Understanding blood gases/ acid–base balance

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Abstract

Acid–base balance is regulated by intracellular & extracellular buffers and by the renal and respiratory systems. Normal pH is necessary for the optimal function of cellular enzymes and metabolism. Disorders of acid–base balance can interfere with these physiological mechanisms leading to acidosis or alkalosis and can be potentially life threatening. Blood gas analysis is a routine procedure performed in the neonatal unit and combined with non-invasive monitoring, aids in the assessment and management of ventilation and oxygenation and provides an insight into the metabolic status of the patient. The following discussion details the basic terminology and pathophysiology of acid–base balance and the main disorders. It aims to provide a logical and systematic approach to the understanding and interpretation of blood gases in the newborn period. The application of these concepts, together with relevant history and examination, will help the clinician assess the medical condition, make therapeutic decisions and evaluate the effectiveness of any intervention provided.

Keywords acid–base balance; acidosis; alkalosis; anion gap; base deficit; blood gas analysis; pH

Introduction & terminology

Acid–base balance is the complex physiological process, which acts to maintain a stable extracellular pH within the body. It is regulated by intracellular & extracellular buffers and by the renal and respiratory systems. Any derangement in this balance can interfere with physiological processes and can be potentially life threatening. An understanding of acid–base balance is required for the interpretation of blood gases, to assess both the respiratory and metabolic status of patients and thereby enable their effective clinical management.

Normal pH is maintained between 7.35 and 7.45, which creates an optimal environment for cellular metabolism. The pH is inversely related to the concentration of H^+ ions.

$$pH \propto 1/H^+$$

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An acid (HA) is a substance that donates H^+ ions (e.g. carbonic acid). In contrast, a base (A^-) accepts H^+ ions, (e.g. hydroxyl ions, ammonia) and in solution combines with the acid to neutralize it. An acid can dissociate into H^+ and a conjugate base.

$$HA \leftrightarrow H^+ + A^-$$

Equilibrium is maintained based on the above equation. Thus addition of acid (HA) increases H^+ and A^- and shifts the equation towards the right. During normal metabolism, H^+ ions are constantly being produced and neutralized to maintain pH homeostasis. Neonates produce higher levels of H^+ due to their rapid growth and metabolism and therefore maintaining balance can be challenging in newborn period.

Normal acid–base regulation

The process of maintaining pH balance during normal metabolism involves buffer systems and compensatory mechanisms in the respiratory and renal systems.

Buffer systems

Buffers are substances that attenuate the change in pH when acid/base levels increase. On addition of acid, they bind to any extra H^+ ions and prevent decline in pH. Similarly when base is added, the buffers prevent a rise in pH by releasing H^+ ions. The best buffers are weak acids and bases and work best when they are 50% dissociated. The pH at which this happens is called pK and is close to 7.40 for some buffers. The Henderson–Hasselbalch equation expresses the relationship between pH, pK and concentrations of an acid and its conjugate base.

$$pH = pK + \log[A^-]/[HA]$$

Extracellular buffers: the bicarbonate system is the principal buffer in the extracellular fluid (ECF) and is based on the relationship between carbon dioxide (CO_2) and bicarbonate (HCO_3^-), where the former combined with water acts as an acid (carbonic acid H_2CO_3) and the latter as base.

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

The pK for this buffer is 6.1. For bicarbonate buffer, the Henderson–Hasselbalch equation is:

$$pH = 6.1 + \log[HCO_3^-]/[CO_2]$$

Mathematical manipulation of the above equation produces the following relationship,

$$[H^+] = 24 \times pCO_2/[HCO_3^-]$$

which emphasizes that H^+ ion concentration and hence pH is determined by the ratio of pCO_2 and HCO_3^- concentration, and not their absolute values.

When H^+ ions are added to the system, the equation shifts to right and pH is maintained at the expense of HCO_3^- ions, referred

to as '**Base Deficit**'. There is also an increase in dissolved CO_2 levels (as H_2CO_3), which can be clinically estimated by measuring the partial pressure of CO_2 (pCO_2). Thus with addition of H^+ ions, the pH decreases with a decrease in base and an increase in CO_2 levels. The lungs then excrete the excess CO_2. With addition of base, there is a decrease in CO_2 and the lungs then reduce CO_2 excretion. In this way the bicarbonate buffer system works as an open system and plays an important role in pH homeostasis.

Intracellular buffers: these are non-bicarbonate buffers and include various proteins and organic phosphates. The proteins consist of acid histidine, with a side chain, which accepts H^+ ions in exchange for intracellular potassium (K^+) and sodium (Na^+) ions. In acute metabolic acidosis, hyperkalaemia can develop due to the exchange of K^+ for H^+.

