalosis without hypochloremia. The processes themselves, HCl loss and NaHCO_3 loss, do not necessarily involve hypochloremia or hyponatremia; there might be simultaneously a third process involving input of NaCl.

Dilution acidosis and contraction alkalosis are special types of acidosis and alkalosis. Dilution acidosis may be caused by infusion of isosmotic glucose or isotonic saline. The explanation is that titrating these solutions to $\text{pH} = 7.40$ at $p\text{CO}_2 = 5.3$ kPa (40 mmHg) using NaOH, would require 25 mmol of NaOH per liter.

After titration the bicarbonate concentration would be 25 mmol/L. In other words, the solutions have a hydrogen-ion excess of 25 mmol/L. For example, the effects of diluting normal plasma 50/50 with physiological saline (154 mmol/L) would be a rise in Na^+ from 141 to 147.5 mmol/L, a rise in Cl^- from 103 to 128.5 mmol/L, and a rise in hydrogen-ion excess from 0 to 12.5 mmol/L.

If $p\text{CO}_2$ remains 5.3 kPa, pH would be 7.155; bicarbonate would fall from 24.3 to 13.3, and albuminate from 12 to 4.7 mmol/L. All values were calculated by simple algebra together with a computer program for calculating acid-base values.

In the Stewart terminology, these values would indicate a severe hyperchloremic acidosis partly neutralized by a hypoalbuminemic alkalosis and a hypernatremic alkalosis; terms that hardly reflect the underlying process.

Undetermined anions

Although buffer base is defined as the difference between cations and anions, neither BB^- , nor BE, nor ctH^+ has anything to do with the Anion Gap, also called Undetermined Anions. UA^- is the sum of the measured cations minus the sum of the measured and calculated anions. HCO_3^- may be calculated from pH and $p\text{CO}_2$, albuminate from pH and the total albumin concentration.

If the measured cations include Na^+ , K^+ , 2Ca^{2+} and 2Mg^{2+} and the anions include Cl^- , HCO_3^- , albuminate, phosphate and lactate, then UA^- is about 3 mmol/L, representing sulfate, carboxylate (free fatty acid), 3-OH-butyrate, pyruvate and minor amounts of a number of organic anions from the intermediary metabolism, including acetacetate.

An increased value indicates an increase in one or more of these latter anions or an increase in a pathological anion such as formate in the case of methanol poisoning or salicylate.

Both of these may be measured and included in the calculation of UA^- . Unmeasured cations may be Li^+ after lithium medication or NH_4^+ , which may reach concentrations of a few mmol/L in newborns with inborn errors of the urea metabolism.

UA^- cannot be calculated with great precision due to the many variables involved. If there is suspicion of increased lactate, 3-OH-butyrate, formate or salicylate, these ions should be measured directly.

Summary

Base excess (BE) should be replaced by hydrogen-ion excess (xH or ctH^+) as a measure of hydrogen ions accumulated in the blood, because the hydrogen ion is the relevant component, not the hydrogen-ion-binding groups. If we want a quantity independent of pCO_2 in vivo, ctH^+ should refer to the extended extracellular fluid, ctH^+_{Ecf} , and it should apply to the actual hemoglobin oxygen saturation.

ctH^+_{Ecf} may be calculated with the computer program "the oxygen status algorithm (OSA)", freely downloadable at www.siggaard-andersen.dk. The program uses the most recent (2006) version of the Van Slyke equation [7].

Several e-mails I have received have encouraged me to write the present comments. Dr. med. Jürgen Gehrke, PhD, Bad Kissingen, requested an online version of the Windows-based OSA program.

He uses the old DOS version, where online collection of data was possible with a printout including a graphical representation of the acid-base and the oxygen status of the blood. He hands the printout to his patients to explain the diagnosis. Dr. Gehrke is so far the only one who has shown interest in an online version. If others are interested in this possibility, my son M. Siggaard-

Andersen has promised to help with the necessary programming.

References

1. Arrhenius S. Über die Dissociation der Wasser gelöste Stoffe. Z Phys Chem 1887; 1: 631-48.
2. Brønsted JN. Einige Bemerkungen über den Begriff der Säuren und Basen. Rec Trav Chim Pays-Bas 1923; 42: 718-28.
3. Gambino SR, Astrup P, Bates RG, Campbell EJM, Chinard FP, Nahas GG, Siggaard-Andersen O, Winters RW. Report of the ad hoc committee on acid-base terminology. Annals New York Acad Sci 1966; 133: 259-67.
4. Shaw LA, Messer AC. The transfer of bicarbonate between the blood and tissues caused by alterations of carbon dioxide concentration in the lungs. Amer J Physiol 1932; 100: 122-36.
5. Siggaard-Andersen O. Acid/base disturbances (letter). Lancet 1964; i: 1104.
6. Siggaard-Andersen O. The Van Slyke equation. Scand J Clin Lab Invest 1977, Suppl 146: 15-20.
7. Siggaard-Andersen O. Acid-base balance. In: Laurent GJ, Shapiro SD (eds.). Encyclopedia of Respiratory Medicine. Elsevier Ltd. 2006; 5-10. ISBN: 0-12-438360-2.
8. Singer RB, Hastings AB. An improved clinical method for the estimation of disturbances of the acid-base balance of human blood. Medicine (Baltimore) 1948; 27: 223-42.
9. Stewart PA. Modern quantitative acid-base chemistry. Can J Physiol Pharmacol 1983; 61: 1444-61.
10. Van Slyke DD, Hastings AB, Hiller A, Sendroy J Jr. Studies of gas and electrolyte equilibria in blood. XIV. The amounts of alkali bound by serum albumin and globulin. J Biol Chem 1928; 79: 769-80.