

Acid–base balance: maintenance of plasma pH

John C Atherton

Abstract

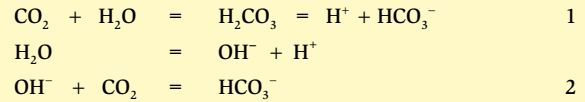
Maintenance of the alkaline environment (pH~7.4) of body fluids in the face of the production of vast quantities of acid as volatile acid (CO₂) or non-volatile acids from metabolism requires defence mechanisms for both short- and long-term regulation. Short-term regulation is achieved through intracellular and extracellular buffer systems, with the main buffer system in plasma being H₂CO₃/HCO₃⁻ and the removal of CO₂ 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 HCO₃⁻ reabsorption, and the excretion of NH₄⁺ and acid buffer salts, both of which result in HCO₃⁻ 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-HCO₃⁻ buffer systems and corrected through changes in renal function, whereas the effects of metabolic disturbances are minimized by both HCO₃⁻ and non-HCO₃⁻ 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 CO₂) 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, CO₂ provides the largest contribution at 15–20 mol/day. This can occur either by hydration of CO₂ to form the weak, volatile carbonic acid (equation 1) or by hydroxylation of CO₂ following the splitting of water (equation 2). The products of both reactions are H⁺ and HCO₃⁻.

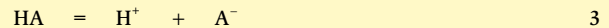


Production of this amount of acid would certainly change the plasma pH if it were not for the fact that most of the CO₂ is excreted from the lungs.

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 HCO₃⁻ 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 HCO₃⁻, 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:



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:

$$\text{pH} = \text{pK}' + \log_{10} \frac{\text{buffer salt}}{\text{weak acid}} = \log_{10} \frac{[\text{HCO}_3^-]}{[\text{H}_2\text{CO}_3]} \quad 4$$

where pK' is the apparent dissociation constant.

Since there is little H₂CO₃, the acid moiety of the system is primarily CO₂ which is proportional to the partial pressure of CO₂ (pCO₂ mm Hg). Thus:

$$\begin{aligned} \text{pH} &= 6.1 + \log_{10} \frac{[\text{HCO}_3^-]}{0.03 \times \text{pCO}_2} \quad 5 \\ &\text{where } 0.03 \text{ is the solubility coefficient of CO}_2 \text{ in plasma} \\ &= 6.1 + \log_{10} \frac{24 \text{ mmol/litre}}{(0.03 \times 40 \text{ mm Hg}) \text{ mmol/litre}} = 7.4 \end{aligned}$$

Main buffer systems in body fluids

Blood

• Plasma proteins	HPr	=	Pr ⁻	+	H ⁺
• Haemoglobin	HHb	=	Hb	+	H ⁺
• Bicarbonate	H ₂ CO ₃	=	HCO ₃ ⁻	+	H ⁺

Interstitial fluid

• Bicarbonate	H ₂ CO ₃	=	HCO ₃ ⁻	+	H ⁺
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Intracellular fluid

• Proteins	HPr	=	Pr	+	H ⁺
• Phosphate	H ₂ PO 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 pCO₂ through changes in alveolar ventilation and subsequent evolution of CO₂; 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 HCO₃⁻ concentration) or the denominator (plasma pCO₂). Respiratory disturbance occurs if the primary change is altered pCO₂ whereas metabolic (non-respiratory) disturbance occurs if the primary change is altered plasma HCO₃⁻. Thus, if pCO₂ 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 HCO₃⁻ 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 pCO₂ can be compensated for by decreasing or increasing plasma HCO₃⁻, whereas acid-induced changes in plasma HCO₃⁻ can be compensated for by opposite changes in pCO₂. In other words, primary respiratory disturbances are compensated for by metabolic responses, and primary metabolic disturbances by respiratory responses.

Respiratory acidosis

Increasing pCO₂ 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 HCO₃⁻. CO₂ 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 CO₂ is hydrated or hydroxylated in the presence of the catalytic enzyme, carbonic anhydrase, with the end-products being H⁺ and HCO₃⁻. 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.

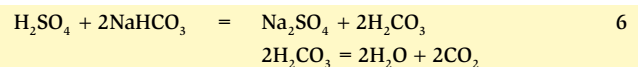
The third line of defence, renal compensation, is important; H⁺ is excreted and plasma HCO₃⁻ is increased by the renal tubular cells reclaiming virtually all the filtered HCO₃⁻ and producing HCO₃⁻. As stated above, it can take days to compensate fully for the increase in CO₂. Hence, primary respiratory disturbances are followed by a few days of lowered plasma pH before compensation occurs.

Respiratory alkalosis

Decreasing pCO₂ 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 HCO₃⁻ 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 HCO₃⁻, by reducing HCO₃⁻ 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 HCO₃⁻ and the non-bicarbonate buffer systems:



Thus, the added H⁺ is buffered so the concentrations of Hb⁻, negatively charged plasma proteins and HCO₃⁻ are reduced. The H₂CO₃ so formed dissociates into CO₂ and H₂O; the CO₂ is rapidly excreted by alveolar ventilation. In addition, the increase in plasma H⁺ stimulates alveolar ventilation so that a further reduction in pCO₂ 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 HCO₃⁻.

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