Analysis of blood gases and acid–base balance

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Abstract
Analysis of blood gases is widely used for patients with many different conditions from surgical, medical and intensive care fields. Knowledge of the basic science behind the subject is essential to gain a full understanding of what the results mean on a typical blood gas result. Understanding the history of acid–base physiology and why certain analytical tools were developed can make interpretation easier. The scope of this article is to explain some of the background to this area and show how it relates to clinical medicine.

Keywords Acid–base balance; acidosis; alkalosis; blood gas analysis

Background to acids and bases

In 1909, Sorensen introduced the pH terminology to measure hydrogen ion concentration:

$$pH = -\log_{10}[H^+]$$

pH is thus a compressed, non-linear and dimensionless scale. This is useful for chemists who work with a large range of concentrations but clinicians only deal with a clinical range of 20–160 nmol/litre.

In 1909, Henderson rearranged the equilibrium reaction for carbonic acid:

$$CO_2 + H_2O \rightarrow H_2CO_3 \rightarrow H^+ \rightarrow HCO_3^-$$

To give the 'Henderson equation':

$$[H^+] = K_1 \times [H_2CO_3]/[HCO_3^-]$$

where K_1 = dissociation constant. Substituting $[CO_2]$ for $[H_2CO_3]$ gives:

$$[H^+] = K_1 \times [CO_2]/[HCO_3^-]$$

Hasselbalch (1916) further changed the equation to fit in with Sorensen's (1909) pH terminology by taking logarithms and substituting $[CO_2]$ for the partial pressure of carbon dioxide (P_{CO_2}). This yields the familiar Henderson–Hasselbalch equation (H–H equation):

$$pH = pK + \log_{10}[HCO_3^-]/P_{CO_2} \times 0.23$$

where 0.23 is the solubility coefficient for CO_2.

In this negative logarithmic scale a small change in pH reflects a relatively large change in $[H^+]$ in the opposite direction. A change of 0.3 pH units is equivalent to doubling or halving the $[H^+]$. The range of $[H^+]$ compatible with life is 20–160 nmol/l (pH 7.70–6.80). See Table 1 for pH values against hydrogen ion concentrations.

The start of clinical acid–base measurement was the poliomyelitis epidemic in the 1950s. Large numbers of patients needed artificial ventilation for extended periods. This was really the birth of intensive care as a speciality. To titrate ventilation, measurements of carbon dioxide partial pressure (P_{CO_2}) were needed; this was initially achieved by measuring pH and HCO_3^- and using the H–H equation to derive P_{CO_2}.

Chemistry of water

The human body is composed mostly of water. Water is a simple triatomic molecule with strong ionic bonds between O and H with unequal charge distribution. This gives rise to the physical characteristics of water. Water has a large dielectric constant so molecules with strong ionic bonds dissociate when in water. Water itself dissociates only slightly.

$$K \times [H_2O] = [H^+] \times [OH^-]$$

The concentration of water is altered only slightly by dissociation so the left hand of the equation can be taken as a constant. This is termed K′w (the ion product of water). Therefore:

$$K'w = [H^+] \times [OH^-]$$

For electroneutrality, $[H^+]$ must equal $[OH^-]$. At 25 °C, pure water has a K′w of 1.008×10^{-14} mol^2/litre^3. Thus we can say that $[H^+] = [OH^-] = 1 \times 10^{-7}$ Eq/litre. Using Sorensen's pH scale this gives a pH of 7. However, as temperature changes, so does molecular activity and at 37 °C, for solutions in the body, K′w = 4.4×10^{-14} mol^2/litre^3. Thus $[H^+]$ and $[OH^-]$ are both increased in proportion. In other words, a 'neutral' pH of 7 is only true for a temperature of 25 °C. At body temperature, acid–base 'neutral' pH is 6.8. At 0 °C 'neutral' pH is 7.5 and at 100 °C 'neutral' pH is 6.1. pH is therefore simply a measure of

pH and $[H^+]$ concentration

pH	H^+ concentration (nmol/litre)	mol/litre
9.0	1	10^{-9}
8.0	10	10^{-8}
7.4	40	$10^{-7.4}$
7.3	50	$10^{-7.3}$
7.0	100	10^{-7}

Table 1

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hydrogen concentration and does not necessarily reflect acid–base neutrality.

