Acid–base physiology and blood gas interpretation in the neonate

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Abstract

Acid–base balance describes the complex processes that work to maintain a stable extracellular pH for optimal cellular function. The process of balancing the production and neutralization of tissue acid provides a great challenge for newborn infants who have significantly higher rates of acid production than adults. Factors which help maintain a stable acid–base balance include buffers, the respiratory system and renal system. Both intracellular and extracellular buffers resist changes in pH; the most important extracellular buffer system for maintaining stable pH is the bicarbonate system. In response to acidosis or alkalosis the respiratory system balances the production of acid with the clearance of CO₂ by altering respiratory rate. The kidneys provide a delayed but sustained response to pH imbalance by excreting either acidic or alkaline urine in response to systemic acidosis and alkalosis, respectively. In sick premature infants these systems have a limited capacity completely to control pH. This review discusses the physiology of the three systems which control acid–base balance. Patterns of clinical abnormalities in acid–base status and their underlying causes are discussed. We present a systematic approach to blood gas analysis and interpretation in newborn infants.

Keywords: acidosis; alkalosis; bicarbonate; blood–gas analysis; metabolic; pH

Introduction

Blood gas analysis is a routine procedure performed on newborn babies receiving respiratory support in the neonatal intensive care. The combination of invasive and non-invasive assessment of ventilation and oxygenation enables clinicians appropriately to modify respiratory care according to each individual baby’s rapidly changing clinical status.

Understanding the fundamentals of acid–base balance helps us to use blood gas analysis not only to assess respiratory status but also to provide information on metabolic status and the adequacy of tissue perfusion.

What is understood by acid–base balance?

Acid–base balance refers to the complex physiological processes used by the body to maintain a stable extracellular pH.¹ A serum pH within the range of 7.35–7.45 provides the ideal environment for cellular metabolism. Maintaining a stable pH is critical as the metabolic activity of proteins is pH dependent and small changes in hydrogen ion (H⁺) concentration can potentially alter physiological function.

Acids are substances that yield free H⁺ in solution, while a base accepts H⁺ and in solution combines with an acid to neutralize it. In the normal metabolic state, H⁺ are continuously produced and neutralized to maintain a steady pH balance.¹² The rate of H⁺ production is two to three times higher in neonates because of their rapid growth rates and increased acid production from protein turnover and bone mineralization. The challenge of maintaining a stable pH through processing and neutralizing H⁺ is therefore greatest in newborn infants.

Using exact values of H⁺ concentration to assess acid–base status is cumbersome and it is more commonly expressed as pH, defined by the equation:

\[ pH = -\log H^+ \]

Maintaining acid–base balance

The balance between production and excretion of acids in the body is controlled by buffer systems which have an immediate effect, and by the respiratory and the renal systems.

Buffer systems

Buffer solutions resist change in pH when acid or alkali is added, due to their capacity to absorb or give up H⁺. The three main buffer systems in the body are the bicarbonate, phosphate and protein systems.¹³ The protein and phosphate buffer systems are intracellular and act as ‘sinks’ for extracellular H⁺ which are exchanged with intracellular potassium (K⁺) and sodium ions (Na⁺). In an acute metabolic acidosis, hyperkalaemia may develop due to this H⁺ exchange.⁴

The bicarbonate buffer system is extracellular and consists of a mixture of carbonic acid (H₂CO₃) and sodium bicarbonate (NaHCO₃). This buffer system helps maintain a stable pH by soaking up excess H⁺ with HCO₃⁻, which in solution forms carbonic acid (H₂CO₃). Carbonic acid is a weak acid and readily dissociates to give CO₂, which is transported in dissolved form to the lungs for excretion.

\[ H^+ + HCO_3^- \rightarrow H_2CO_3 \rightarrow H_2O + CO_2 \]

The bicarbonate system therefore completes the neutralization of excess H⁺ and a stable plasma pH is maintained. The relationships between pH, HCO₃⁻ and CO₂ in this system are described by the Henderson–Hasselbalch equation¹⁵:

\[ pH = 6.1 + \log HCO_3^- / 0.03 \times CO_2 \]

where 6.1 is the log of the dissociation coefficient of carbonic acid and 0.03 the solubility of CO₂ in plasma. Buffers are most potent when there are equal amounts of H⁺ and HCO₃⁻ in solution. The
bicarbonate system is not a potent buffer; however, as \( \text{HCO}_3^- \) and \( \text{CO}_2 \) are readily altered by the body, this system plays a very powerful role in pH homeostasis.\(^1,5\)

**Respiratory regulation**

The respiratory system adapts within minutes to hours as part of the acute response to acidosis. This system modifies pH by balancing production of \( \text{H}^+ \) with ventilatory clearance of \( \text{CO}_2 \).

