Acid – Base balance and disbalance

The Hydrogen Ion and pH

The hydrogen ion consists of a single positively charged particle (the proton) that is not orbited by any electrons. The hydrogen ion is, therefore, the smallest ionic particle and is extremely reactive. It is this fact that accounts for its profound effect on the functioning of biological systems at very low concentrations.

In the environment hydrogen ion concentrations vary over an enormous scale (from less than 10-14 mol/l to more than 1mol/l).

The pH scale was developed in order to simplify (or perhaps further complicate!) the mathematics of handling such a large range of numbers. The pH is calculated by taking the negative logarithm of the hydrogen ion concentration, as shown below.

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

where \([H^+]\) is the hydrogen ion concentration.

Figure 1 gives an example of how pH is calculated.

Table 1 gives examples of pH values and corresponding hydrogen ion concentrations. It is important to note that an increase of one pH point results in a ten-fold decrease in hydrogen ion concentration.

<table>
<thead>
<tr>
<th>pH</th>
<th>([H^+]) nanomol/l</th>
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<tbody>
<tr>
<td>6.0</td>
<td>1000</td>
</tr>
<tr>
<td>7.0</td>
<td>100</td>
</tr>
<tr>
<td>8.0</td>
<td>10</td>
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<tr>
<td>9.0</td>
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Teaching point

As a solution becomes more acidic or less alkaline, the pH falls (hydrogen ion concentration rises). The opposite happens when solutions become less acidic or more alkaline.
Acids, Bases and Buffers

**Acids:** An acid is defined as any compound, which forms hydrogen ions in solution. For this reason acids are sometimes referred to as "proton donors". To aid understanding of these concepts consider an imaginary acid with the chemical formula HA. In the first example in Figure 2, the acid dissociates (separates) into hydrogen ions and the conjugate base when in solution.

**Bases:** A base is a compound that combines with hydrogen ions in solution. Therefore, bases can be referred to as "proton acceptors".

**Strong Acids:** A strong acid is a compound that ionizes completely in solution to form hydrogen ions and a base. Example 2 illustrates a strong acid in solution, where this dissociation is complete.

**Weak Acids and Bases:** these are compounds that are only partially ionised in solution. Example 3 shows a weak acid in solution with incomplete dissociation.

**Buffers:** A buffer is a compound that limits the change in hydrogen ion concentration (and so pH) when hydrogen ions are added or removed from the solution. It may be useful to think of the buffer as being like a sponge. When hydrogen ions are in excess, the sponge mops up the extra ions. When in short supply the sponge can be squeezed out to release more hydrogen ions!

All buffers are in fact weak acids or bases. Figure 3 shows how as hydrogen ions are added to a buffer solution they combine with A⁻ (the conjugate base) and the reaction is pushed to the left. This creates more HA whilst removing the excess H⁺ from the solution. Similarly, as hydrogen ions are removed from solution by addition of a strong base the reaction moves to the right restoring the hydrogen ion concentration and reducing the quantity of HA.
The effects of buffers can also be illustrated graphically. If a strong acid is added slowly to a buffer solution and the hydrogen ion concentration \([H^+]\) is measured then a plot similar to the one in figure 4 will be generated. Notice that during the highlighted portion of the curve a large volume of acid is added with little change in \([H^+]\) or pH.

As we shall see later buffers are crucial in maintaining hydrogen ions within a narrow range concentrations in the body.

The Importance of Hydrogen Ion Concentration

Hydrogen ion concentration has a widespread effect on the function of the body's enzyme systems. The hydrogen ion is highly reactive and will combine with bases or negatively charged ions at very low concentrations. Proteins contain many negatively charged and basic groups within their structure. Thus, a change in pH will alter the degree ionization of a protein, which may in turn affect its functioning. At more extreme hydrogen ion concentrations a protein's structure may be completely disrupted (the protein is then said to be denatured).

Enzymes function optimally over a very narrow range of hydrogen ion concentrations. For most enzymes this optimum pH is close to the physiological range for plasma (pH= 7.35 to 7.45, or \([H^+]= 35\text{ to } 45\text{nmol/l}\)). Figure 5 shows a typical graph obtained when enzyme activity is plotted against pH. Notice that the curve is a narrow bell shape centred around physiological pH.