Acid–base physiology

Hydrogen ion concentration has important effects on body proteins. Organs such as the heart and brain are sensitive to changes in $[H^+]$.

The acid load produced by the body each day is substantial. The acid produced is either volatile (CO_2) or non-volatile acids. These non-volatile acids are also termed 'fixed' acids. These are usually referred to by their anion (lactate, phosphate, sulphate, acetoacetate, β-hydroxybutyrate). Note that these are bases and not actually acidic. This terminology is common place because they have been formed by the liberation of an H^+ from their parent acid.

Around 13,000 mEq/day of acid are excreted by the lungs as CO_2 compared with 100 mEq/day as metabolic acids.

There are a number of 'defence' mechanisms to try to resist changes in $[H^+]$ which is important for homeostasis:

1. **Buffering:** is a rapid physico-chemical response. The body has a huge buffering capacity which is virtually immediate in effect. A buffer is a solution that resists changes in pH when acid or alkalis are added. An acidic buffer consists of a weak acid and a salt of the acid. The buffering systems present are either:
    - blood (carbonic acid/bicarbonate, haemoglobin, plasma proteins, phosphate)
    - intracellular fluid (proteins, phosphate).
2. **Respiratory:** alteration in arterial carbon dioxide pressure (P_{CO_2}). An increase in ventilation will reduce the level of carbon dioxide. The lungs have a huge capacity to increase ventilation and remove carbon dioxide from the body. Removal of carbon dioxide is useful as it will reduce intracellular pH as carbon dioxide can cross membranes very easily.
3. **Renal:** alteration in HCO_3^- excretion. The kidneys are responsible for adjustment of bicarbonate excretion but the process is much slower taking several days to reach maximal capacity.

Measurement of blood gases: arterial blood gas analysis

A standard blood gas analyser gives us the figures for many variables. The most common in use is the **Radiometer** developed in Denmark. Some of these variables are measured directly by the machine and some are derived.

Directly measured variables are:

- **pH:** measured using a pH electrode. It consists of two half cells. A stable reference electrode is connected to the pH electrode, the induced voltage being proportional to the $[H^+]$. The pH electrode separates a buffered solution and the sample with a pH sensitive glass membrane. The potential difference across this membrane is measured.
- **PaO_2:** measured using a polarographic (Clark) electrode. This comprises a silver/silver chloride anode and platinum cathode in an electrolyte bath. A small potential difference is applied across the electrodes and the current measured. The induced current is directly related to the PO_2.
- **$PaCO_2$:** measured using a Severinghaus electrode. It measures PCO_2 directly. CO_2 diffuses across a membrane where a chemical reaction releases H^+ ions. $[H^+]$ is measured using a modified pH electrode.

Derived variables include:

- **Actual bicarbonate:** is usually 24 mmol/litre and is derived from the H–H equation, and is the actual concentration in the sample. Plasma is equilibrated with PCO_2 5.3 kPa (40 mmHg) at 20 °C and actual HCO_3^- calculated from the volume of PCO_2 evolved when acid (HCl) is added to the sample.
- **Standard bicarbonate:** is the concentration of bicarbonate when the sample is equilibrated with PCO_2 5.3 kPa (40 mmHg) at 37 °C, and with haemoglobin fully saturated with O_2. The effects of respiratory acidosis/alkalosis are eliminated. Normal range is 24–33 mmol/litre.
- **Base excess:** the quantity of strong acid (or base) required to titrate 1 litre of blood back to pH 7.4 at PCO_2 5.3 kPa (40 mm Hg) and 37 °C.
- **Standard base excess:** is the base excess when the [Hb] is set at 5 g/dl which is an approximation for all extracellular fluid (ECF) not just blood. This is important given the high buffering capacity of Hb.
- **See Table 2 for other variables that are also routinely included.**