\( \text{H}^+ \) directly stimulates chemoreceptors in the respiratory centre of the brainstem, producing an increase in respiratory rate.\(^2,6\)

The response to respiratory acidosis is very rapid as \( \text{CO}_2 \) easily diffuses across the blood–brain barrier; however, in metabolic acidosis compensation is delayed until plasma bicarbonate fully equilibrates with cerebrospinal fluid (CSF) bicarbonate. There is an inverse relationship between alveolar ventilation and partial pressure of dissolved carbon dioxide (\( \text{PaCO}_2 \)): a reduction in alveolar ventilation raises \( \text{PaCO}_2 \) and decreases pH. Changes in pH therefore affect alveolar ventilation and conversely changes in alveolar ventilation cause significant changes in pH.

**Renal regulation**

The kidneys provide a delayed but sustained response to acid–base imbalances by excreting either acidic or alkaline urine. In full-term and preterm babies the capacity for acid excretion and bicarbonate reabsorption is reduced as glomerular filtration rates are low and tubular function immature.\(^7\) Renal function matures with gestation, postnatal age and glucocorticoid and thyroid hormones.\(^7,9\) Due to their limited capacity to preserve \( \text{HCO}_3^- \) newborn infants have lower serum bicarbonate levels and are predisposed to acidosis.\(^7\)

Bicarbonate is not effectively reabsorbed due to its size and electrical charge. Instead, intraluminal \( \text{HCO}_3^- \) combines with secreted \( \text{H}^+ \) in tubular luminal fluid to produce carbonic acid which dissociates to give \( \text{H}_2\text{O} \) and \( \text{CO}_2 \). This \( \text{CO}_2 \) diffuses into tubular cells, combines with intracellular \( \text{H}_2\text{O} \), and forms carbonic acid which liberates \( \text{HCO}_3^- \) and \( \text{H}^+ \). \( \text{HCO}_3^- \) is then recovered to the circulation by exchange for chloride ions (\( \text{Cl}^- \)) through the basal cell membrane.\(^2,4,7\)

Renal acid secretion occurs at all sites except the loop of Henle. Primary active transport accounts for 5% and secondary for the remaining 95% of total \( \text{H}^+ \) excretion. Secondary transport involves an exchange between luminal \( \text{Na}^+ \) and intracellular \( \text{H}^+ \). Both ions bind to a membrane transport protein. The \( \text{Na}^+ \) concentration gradient between the tubular lumen and cells enables \( \text{Na}^+ \) drag into the cell, which generates energy to fuel active \( \text{H}^+ \) excretion into the tubular lumen.\(^1-4,7\)

**Quantifying acidosis**

*Standard base excess* is a calculated value derived from \( \text{PaCO}_2 \) and pH. It is expressed as the mmol/litre of base, above or below normal buffer bases, required to correct the pH to 7.4 at a \( \text{PaCO}_2 \) of 40 mmHg. A negative base excess or base deficit indicates an acidosis, while a positive base excess indicates a relative alkalosis.\(^1,5\)

Anion gap is the measured difference between anions and cations in the blood.

\[
\text{Anion gap} = (\text{Na}^+ + \text{K}^+) - (\text{HCO}_3^- + \text{Cl}^-)
\]

Calculation of the anion gap enables clinicians better to define the underlying cause of a metabolic acidosis.\(^9\) The common causes of an increased anion gap acidosis in neonates include lactic acidosis due to tissue hypoperfusion and hypoxia; it may also be seen with certain inborn errors of metabolism and in uraemia.\(^9,10\) The anion gap can help distinguish between the relatively benign non-anion gap hyperchloremic acidosis seen in premature infants and a pathological lactic acidosis due to poor end-organ perfusion.\(^10,11\)

**Strong ion theory**

Stewart described a complex acid–base model which proposed that \( \text{H}^+ \) concentration results from the dissociation of water, which is influenced by \( \text{PaCO}_2 \), the strong ion difference and plasma weak acids.\(^12\)

Strong ions are ions that dissociate at normal body pH and include \( \text{Na}^+ \), \( \text{K}^+ \) and \( \text{Cl}^- \). Weak acids in plasma which contribute include albumin, inorganic phosphate and plasma proteins; their concentrations do not change with pH and are therefore a constant. The effect of these factors and other unmeasured tissue ions on acid–base status can be quantified by the calculation of the strong ion gap (SIG).\(^1,12\) In the neonatal unit, it is perhaps more important that we consider how principles of this model may relate to acid–base status rather than fully to quantify the SIG. Theoretically, low albumin and phosphate levels which frequently occur in premature infants, by reducing the concentration of weak acids, can produce a relative alkalosis, while high phosphate levels in renal failure may contribute to acidosis.