Although most enzymes function optimally around physiological pH it should be noted that a few enzymes function best at a much higher hydrogen ion concentration (ie: at a lower pH). The most notable of these enzymes is pepsin, which works best in the acid environment of the stomach - optimum pH 1.5-3 or \([H^+]= 3-30\text{ million nanomol/l}\).

As enzymes have a huge number of functions around the body, an abnormal pH can result in disturbances in a wide range of body systems. Thus, disturbances in pH may result in abnormal respiratory and cardiac function, derangements in blood clotting and drug metabolism, to name but a few. From these few examples it is clear that the anaesthetist should strive to ensure that hydrogen ion concentration is maintained within the normal range.
Production of Hydrogen Ions

The processes of metabolism generate hydrogen ions. Small amounts (40-80mmol/24h) are formed from the oxidation of amino acids and the anaerobic metabolism of glucose to lactic and pyruvic acid. Far more acid is produced as a result of carbon dioxide (CO₂) release from oxidative (aerobic) metabolism - 15,000mmol/24h (15x10³ mmol/24h). Although CO₂ does not contain hydrogen ions it rapidly reacts with water to form carbonic acid (H₂CO₃), which further dissociates into hydrogen and bicarbonate ions (HCO₃⁻). This reaction is shown below:

\[
\text{CO}_2 + \text{H}_2\text{O} \rightleftharpoons \text{H}_2\text{CO}_3 \rightleftharpoons \text{HCO}_3^- + \text{H}^+
\]

This reaction occurs throughout the body and in certain circumstances is speeded up by the enzyme carbonic anhydrase. Carbonic acid is a weak acid and with bicarbonate, its conjugate base, forms the most important buffering system in the body.

Acids or bases may also be ingested, however, it is uncommon for these to make a significant contribution to the body's hydrogen ion concentration, other than in deliberate overdose.

Control of Hydrogen Ion Concentration

With hydrogen ion concentration being so critical to enzyme function, the body has sophisticated mechanisms for ensuring pH remains in the normal range. Three systems are involved: blood and tissue buffering, excretion of CO₂ by the lungs and the renal excretion of H⁺ and regeneration of HCO₃⁻.

1. Buffers

As we have seen, buffers are able to limit changes in hydrogen ion concentration. This prevents the large quantities of hydrogen ions produced by metabolism resulting in dangerous changes in blood or tissue pH.

a) Bicarbonate

This is the most important buffer system in the body. Although bicarbonate is not an efficient buffer at physiological pH its efficiency is improved because CO₂ is removed by the lungs and bicarbonate regenerated by the kidney. There are other buffers that act in a similar way to bicarbonate, for example: hydrogen phosphate (HPO₄²⁻), however, these are present in smaller concentrations in tissues and plasma.

b) Proteins

As mentioned earlier many proteins, and notably albumin, contain weak acidic and basic groups within their structure. Therefore, plasma and other proteins form important buffering systems. Intracellular proteins limit pH changes within cells, whilst the protein matrix of bone can buffer large amounts of hydrogen ions in patients with chronic acidosis.

c) Haemoglobin

Haemoglobin (Hb) is not only important in the carriage of oxygen to the tissues but also in the transport of CO₂ and in buffering hydrogen ions (The physiology of oxygen delivery, Update in anaesthesia 1999; 10:8-14).
Haemoglobin binds both CO₂ and H⁺ and so is a powerful buffer. Deoxygenated haemoglobin has the strongest affinity for both CO₂ and H⁺; thus, its buffering effect is strongest in the tissues. Little CO₂ is produced in red cells and so the CO₂ produced by the tissues passes easily into the cell down a concentration gradient. Carbon dioxide then either combines directly with haemoglobin or combines with water to form carbonic acid. The CO₂ that binds directly with haemoglobin combines reversibly with terminal amine groups on the haemoglobin molecule to form carbaminohaemoglobin. In the lungs the CO₂ is released and passes down its concentration gradient into the alveoli.

The buffering of hydrogen ions formed from carbonic acid is more complicated. The chain of events that occurs within the red cell is most easily understood by referring to figure 6.