Temperature correction

The blood gas machine analyses the samples at 37 °C. There is a function to temperature correct the sample (e.g. if the patient is hypothermic). If temperature correction is performed then the reference ranges are not applicable as these are for 37 °C only. Current practice is to not temperature correct.

Analytical approaches to acid–base disorders

Although blood gas analysis is widely used it provides incomplete information about acid–base chemistry. The variables above reflect the effect, but not the cause, of acid–base disorders.

Over time a number of analytical methods have been developed to try to identify the causes of the acid–base disturbance that are measured. None of the following methods are fully accurate and each has their own groups of followers.

Other variables also routinely included

Oximetry status
- Alveolar arterial oxygen gradient
- Oximetry values
- Haemoglobin concentration
- Oxygen saturation
- % of oxyhaemoglobin
- % of carbaminohaemoglobin
- % of methaemoglobin
- Haematocrit

Electrolyte values
- Potassium
- Sodium
- Calcium
- Chloride

Metabolic values
- Glucose
- Lactate

Oxygen status
- Oxygen content
- Oxygen p50

Table 2

The initial approach was termed the 'Boston' approach, developed by researchers from that city. They used acid–base maps in chronic patients to calculate how serum bicarbonate is related to carbon dioxide tension using the Henderson–Hasselbalch equation. The main drawback is that it assumes that bicarbonate and carbon dioxide are independent rather than interdependent variables. It also runs into trouble when trying to explain critically ill patients who may have a number of acidifying and alkalinizing processes coexisting.

Researchers in Copenhagen developed another approach moving away from the Henderson–Hasselbalch equation. They concentrated on the metabolic component of acid–base disturbances. They developed the concept of the 'buffer base'. This was the sum of all the buffering agents in the blood. The drawback with this concept was the alteration of buffering capacity associated with changes in haemoglobin concentrations.

This approach was refined by the base deficit/excess concept as a measure of metabolic acid/base activity. To overcome the change in haemoglobin concentration and its effect the approach was modified to use serum and calculate the standard base excess.

Other approaches are the anion gap (which we describe later) and Stewart's theory. In 1983, Stewart, a Canadian physiologist, argued that the Henderson–Hasselbalch concept of acid/base balance was an oversimplification, since it assumed that P_{CO_2} and HCO_3^- are independent variables, but in fact they are in dynamic equilibrium i.e. interdependent. His model is based on the following properties of water-based solutions:

i. *Dissociation*: body fluids can be considered as aqueous solutions that contain:
   a. Strong ions (fully dissociated e.g. NaCl)
   b. Weak ions (partially dissociate e.g. CO_2 and weak acids)
   c. Non-electrolytes (non charged species)
ii. *Electroneutrality*: in aqueous solution, the sum of all the positive charged ions must equal the sum of all the negative charged ions.
iii. *Mass conservation*: the amount of any substance remains constant unless it is added, removed, generated or destroyed.

In plasma, Stewart identified three principal mathematically independent variables which, when changed, dictate the acid–base balance. These variables are:

- carbon dioxide
- total weak acid concentration – mainly plasma proteins (principally albumin) and phosphates
- strong ion difference (SID) given by the total concentration (in mequiv/litre) of fully dissociated cations in solution minus the total concentration of fully dissociated anions in solution.

In plasma, strong cations (mainly Na^+) outnumber strong anions (mainly Cl^-): the difference between them is as follows:

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

Of note bicarbonate is not a strong ion. The SID has a powerful electrochemical effect on water dissociation, and hence on $[H^+]$. In healthy humans, plasma SID is 40–44 mmol/litre. Metabolic acidosis is produced by a decrease in SID. As SID decreases (i.e. becomes less positive), water dissociates more to maintain electrical neutrality.