**Tissue oxygenation**

Oxygenation is closely linked to acid–base status as optimal cellular function requires oxygen to fuel aerobic metabolism and produce energy. In hypoxic conditions anaerobic metabolism predominates, which is energy inefficient and results in a lactic acidosis.\(^10,11\)

Tissue oxygen availability is related to regional blood flow, haemoglobin level and haemoglobin oxygen affinity. Arterial blood gases measure the partial pressure of dissolved oxygen (\( \text{PaO}_2 \)), which represents a small component of total oxygen content, the majority being transported bound to haemoglobin. The relationship between percentage haemoglobin saturation (\( \text{SaO}_2 \)) and \( \text{PaO}_2 \) is described by the sigmoidal oxyhaemoglobin dissociation curve, which enables us to relate the two measures to each other.\(^2,3,5\) The affinity of haemoglobin for oxygen is altered by local tissue factors. Increases in temperature, \( \text{H}^+ \), \( \text{PaCO}_2 \) and 2,3-diphosphoglycerate (DPG) levels shift the oxyhaemoglobin dissociation curve to the right, reducing affinity for oxygen. Decreases in temperature, \( \text{H}^+ \), \( \text{PaCO}_2 \) and 2,3-DPG, levels shift the curve to the left, increasing oxygen affinity.\(^1-3,5\) In the body haemoglobin oxygen affinity continuously changes, increasing in the lungs to enable efficient oxygen uptake and decreasing at tissue level to provide efficient oxygen delivery to metabolically active tissues.

Avoiding both hypoxia and hyperoxia is important in the neonatal unit as deleterious effects of hypoxia are seen in infants with pulmonary hypertension.\(^13,14\) while hyperoxia is associated with an increased incidence of retinopathy of prematurity.\(^15,16\)
Clinical acid–base imbalances

Clinical acid–base imbalances can be respiratory, metabolic or a mixture of both. These abnormalities may be corrected by the acid–base regulatory mechanisms in the body in an attempt to maintain normal pH (Figure 1).

Respiratory acidosis

This occurs when any disorder leads to decreased alveolar ventilation. Common causes of respiratory acidosis are listed in Table 1. Reduced respiratory clearance of CO₂ means more dissolved CO₂ accumulates in the plasma, leading to increased production of carbonic acid and H⁺. Through chemoreceptor stimulation, respiratory acidosis rapidly alters ventilation in an attempt to reduce CO₂. Chemoreceptor mediated ventilatory increases may only partly adjust in premature infants with underlying lung disease. In babies with a sustained respiratory acidosis, e.g., in chronic lung disease, then metabolic compensation occurs through increased renal excretion of H⁺ and reabsorption of HCO₃⁻, slowly restoring pH to around 80% of normal.

Respiratory alkalosis

This occurs when more CO₂ is excreted than is produced by the body. Pathological conditions leading to respiratory alkalosis are rare. Hyperventilation in the neonatal setting is often iatrogenic or may be due to disorders in brainstem control of breathing, including hypoxic–ischaemic encephalopathy or primary central nervous system abnormalities (see Table 1).

If respiratory alkalosis is sustained, it may be compensated for by reduced reabsorption of filtered bicarbonate. Reported adverse associations of low PaCO₂ include periventricular leucomalacia and intraventricular haemorrhage.

The management of PaCO₂ levels in infants receiving mechanical ventilation has important clinical implications. Premature babies have impaired cerebral autoregulation and adverse neurological sequelae are reported in association with high PaCO₂ levels. Ventilation strategies which advocate ‘permissive hypercarbia’ have been developed to minimize airways damage from mechanical ventilation. Published data suggest pulmonary benefits; however, the safe level of PaCO₂ remains to be defined in premature infants.

Figure 1 Mechanisms for regulation of extracellular pH. IEM, inborn errors of metabolism; RDS, respiratory distress syndrome.
Metabolic acidosis

This frequently affects infants in the neonatal unit and has many causes. There may be overproduction of tissue acid, impaired acid clearance, gastrointestinal loss of bicarbonate or an exogenous increased acid load, e.g. chloride, total parenteral nutrition (TPN) or albumin.

Calculation of the anion gap to distinguish an increased anion gap acidosis from a non-anion gap acidosis is important both for treatment and prognosis. Acidosis stimulates respiratory compensation but this is limited in unstable infants. Similarly, renal compensation with improved HCO$_3^−$ conservation is constrained by tubular immaturity. Treatment of the acidosis should be directed at the underlying cause, e.g. hypoxia, hypotension or excess Cl$^−$ rather than by administration of base.

