Acid–base balance: maintenance of plasma pH

John C Atherton

Abstract

Maintenance of the alkaline environment (pH~7.4) of body fluids in the face of the production of vast quantities of acid as volatile acid (CO_2) or non-volatile acids from metabolism requires defence mechanisms for both short- and long-term regulation. Short-term regulation is achieved through intracellular and extracellular buffer systems, with the main buffer system in plasma being H_2CO_3/HCO_3^- and the removal of CO_2 through altered alveolar ventilation, but these can only limit the change in pH. Long-term regulation that can restore plasma pH involves regulation of renal tubular H^+ secretion, the major determinant of HCO_3^- reabsorption, and the excretion of NH_4^+ and acid buffer salts, both of which result in HCO_3^- production by renal tubular cells. Disturbances in acid–base balance can be subdivided into those of either respiratory or metabolic (non-respiratory) origin and include both acidosis and alkalosis. As a general rule the effects of respiratory disturbances can be minimized by non-HCO_3^- buffer systems and corrected through changes in renal function, whereas the effects of metabolic disturbances are minimized by both HCO_3^- and non-HCO_3^- buffer systems and changes in alveolar ventilation and corrected through changes in renal function.

Keywords acidosis; alkalosis; buffers; renal; ventilation

Maintenance of plasma pH ($-\log_{10}[H^+]$) within the range 7.38–7.42 is an essential requirement for life, because many metabolic processes (e.g. enzymatic reactions) are exquisitely sensitive to changes in H^+ concentration. The range compatible with life is 7.00–7.70 (i.e. a 5-fold change in H^+ concentration). The intracellular H^+ concentration is higher (about pH 7.00) than that in extracellular fluid (ECF), but is sensitive to changes in extracellular H^+ concentration. ECF is normally alkaline. This narrow pH range must be maintained in the face of the production of large quantities of volatile acid from cellular metabolism (mainly CO_2) and non-volatile acid from the metabolism of fats and certain proteins. The main problem encountered in the homeostatic control of plasma pH is the defence of the alkaline environment in the face of this massive, daily acid load.

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Volatile acid: in terms of the total acid production, CO_2 provides the largest contribution at 15–20 mol/day. This can occur either by hydration of CO_2 to form the weak, volatile carbonic acid (equation 1) or by hydroxylation of CO_2 following the splitting of water (equation 2). The products of both reactions are H^+ and HCO_3^-.

$$CO_2 + H_2O = H_2CO_3 = H^+ + HCO_3^- \quad (1)$$

$$H_2O = OH^- + H^+$$

$$OH^- + CO_2 = HCO_3^- \quad (2)$$

Production of this amount of acid would certainly change the plasma pH if it were not for the fact that most of the CO_2 is excreted from the lungs.

Non-volatile acids contribute much less to daily acid production. Such acids include sulphuric acid from sulphur-containing amino acids (e.g. cysteine, methionine), hydrochloric acid from cationic amino acids (e.g. lysine, arginine) and phosphoric acid from the metabolism of phospholipids and phosphorylated amino acids (e.g. phosphoserine). In addition, faecal loss of HCO_3^- from gastrointestinal secretions can be regarded as a significant (and variable) contribution to non-volatile acid production. Metabolism of anionic amino acids (e.g. aspartic, glutamic) and some organic anions (e.g. citrate) yield HCO_3^-, which will partially offset some of the non-volatile acid production. The contribution of non-volatile acids to total acid production depends on dietary composition. If meat is a major component of the diet, non-volatile acids are significant (about 50 mmol/ day), whereas this value is lower if the major components are vegetables and fruit.

Buffer systems in body fluids

A buffer system consists of an undissociated weak acid (HA) and its base (A^-), and can be represented by:

$$HA = H^+ + A^- \quad (3)$$

Following the addition of a strong acid, some of the H^+ is mopped up through the formation of more HA and thus the change in free H^+ is limited. Conversely, the decrease in H^+ caused by the addition of strong alkali is limited by freeing H^+ from the weak acid. The main buffer systems in body fluids are given in Table 1. The main buffer system in plasma is bicarbonate/carbonic acid, therefore pH can be represented using the Henderson–Hasselbalch equation:

$$pH = pK' + \log_{10}\frac{\text{buffer salt}}{\text{weak acid}} = \log_{10}\frac{[HCO_3^-]}{[H_2CO_3]} \quad (4)$$

where pK′ is the apparent dissociation constant.

Since there is little H_2CO_3, the acid moiety of the system is primarily CO_2 which is proportional to the partial pressure of CO_2 (pCO_2 mm Hg). Thus:

$$pH = 6.1 + \log_{10}\frac{[HCO_3^-]}{0.03 \times pCO_2} \quad (5)$$

where 0.03 is the solubility coefficient of CO_2 in plasma

$$= 6.1 + \log_{10}\frac{24 \text{ mmol/litre}}{(0.03 \times 40 \text{ mm Hg}) \text{ mmol/litre}} = 7.4$$

Main buffer systems in body fluids

Blood					
• Plasma proteins	HPr	=	Pr^-	+	H^+
• Haemoglobin	HHb	=	Hb	+	H^+
• Bicarbonate	H_2CO_3	=	HCO_3	+	H^+
Interstitial fluid					
• Bicarbonate	H_2CO_3	=	HCO_3	+	H^+
Intracellular fluid					
• Proteins	HPr	=	Pr	+	H^+
• Phosphate	H_2PO_4	=	HPO_4	+	H^+

Table 1

Defence mechanisms

Defence of the alkaline environment is achieved through the operation of three basic mechanisms.