Explaining common acid–base disturbances

Acid–base disturbances can be *acute* or *chronic* or have a degree of *compensation*. An *acidaemia* refers to a pH < 7.35 whereas an *alkalaemia* refers to a pH > 7.45. An *acidosis* refers to a process that will produce acid (the pH does not strictly have to be <7.35). Likewise an alkalosis refers to the process rather than the state. It is deemed to be inaccurate to refer to a compensatory process as either an acidosis or alkalosis, e.g. hyperventilating in response to an acidosis should be referred to as respiratory compensation and not a respiratory alkalosis.

We will discuss the common changes under the broad headings 'respiratory' and 'metabolic'.

Respiratory acid–base disturbances

Respiratory acidosis is a process caused by a rise in $PaCO_2$. $PaCO_2$ is proportional to VCO_2/V_A (where VCO_2 is CO_2 production by the body and V_A is alveolar ventilation). A rise in $PaCO_2$ can therefore only be caused by presence of CO_2 in inspired gas, alveolar hypoventilation or increased production by the body. Most causes are due to alveolar hypoventilation, which also usually causes a decrease in oxygen uptake. Arterial hypoxaemia can be corrected by supplemental oxygen although this does nothing to correct the level of CO_2. Increased CO_2 production occurs in exercise and in malignant hyperthermia.

The $PaCO_2$ rises and causes an increase in hydrogen ion concentration depressing the pH. If this persists then renal compensation may occur by reabsorbing HCO_3^-. This is prompted by an increase in CO_2 in the renal tubular cells. This then becomes a 'compensated respiratory acidosis'.

Respiratory alkalosis is a process caused by a fall in $PaCO_2$ which causes a decrease in $[H^+]$, elevating the pH. A respiratory alkalosis is always due to alveolar hyperventilation. This can occur by excessive minute ventilation if the patient's lungs are mechanically ventilated or as a physiological response to hypoxia. Renal compensation then occurs by increasing the amount of HCO_3^- excreted. If the hyperventilation is persistent e.g. at altitude then compensation may be complete.

Metabolic acid–base disturbances

Metabolic alkalosis is a process caused by a rise in plasma $[HCO_3^-]$. Whenever plasma $[HCO_3^-]$ rises >24 mmol/litre, HCO_3^- is excreted by the kidney. The kidney's response is quick and effective. If 100 ml 8.4% $NaHCO_3$ is infused in a healthy subject, the rise in plasma $[HCO_3^-]$ is only brief. If alkalosis supervenes, there must therefore be a process at work, which acts to inhibit or overcome this rapid excretion of excess bicarbonate. *Initiating causes* of an alkalosis include:

- an increase in alkali in the ECF, e.g. infusion of $NaHCO_3$, citrate from stored blood, etc
- a loss of acid from ECF, e.g. diuretics, vomiting or nasogastric suction.

Processes for *maintaining* an alkalosis include:

- chloride depletion
- potassium depletion.

These last need a little explanation. Chloride deficiency causes the kidney to reabsorb more HCO_3^- than normal: an adequate anion level is required for electroneutrality with the cations Na^+ and K^+. Chloride and HCO_3^- are the only anions in significant

concentrations, so a deficiency in one (e.g. chloride) will lead to rise in the other (e.g. HCO_3^-) to maintain electroneutrality. The commonest causes of metabolic alkalosis are those causing chloride depletion: loss of gastric acid, either through nasogastric drainage or vomiting, and diuretic use. The gastric secretion of H^+ produces HCO_3^-, which is returned to the blood. A metabolic alkalosis is most likely in pyloric stenosis where only acidic gastric secretions are lost. In other causes of vomiting, alkaline duodenal secretions may be lost too, mitigating the degree of acid–base disturbance. If there is concurrent use of proton pump inhibitors then metabolic acidosis may occur paradoxically, as the H^+ load of the gastric secretions is reduced.