In the tissues, dissolved CO₂ passes into the red blood cell down its concentration gradient where it combines with water to form carbonic acid. This reaction is catalysed by the enzyme carbonic anhydrase. Carbonic acid then dissociates into bicarbonate and hydrogen ions. The hydrogen ions bind to reduced haemoglobin to form HHb. Bicarbonate ions (HCO₃⁻) generated by this process pass back into the plasma in exchange for chloride ions (Cl⁻). This ensures that there is no net loss or gain of negative ions by the red cell. In the lungs this process is reversed and hydrogen ions bound to haemoglobin recombine with bicarbonate to form CO₂ which passes into the alveoli. In addition, reduced Hb is reformed to return to the tissues.

2. Carbon Dioxide Elimination

As mentioned earlier CO₂ is responsible for the majority of hydrogen ions produced by metabolism. Therefore, the respiratory system forms the single most important organ system involved in the control of hydrogen ions. From respiratory physiology it should be remembered that the arterial partial pressure of CO₂ (PaCO₂) is inversely proportional to alveolar ventilation (ie: if alveolar ventilation falls the PaCO₂ rises). Therefore, relatively small changes in ventilation can have a profound effect on hydrogen ion concentration and pH. An acute rise in PCO₂ of 1Kilopascal (kPa) results in a 5.5nmol/l rise in the hydrogen ion concentration (resulting in a fall in plasma pH from 7.4 to 7.34).

The importance of PaCO₂ and hydrogen ion concentration is underlined by the fact that the control of ventilation is brought about by the effect of CO₂ on cerebrospinal fluid (CSF) pH. The detail of the control of breathing and elimination of CO₂ are beyond the remit of article but have been discussed in a previous issue of update (Update in anaesthesia 1999; 10:8-14)

3. Renal Handling of Bicarbonate and Hydrogen Ions

The kidneys not only secrete hydrogen ions but they also regenerate bicarbonate ions. The renal handling of electrolytes also influences acid base balance. All aspects of renal involvement in acid base balance are interlinked, but for clarity are dealt with separately below.
a) Regeneration of Bicarbonate:
Bicarbonate ions are freely filtered by the glomerulus. The concentration of bicarbonate in the tubular fluid is equivalent to that of plasma. If bicarbonate were not reabsorbed the buffering capacity of the blood would rapidly be depleted.

The process of reabsorption of bicarbonate occurs mostly in the proximal convoluted tubule and is summarised in figure 7.

Filtered bicarbonate combines with secreted hydrogen ions forming carbonic acid. Carbonic acid then dissociates to form CO₂ and water. This reaction is catalysed by carbonic anhydrase, which is present in the brush border of the renal tubular cells. This CO₂ readily crosses into the tubular cell down a concentration gradient.

Inside the cell the CO₂ recombines with water, again under the influence of carbonic anhydrase, to form carbonic acid. The carbonic acid further dissociates to bicarbonate and hydrogen ions. The bicarbonate passes back into the blood stream whilst the H⁺ passes back into the tubular fluid in exchange for sodium. In this way, virtually all the filtered bicarbonate is reabsorbed in the healthy individual.

b) Excretion of Hydrogen Ions
Hydrogen ions are actively secreted in the proximal and distal tubules, but the maximum urinary [H⁺] is around 0.025mmol/l (pH 4.6). Therefore, in order to excrete the 30-40mmol of H⁺ required per day, a urine volume of 1200 litres would have to be produced. However, buffering of hydrogen ions also occurs in the urine. This allows the excretion of these large quantities of H⁺ without requiring such huge urine volumes. Hydrogen ion secretion occurs against a steep concentration gradient, 40nmol/l in plasma against up to 25000nmol/l (25x10⁶nmol/l) in urine. Therefore, hydrogen ion secretion is an active process and requires energy in the form of ATP.

The predominant buffers in the urine are phosphate (HPO₄²⁻) and ammonia (NH₃). Phosphate is freely filtered by the glomerulus and passes down the tubule where it combines with H⁺ to form H₂PO₄⁻. Hydrogen ions are secreted in exchange for sodium ions; the energy for this exchange comes from the sodium-potassium ATPase that maintains the concentration gradient for sodium. These events are summarised in figure 8.
Ammonia is produced in renal tubular cells by the action of the enzyme glutaminase on the amino acid glutamine. This enzyme functions optimally at a lower (more acidic) than normal pH. Therefore, more ammonia is produced during acidosis improving the buffering capacity of the urine. Ammonia is unionised and so rapidly crosses into the renal tubule down its concentration gradient. The ammonia combines with H⁺ to form the ammonium ion, which being ionised does not pass back into the tubular cell. The ammonium ion is therefore lost in the urine, along with the hydrogen ion it contains. See figure 9 below.

c) Electrolytes
Sodium/Potassium: sodium reabsorption and hydrogen ion excretion are interlinked. Sodium reabsorption is controlled by the action of aldosterone on ion exchange proteins in the distal tubule. These ion exchange proteins exchange sodium for hydrogen or potassium ions. Thus, changes in aldosterone secretion may result in altered acid secretion.