- Physicochemical buffering (i.e. removal of the H^+ by the various reactions listed in Table 1) is instantaneous but only limits the fall in pH.
- Respiratory compensation is rapid (in minutes) and operates via the control of plasma pCO_2 through changes in alveolar ventilation and subsequent evolution of CO_2; plasma pH is returned towards the normal values, but acid–base status cannot be corrected completely.
- Renal compensation is slower (measured in hours or days) and operates via the control of plasma bicarbonate through changes in the renal secretion of H^+, reabsorption and production of bi-carbonate; acid–base status can be corrected.

Disturbances in acid–base balance

It is evident from equations 4 and 5 that disturbances in acid–base balance can occur via changes in either the numerator (plasma HCO_3^- concentration) or the denominator (plasma pCO_2). Respiratory disturbance occurs if the primary change is altered pCO_2 whereas metabolic (non-respiratory) disturbance occurs if the primary change is altered plasma HCO_3^-. Thus, if pCO_2 is either increased (e.g. asphyxia, chronic pulmonary disease, hypoventilation such as following opiate administration) or decreased (e.g. anxiety attacks, rapid ascent to high altitude, voluntary hyperventilation), these disturbances are referred to as respiratory acidosis and respiratory alkalosis, respectively. If plasma HCO_3^- is decreased by addition of non-volatile acids (e.g. uncontrolled diabetes mellitus, renal failure, severe diarrhoea, ammonium chloride ingestion) or increased (e.g. excessive vomiting, sodium bicarbonate ingestion for chronic dyspepsia), these disturbances are referred to as metabolic acidosis and metabolic alkalosis, respectively.

Compensatory responses to these changes can also be predicted from equations 4 and 5. Thus, increasing or decreasing pCO_2 can be compensated for by decreasing or increasing plasma HCO_3^-, whereas acid-induced changes in plasma HCO_3^- can be compensated for by opposite changes in pCO_2. In other words, primary respiratory disturbances are compensated for by metabolic responses, and primary metabolic disturbances by respiratory responses.

Respiratory acidosis

Increasing pCO_2 leads to a reduction in pH (i.e. the equilibrium in equation 1 is shifted to the right with an increase in H^+ concentration). The plasma bicarbonate buffer system cannot be used to compensate for this change because to do so would need the equilibrium simultaneously moving to the left (i.e. in a direction opposite to that which is causing the change). However, some H^+ will be taken up by non-bicarbonate buffers (plasma proteins and phosphates) with a subsequent small elevation in plasma HCO_3^-. CO_2 readily diffuses across all cell membranes, including capillary and RBC membranes. Thus, interstitial fluid H^+ increases and thereby lowers pH to a large extent because the concentration of non-bicarbonate buffers is low. However, the haemoglobin buffer system makes a significant contribution. Thus, the increasing intracellular CO_2 is hydrated or hydroxylated in the presence of the catalytic enzyme, carbonic anhydrase, with the end-products being H^+ and HCO_3^-. The former is buffered by the haemoglobin system and the latter is exchanged for Cl^- across the cell membrane (known as the chloride shift). Thus, the first line of defence (physicochemical buffering) limits but does not restore plasma pH.

It is evident that the second line of defence, respiratory compensation, does not contribute since the primary cause of the change in pH is respiratory.

The third line of defence, renal compensation, is important; H^+ is excreted and plasma HCO_3^- is increased by the renal tubular cells reclaiming virtually all the filtered HCO_3^- and producing HCO_3^-. As stated above, it can take days to compensate fully for the increase in CO_2. Hence, primary respiratory disturbances are followed by a few days of lowered plasma pH before compensation occurs.

Respiratory alkalosis

Decreasing pCO_2 lowers the denominator of equation 4, and the pH becomes more alkaline. Again, the plasma bicarbonate buffer system cannot contribute H^+ since this would require a simultaneous shift in the equilibrium (equation 1) to the right. Non-bicarbonate buffers contribute by releasing H^+ and produce a small reduction in plasma HCO_3^- which restricts, but does not prevent, the rise in pH. Respiratory compensation cannot contribute because the primary disturbance is respiratory. Renal compensation is important in lowering plasma HCO_3^-, by reducing HCO_3^- re-absorption and production by the renal tubular cells.

Metabolic acidosis

Increased production or addition of non-volatile acid to plasma lowers pH. However, the change in pH is limited by both HCO_3^- and the non-bicarbonate buffer systems:

$$H_2SO_4 + 2NaHCO_3 = Na_2SO_4 + 2H_2CO_3 \quad (6)$$
$$2H_2CO_3 = 2H_2O + 2CO_2$$

Thus, the added H^+ is buffered so the concentrations of Hb^-, negatively charged plasma proteins and HCO_3^- are reduced. The H_2CO_3 so formed dissociates into CO_2 and H_2O; the CO_2 is rapidly excreted by alveolar ventilation. In addition, the increase in plasma H^+ stimulates alveolar ventilation so that a further reduction in pCO_2 occurs. Although these compensatory changes minimize any change in pH, full compensation to return acid–base status to normal requires renal excretion of H^+, and tubular reabsorption and production of HCO_3^-.