Diuretics such as frusemide and thiazides reduce Cl^- and Na^+ reabsorption in the renal tubules. Urinary losses of Cl^- then exceed those of HCO_3^-, which is retained in blood to cause alkalosis. The patients that develop metabolic alkalosis the most are those that are volume depleted and salt restricted. Hypokalaemia also occurs. Proper correction of these abnormalities is therefore with volume and chloride replacement, for example normal saline infusion.

Another rarer cause is a villous adenoma which typically secretes HCO_3^- leading to a hyperchloraemic metabolic acidosis. Some can predominantly secrete Cl^- in which case a hypochloraemic metabolic alkalosis would result.

Metabolic acidosis is caused by a reduction in plasma $[HCO_3^-]$, by two mechanisms:

- a gain of strong acid (e.g. endogenous ketoacids in diabetes)
- a loss of base (e.g. from the bowel in diarrhoea or from kidney in as a result of carbonic anhydrase inhibitors).

Metabolic acidosis tends to be the most common acute surgical acid–base disturbance. A common way to classify a metabolic acidosis is to refer to whether the 'anion gap' is raised or normal. This concept was developed to try to address limitations in the Boston and Copenhagen approaches (referred to above) to acid–base analysis. The anion gap (AG) is not a physiological reality (i.e. there is no true gap in anions) but simply an artefact of measurement in the commonly measured anions (i.e. Cl^- and HCO_3^-) vs the commonly measured cations (Na^+, K^+). The unmeasured anions include serum proteins, phosphate, sulphate and organic anions (e.g. lactate and ketoacids). The 'unmeasured' cations include Ca^{2+}, Mg^{2+}, Li^+. Thus the 'gap' is mainly due to the negative charge of the plasma proteins, particularly albumin:

$$AG = \left(\left[Na^+\right] + \left[K^+\right]\right) - \left(\left[Cl^-\right] + \left[HCO_3^-\right]\right)$$

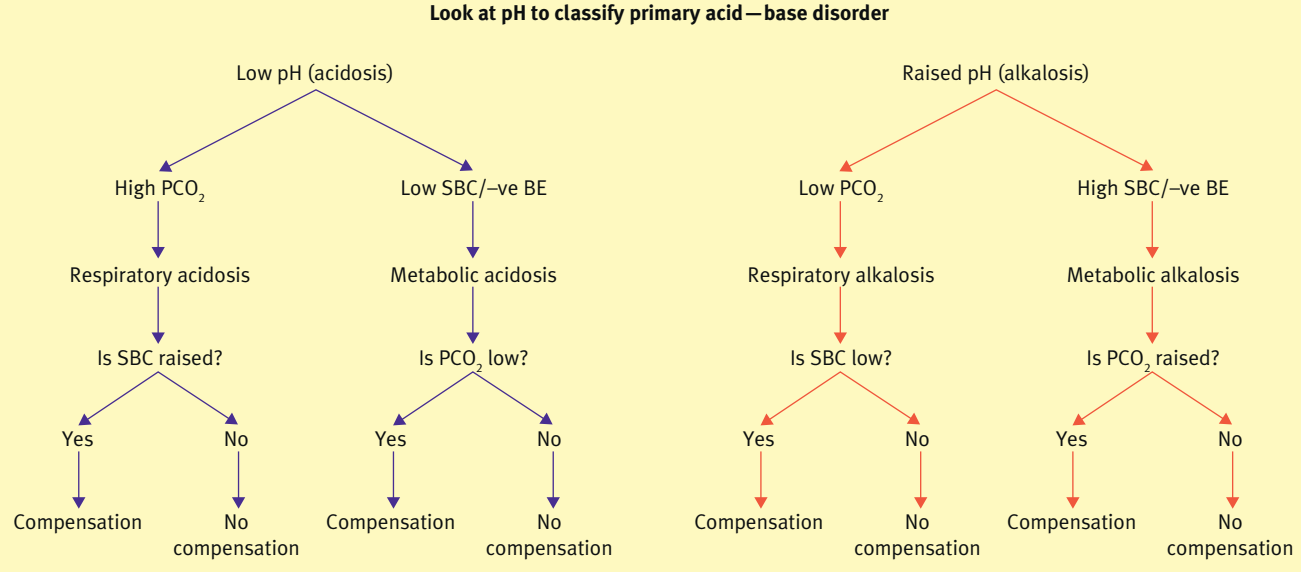
The normal range is 3–11 mmol/litre, but several terms in the equation each with inherent measurement errors, a range with an error of ±2 mmol/litre should be used. Albumin is a potent and plentiful contributor towards the normal anion gap, being an anion itself. Therefore as albumin falls it tends to reduce the size of the anion gap, or have an alkalinizing effect. The anion gap can be underestimated in hypoalbuminaemia. A correction can be used, assuming a normal albumin correction of 40 g/litre,