Chloride: The number of positive and negative ions in the plasma must balance at all times. Aside from the plasma proteins, bicarbonate and chloride are the two most abundant negative ions (anions) in the plasma. In order to maintain electrical neutrality any change in chloride must be accompanied by the opposite change in bicarbonate concentration. Therefore, the chloride concentration may influence acid base balance. 

Disorders of Hydrogen Ion Homeostasis

Disturbance of the body's acid base balance results in the plasma containing either too many hydrogen ions (acidaemia) or too few hydrogen ions (alkalaemia). In other words, the pH is too low in acidaemia (less than 7.35) whilst in alkalaemia the pH is too high (more than 7.45). These disturbances may be due to respiratory causes (ie: changes in PaCO₂) or non-respiratory (metabolic) causes. When the cause of the acid base disturbance has been discovered, the words acidosis or alkalosis may be used in conjunction with the physiological cause of the disturbance (ie: respiratory acidosis, metabolic alkalosis etc). These are discussed in more detail below.

Respiratory Acidosis

This results when the PaCO₂ is above the upper limit of normal, >6kPa (45mmHg). The relationship between hydrogen ion concentration and CO₂ was discussed earlier (Production of Hydrogen Ions). Respiratory acidosis is most commonly due to decreased alveolar ventilation causing decreased excretion of CO₂. Less commonly it is due to excessive production of CO₂ by aerobic metabolism.

a) Inadequate CO₂ Excretion: the causes of decreased alveolar ventilation are numerous, they
are summarised in Fig 10. Many of the causes of decreased alveolar ventilation are of interest to the anaesthetist and many are under our control.

b) Excess CO\(_2\) Production: respiratory acidosis is rarely caused by excess production of CO\(_2\). This may occur in syndromes such as malignant hyperpyrexia, though a metabolic acidosis usually predominates. More commonly, modest overproduction of CO\(_2\) in the face of moderately depressed ventilation may result in acidosis. For example, in patients with severe lung disease a pyrexia or high carbohydrate diet may result in respiratory acidosis.

**Respiratory Alkalosis**

Results from the excessive excretion of CO\(_2\), and occurs when the PaCO\(_2\) is less than 4.5kPa (34mmHg). This is commonly seen in hyperventilation due to anxiety states. In more serious disease states, such as severe asthma or moderate pulmonary embolism, respiratory alkalosis may occur. Here hypoxia, due to ventilation perfusion (V/Q) abnormalities, causes hyperventilation (in the spontaneously breathing patient). As V/Q abnormalities have little effect on the excretion of CO\(_2\) the patients tend to have a low arterial partial pressure of oxygen (PaO\(_2\)) and low PaCO\(_2\).

**Metabolic Acidosis**

May result from either an excess of acid or reduced buffering capacity due to a low concentration of bicarbonate. Excess acid may occur due increased production of organic acids or, more rarely, ingestion of acidic compounds.

a) Excess H\(^+\) Production: this is perhaps the commonest cause of metabolic acidosis and results from the excessive production of organic acids (usually lactic or pyruvic acid) as a result of anaerobic metabolism. This may result from local or global tissue hypoxia. Tissue hypoxia may occur in the following situations:

- Reduced arterial oxygen content: for example anaemia or reduced PaO\(_2\).
- Hypoperfusion: this may be local or global. Any cause of reduced cardiac output may result in metabolic acidosis (eg: hypovolaemia, cardiogenic shock etc). Similarly, local hypoperfusion in conditions such as ischaemic bowel or an ischaemic limb may cause acidosis.
- Reduced ability to use oxygen as a substrate. In conditions such as severe sepsis and cyanide poisoning anaerobic metabolism occurs as a result of mitochondrial dysfunction.