Metabolic alkalosis

This is unusual in neonates and is most frequently seen in infants with chronic lung disease or heart failure who are receiving diuretics. Diuretics cause alkalosis by increasing renal fluid and Na$^+$ losses. An active process to reabsorb Na$^+$ occurs in tubule cells which through enhanced H$^+$ secretion and HCO$_3^−$ reabsorption produce alkalosis.

Metabolic alkalosis may also occur with excessive loss of gastrointestinal contents, e.g. protracted vomiting or inadequate replacement of nasogastric aspirates.

Interpreting blood gases

Blood gas measurements can provide important diagnostic and prognostic information, and a systematic approach to blood gas analysis is described in Table 2. The clinical management of infants with abnormal gases requires a good understanding of acid–base physiology and tissue oxygenation and an appreciation of factors which may affect the reliability of samples.

Arterial blood sampling is the gold standard; however, indwelling arterial catheters and arterial stab samples are usually restricted to infants who are critically ill or those who require significant ongoing intervention. Gases are most frequently measured in capillary or venous samples, which correlate well with arterial samples for PaCO$_2$, pH and base excess in babies and children receiving intensive care. These correlations, however, are not valid in infants with peripheral vasoconstriction and hypotension.

Non-invasive monitoring techniques may enable us to reduce the frequency of blood gas sampling. Transcutaneous monitoring
A systematic approach to blood gas analysis

1. Collect the relevant information
   - Type of gas – capillary or arterial
   - Current respiratory support – document level
   - Transcutaneous CO₂ and SaO₂ levels
   - Clarify no significant clinical events before sampling

2. pH: Accept a range between 7.30 and 7.45 in newborn babies; this is lower than in older children. Is there an alkalosis (pH > 7.45) or an acidosis (< 7.30)?

3. CO₂: Aim for a range between 4.5 and 6.5 kPa. A PaCO₂ level more than 6.5 kPa suggests inadequate alveolar ventilation while less than 4.5 kPa suggests hyperventilation. Correlate values with non-invasive measures

4. O₂: Can only be assessed from arterial gases. Aim for PaO₂ between 6.0 and 8.0 kPa. Correlate results with pulse oximetry levels

5. HCO₃⁻ and base excess: Normal HCO₃⁻ level is between 20 and 24 mmol/litre and bases excess +3 to −3.

6. Anion gap: Look at the anion gap and lactate to help identify the cause of an acidosis. Normal lactate levels should be less than 2 mmol/litre

7. Respiratory or metabolic compensation: Look at the pH and assess whether it is appropriate for the CO₂ level, or is there evidence of compensation?

8. Interpret: Use both the clinical history and blood gas findings to help you identify the primary problem. Aim your management at treating the underlying cause

9. Reassess: If clinical management changes have been made, repeat the blood gas after an appropriate time interval to ensure improvement

Table 2

provides a highly accurate and reliable method for measuring PaCO₂ through the skin; it can however be technically difficult, may cause tissue damage and is of limited reliability when peripheral perfusion is reduced. Continuous end-tidal CO₂ measurements correlate well with arterial CO₂ values in patients with normal ventilation and perfusion; however, in babies with lung disease, alveolar collapse, small tidal volumes and rapid respiratory rates can make these measurements unreliable. Despite its limitations, transcutaneous monitoring provides the best method for CO₂ trend monitoring in the neonatal intensive care unit (NICU).

Oxygen saturation levels can be continuously measured non-invasively using pulse oximetry. While oximetry is easy to perform and accurate, on occasion SaO₂ levels obtained may be unreliable when tissue perfusion is poor or with movement artefact. SaO₂ monitoring is highly sensitive at detecting hypoxia but is limited in detecting hyperoxemia as at levels more than 90% small changes in SaO₂ may result in unacceptably large increases in PaO₂. It is therefore essential that SaO₂ alarm limits are set for all neonates receiving respiratory support to detect hypoxia and prevent hyperoxia.

Continuous non-invasive monitoring provides invaluable information when managing complex infants in the NICU, but it does not replace the need for regular blood gas analysis.

REFERENCES


**Practice points**

- A stable extracellular pH is important for optimal cellular functioning
- Abnormalities in acid–base balance are regulated by buffer systems and the respiratory and renal tract
- Maintaining a stable pH is challenging for newborn babies due to their high rates of acid production and immature regulatory mechanisms
- Arterial or capillary blood gases provide an effective way to monitor acid–base balance in newborns
- Blood gases should be analysed in a structured manner, assessing pH and then respiratory and metabolic components
- The treatment of acid–base abnormalities should be directed at the underlying problem, not merely at correcting pH