$$\text{Albumin gap} = 40 - \text{apparent albumin}$$

$$AG_{corr} = AG + (0.25 \times \text{Albumin gap})$$

The anion gap can be reduced by addition of unmeasured cations. This is rarely seen in clinical practice but can happen in hypermagnesaemia or lithium toxicity. It can also occur with excess immunoglobulin such as myeloma.

Summary guide to interpreting blood gas measurements



SBC, standard bicarbonate; BE, base excess

Figure 1

Acidoses with a high anion gap include:

1. Lactic acidosis
    a Type A (impaired perfusion)
    b Type B (impaired carbohydrate metabolism)
2. Ketoacidosis
    a Starvation
    b Diabetes mellitus
    c Alcoholism
3. Renal failure
    a Uraemic acidosis
    b Acidosis with acute renal failure
4. Toxins
    a Ethylene glycol
    b Methanol
    c Salicylates

Acidoses with a normal anion gap include:

1. Renal causes such as
    a Renal tubular acidosis
    b Carbonic anhydrase inhibitors
2. Gastrointestinal causes
    a Severe diarrhoea
    b Uretero-enterostomy or blockage of ileal conduit
    c Drainage of biliary or pancreatic secretions
    d Small bowel fistula

Patients who are critically ill often have a number of processes occurring at once. The contribution of the various acid–base abnormalities may be difficult to interpret. The delta ratio is a bedside technique that to identify mixed disorders. It is the ratio of the change in the anion gap to the change in bicarbonate concentration:

$$\Delta \text{AG}/\Delta \text{HCO}_3^-$$

The measurement is restricted clinically by the large error associated with its calculation.

Treatment of acid–base disorders

The mainstay is to diagnose the underlying abnormality and the process driving it and aim to treat that. Investigations and laboratory work should complement the clinical assessment and not vice versa (see Figure 1). Some aspects of treatment are self-evident. Lactic acidosis is treated with volume resuscitation and source control. Diabetic ketoacidosis is treated with volume resuscitation and insulin therapy. Renal acidosis is treated with dialysis or filtration. Most acidoses will resolve with physiological stabilization and multiorgan support.

Buffer therapy can be achieved by the use of parenteral $NaHCO_3$ which has three effects: (a) volume expansion; (b) increased SID due to Na^+ loading without an accompanying strong anion (see Stewart hypothesis, above); (c) Increased CO_2 from the HCO_3^-. However, it is felt that buffer therapy may worsen intracellular acidosis. ◆

FURTHER READING

http://www.anaesthesiamcq.com/AcidBaseBook/ABindex.php.
http://www.acid-base.com/
Kellum JA, Elbers PWG. Stewart's textbook of acid–base. USA: Lulu.com, 2009.