Phosphate can bind up to three H^+ ions and in its mono- and di-hydrogen forms acts as an effective buffer in the urine.

$$H_2PO_4^{1-} \leftrightarrow H^+ + HPO_4^{2-}$$

Bone is also an important buffer and releases base on dissolution, so can buffer an acid load, but at the expense of bone density. During bone formation, it also consumes base thus buffering any excess.

Compensatory mechanisms

Although buffers represent the first line of defence against pH changes, they cannot maintain acid–base balance in disease states for prolonged periods of time or with sudden significant alterations of H^+ ion production. Instead, compensatory physiological changes by the renal and respiratory systems are employed. In a primary metabolic disorder, the respiratory system provides the compensation, whereas in a primary respiratory disorder, the regulation is by the renal system. Respiratory responses occur more rapidly (minutes–hours) than renal mechanisms, which take about 3–4 days, with renal base excretion more rapid than acid excretion. These compensatory mechanisms must be followed by corrective measures to normalize the acid–base balance, by treating the primary cause of the imbalance.

Respiratory compensation: the respiratory system modifies pH by balancing the production of H^+ with excretion of CO_2. During normal metabolism CO_2 is generated, which is a weak acid. Any increase in physical activity leads to an increase in metabolism and thus an increase in pCO_2. The lungs respond by increasing ventilation and excreting excess CO_2, thus maintaining a normal pCO_2 (4.5–6 kPa). Conversely, hypoventilation causes CO_2 retention and thus an increase in pCO_2. The resulting increase in H^+ ions directly stimulates chemoreceptors in the brain causing an increase in respiratory rate. Thus changes in alveolar ventilation can alter pH and vice versa.

Renal compensation: the kidneys prevent loss of HCO_3^- in the urine and maintain plasma levels by excreting acid and generating new bicarbonate. They can thus respond to acid–base imbalance by acidifying or alkalinizing the urine. This is accomplished by:

(1) *Reabsorption of filtered HCO_3,* which takes place in the proximal tubules (85%) and in the thick ascending loop of Henle (15%).

Normally large amounts of bicarbonate enter the proximal tubules (PT) daily and if this bicarbonate is not reclaimed by the nephrons, severe acidosis can result. In the proximal tubular cells, CO_2 derived from cell metabolism or diffusion through the tubular lumen, combines with water to form carbonic acid. This dissociates into H^+ ions and bicarbonate via carbonic anhydrase. The bicarbonate is transported back to the circulation, while the H^+ ions are secreted into the tubular lumen, where they combine with the filtered bicarbonate to form H_2O and CO_2. The CO_2 diffuses back in the PT cells to repeat the cycle. The net effect is that for each H^+ ion secreted, one HCO_3^- is retained, so that bicarbonate reserves are continuously regenerated.

Factors causing an increase in H^+ ion secretion and thus increased bicarbonate reabsorption include increased filtered bicarbonate, volume depletion due to any cause and resulting activation of renin–angiotensin system, increased plasma pCO_2 and hypokalaemia. Conversely H^+ ions secretion and thus bicarbonate reabsorption is decreased in conditions with reduced filtered bicarbonate, expansion of ECF volume and decreased plasma pCO_2. Hyperparathyroidism and disease states such as proximal renal tubular acidosis (RTA), cystinosis, or nephrotoxins can also affect proximal tubules and limit bicarbonate reabsorption.

Newborn infants and in particular preterm babies have a lower glomerular filtration rate, immature tubular function and limited capacity to retain bicarbonate and are therefore predisposed to metabolic acidosis.

(2) *Excretion of H^+ ions* which takes place at the distal tubules and the collecting duct, thus acidifying the urine. The principal buffers at these sites are phosphate and ammonia.

In normal conditions large amounts of phosphate ions are present in the tubular fluid, which combine with H^+ ions, forming titratable acid, thus reducing urinary pH. However, phosphate buffering capacity is limited as there is no mechanism for increasing urinary phosphate excretion in response to acid–base status.

Ammonia is generated in the cells of the proximal tubules, diffuses into the tubular fluid and combines with the intraluminal H^+ ions to form ammonium ion, which cannot diffuse back into the tubular cells, thus making ammonia an effective buffer.

These two processes reduce free H^+ in the tubular fluid, thereby increasing H^+ excretion into the urine and allowing the generation of new bicarbonate in the cells, which can then enter the plasma to replenish depleted levels. The major regulator of H^+ secretion in the distal tubule is aldosterone with other influencing factors being pCO_2 and the sodium concentration delivered to these segments. Sodium is reabsorbed in exchange for either potassium or H^+ ions, under the influence of aldosterone. These mechanisms may be impaired by intrinsic defects in the tubules causing primary distal renal tubular acidosis (RTA), or by various insults including nephrocalcinosis, vitamin D intoxication or Amphotericin B administration, which produce secondary distal RTA. Patients with distal RTA cannot acidify their urine and have a urine pH more than 5.5, despite acidosis.