Another form of metabolic acidosis is diabetic ketoacidosis. Cells are unable to use glucose to produce energy due to the lack of insulin. Fats form the major source of energy and result in the production of ketone bodies (aceto- acetate and 3-hydroxybutyrate) from acetyl coenzyme A. Hydrogen ions are released during the production of ketones resulting in the metabolic acidosis often observed.

b) Ingestion of Acids: this is an uncommon cause of metabolic acidosis and is usually the result of poisoning with agents such as ethylene glycol (antifreeze) or ammonium chloride.
c) **Inadequate Excretion of** $^+$: this results from renal tubular dysfunction and usually occurs in conjunction with inadequate reabsorption of bicarbonate. Any form of renal failure may result in metabolic acidosis. There are also specific disorders of renal hydrogen ion excretion known as the renal tubular acidoses. Some endocrine disturbance may also result in inadequate H$^+$ excretion e.g. hypoaldosteronism. Aldosterone regulates sodium reabsorption in the distal renal tubule. As sodium reabsorption and H$^+$ excretion are linked, a lack of aldosterone (e.g. Addison's disease) tends to result in reduced sodium reabsorption and, therefore, reduced ability to excrete H$^+$ into the tubule resulting in reduced H$^+$ loss. The potassium sparing diuretics may have a similar effect as they act as aldosterone antagonists.

d) **Excessive Loss of Bicarbonate**: gastrointestinal secretions are high in sodium bicarbonate. The loss of small bowel contents or excessive diarrhoea results in the loss of large amounts of bicarbonate resulting in metabolic acidosis. This may be seen in such conditions as Cholera or Crohn's disease. Acetazolamide, a carbonic anhydrase inhibitor, used in the treatment of acute mountain sickness and glaucoma, may cause excessive urinary bicarbonate losses. Inhibition of carbonic anhydrase slows the conversion of carbonic acid to CO$_2$ and water in the renal tubule. Thus, more carbonic acid is lost in the urine and bicarbonate is not reabsorbed. The importance of carbonic anhydrase in the reabsorption of bicarbonate was illustrated in Figure 7. ▶

**Metabolic Alkalosis**

May result from the excessive loss of hydrogen ions, the excessive reabsorption of bicarbonate or the ingestion of alkalis.

a) **Excess H$^+$ loss**: gastric secretions contain large quantities of hydrogen ions. Loss of gastric secretions, therefore, results in a metabolic alkalosis. This occurs in prolonged vomiting for example, pyloric stenosis or anorexia nervosa.

b) **Excessive Reabsorption of Bicarbonate**: as discussed earlier bicarbonate and chloride concentrations are linked. If chloride concentration falls or chloride losses are excessive then bicarbonate will be reabsorbed to maintain electrical neutrality. Chloride may be lost from the gastro-intestinal tract, therefore, in prolonged vomiting it is not only the loss of hydrogen ions that results in the alkalosis but also chloride losses resulting bicarbonate reabsorption. Chloride losses may also occur in the kidney usually as a result of diuretic drugs. The thiazide and loop diuretics a common cause of a metabolic alkalosis. These drugs cause increased loss of chloride in the urine resulting in excessive bicarbonate reabsorption.

c) **Ingestion of Alkalis**: alkaline antacids when taken in excess may result in mild metabolic alkalosis. This is an uncommon cause of metabolic alkalosis. ▶

**Compensation**

From earlier in the article it should be clear that the systems controlling acid base balance are interlinked. As explained earlier, maintenance of pH as near normal is vital, therefore
dysfunction in one system will result in compensatory changes in the others. The three mechanisms for compensation mentioned earlier occur at different speeds and remain effective for different periods.

- **Rapid chemical buffering:** this occurs almost instantly but buffers are rapidly exhausted, requiring the elimination of hydrogen ions to remain effective.
- **Respiratory compensation:** the respiratory centre in the brainstem responds rapidly to changes in CSF pH. Thus, a change in plasma pH or PaCO$_2$ results in a change in ventilation within minutes.
- **Renal compensation:** the kidneys respond to disturbances in acid base balance by altering the amount of bicarbonate reabsorbed and hydrogen ions excreted. However, it may take up to 2 days for bicarbonate concentration to reach a new equilibrium.

These compensatory mechanisms are efficient and often return the plasma pH to near normal. However, it is uncommon for complete compensation to occur and over compensation does not occur.

### Interpretation of Acid Base Disturbances in Blood Gas Results

Blood gas analysis is available in the vast majority of acute hospitals in the developed world. Increasingly blood gas machines are available for use in developing countries. In order to obtain meaningful results from any test it is important that they are interpreted in the light of the patient's condition. This requires knowledge of the patient's history and examination findings.

The simplest blood gas machines measure the pH, PCO$_2$ and PO$_2$ of the sample. More complicated machines will also measure electrolytes and haemoglobin concentration. Most blood gas machines also give a reading for the base excess and/or standard bicarbonate. These values are used to assess the metabolic component of an acid base disturbance and are calculated from the measured values outlined above. They are of particular use when the cause of the acid base disturbance has both metabolic and respiratory components.

- **The Base Excess:** is defined as the amount of acid (in mmol) required to restore 1 litre of blood to its normal pH, at a PCO$_2$ of 5.3kPa (40mmHg). During the calculation any change in pH due to the PCO$_2$ of the sample is eliminated, therefore, the base excess reflects only the metabolic component of any disturbance of acid base balance. If there is a metabolic alkalosis then acid would have to be added to return the blood pH to normal, therefore, the base excess will be positive. However, if there is a metabolic acidosis, acid would need to be subtracted to return blood pH to normal, therefore, the base excess is negative.

- **The Standard Bicarbonate:** this is similar to the base excess. It is defined as the calculated bicarbonate concentration of the sample corrected to a PCO$_2$ of 5.3kPa (40mmHg). Again abnormal values for the standard bicarbonate are only due the metabolic component of an acid base disturbance. A raised standard bicarbonate concentration indicates a metabolic alkalosis whilst a low value indicates a metabolic acidosis.
The flow chart on the next page indicates how to approach the interpretation of acid base disturbances. First examine the pH; as discussed earlier a high pH indicates alkalaeemia, whilst a low pH acidaemia. Next look at the PCO₂ and decide whether it accounts for the change in pH. If the PCO₂ does account for the pH then the disturbance is a primary respiratory acid base disturbance. Now look at the base excess or standard bicarbonate) to assess any metabolic component of the disturbance. Finally, one needs to decide if any compensation for the acid base disturbance has happened. Compensation has occurred if there is a change in the PCO₂ or base excess in the opposite direction from that which would be expected from the pH. For example in respiratory compensation for a metabolic acidosis the PCO₂ will be low. A low PCO₂ alone causes an alkalaemia (high pH). The body is therefore using this mechanism to try to bring the low pH caused by the metabolic acidosis back towards normal.

By now the complexity of acid base disturbance should be clear!! As in many complex concepts examples may clarify matters. In the following examples work through the flow charts to interpret the data.

**Example 1:** A 70 year old man is admitted to the intensive care unit with acute pancreatitis. He is hypotensive, hypoxic and in acute renal failure. He has a respiratory rate of 50 breaths per minute. The following blood gas results are obtained:

pH 7.1
PCO₂ 3.0kPa (22mmHg)
BE -21.0mmol

From the flow charts: firstly, he has a severe acidaemia (pH 7.1). The PCO₂ is low, which does not account for the change in pH (a PCO₂ of 3.0 would tend to cause alkalaemia). Therefore, this cannot be a primary respiratory acidosis. The base excess of -21 confirms the diagnosis of a severe metabolic acidosis. The low PCO₂ indicates that there is a degree of respiratory compensation due to hyperventilation. These results were to be expected given the history.

**Example 2:** A 6 week old male child is admitted with a few days history of projectile vomiting. The following blood gases are obtained:

pH 7.50
PCO₂ 6.5kPa (48mmHg)
BE +11.0mmol

The history points to pyloric stenosis. There is an alkalaemia, which is not explained by the PCO₂. The positive base excess confirms the metabolic alkalosis. The raised PCO₂ indicates that there is some respiratory compensation.
Summary

This article has attempted to provide the reader with a grounding in acid base physiology and its importance in anaesthesia and intensive care. It is also hoped that the reader will be able to apply this knowledge in the interpretation of blood gas results. There is an excellent web page to learn more about blood gas results interpretation: