Basic sciences review

Acid-Base Balance: Part I. Physiology

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ABSTRACT

Objective: To review the normal human acid-base physiology and the pathophysiology and management of acid-base disturbances in a two-part presentation.

Data sources: Articles and published peer-review abstracts and a review of studies reported from 1990 to 2000 and identified through a MEDLINE search of the English language literature on acid-base balance.

Summary of review: In a healthy individual the extracellular fluid pH change following addition of a metabolic acid or base, is modified initially by the body’s buffers. Subsequent respiratory compensation, by excretion or retention of CO₂, modifies this change before metabolism of the organic acid or renal excretion of the acid or alkali returns the plasma bicarbonate to normal. A primary respiratory acid-base change is modified initially by cellular buffers, with renal compensatory mechanisms adjusting slowly to this change. However, correction of the respiratory pH disorder only occurs with correction of the primary disease process.

Conclusions: In man the acid-base balance is maintained and regulated by the renal and respiratory systems, which modify the extracellular fluid pH by changing the bicarbonate pair (HCO₃⁻ and PCO₂); all other body buffer systems adjust to the alterations in this pair. (Critical Care and Resuscitation 2001; 3: 181-187)

Key words: Acid-base balance, metabolic acidosis, metabolic alkalosis

By affecting the charge on reactive groups of enzymes within the extracellular and intracellular fluids of the living organism, chemical reactions are influenced by the prevailing pH.¹ Despite the abundance of hydrogen in body fluids, the concentration or chemical activity of the H⁺ ion (or hydronium ion H₃O⁺) is remarkably small and constant. This is largely due to the presence of buffer systems which allow for a rapid turnover of protons to take place with minimal alteration in H⁺ ion activity.

DEFINITIONS

In general, the definitions suggested by the Ad Hoc Committee of the New York Academy of Sciences have been adopted.²

pH. Is the negative logarithm of the H⁺ ion activity (Ha⁺), which is equal to the H⁺ ion concentration when the activity coefficient is unity. The pH is measured using a glass-membrane electrode porous only to H⁺ ions. A transmembrane potential develops which is proportional to the log of the H⁺ ion activity (Ha⁺). This potential is compared with the potential recorded using the glass electrode and a standard solution of selected pH value.

Within the physiological range of pH values in man, the H⁺ ion activity coefficient is unity, therefore the measurement of H⁺ provides an accurate and practical scale of acidity and alkalinity, when compared with its logarithmic counterpart of pH.³ For example, it allows one to use the Henderson equation to assess clearly the

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Buffer. A solution containing substances that have the ability to minimise changes in the pH when an acid or base is added to it.

$pK_a$. The negative logarithm of the dissociation constant. If it describes a buffer system, then it is numerically equal to the pH of the system when the acid and its anion are present in equal concentrations.

Strong ions. An analysis of acid-base chemistry has been proposed based on the law of electroneutrality in aqueous solutions, where the total number of cations must equal the total number of anions. The central tenet to the analysis is that only the independent variables, which are the strong ions (e.g., sodium, potassium, calcium, magnesium, chloride and organic anions), PCO$_2$ and the non-volatile weak acids ($A_{TOT} = HA + A^-$ and in plasma is predominantly the albuminate ions), can change acid-base status, as they change the dependent variables of $[H^+]$ and HCO$_3^-$ to maintain electroneutrality.

The metabolic acid-base abnormality is characterised by calculating the strong-ion difference (or SID = $[Na^+ + K^+ + Ca^{2+} + Mg^{2+}] - [Cl^- + lactate]$), a value which is essentially equal to the sum of the bicarbonate and albuminate ions, (i.e. HCO$_3^-$ = SID - A-) and similar to the buffer base described by Singer and Hastings more than 50 years ago.

This approach has not been helpful in clinical practice (e.g. it leads to the misconceptions that a saline induced dilution acidemia is due to an increase in Cl$^-$ rather than a decrease in HCO$_3^-$, or an elevated or reduced plasma albumin level may lead to metabolic acidosis and metabolic alkalosis, respectively).

REGULATION OF pH [$H^+$] IN BODY FLUIDS

In man, despite wide variations in dietary acid and base, there is no specific centre for $H^+$ ion regulation. The body’s respiratory and renal systems coordinate to regulate $H^+$ homeostasis by regulating HCO$_3^-$ and PCO$_2$. The initial body defense against a change in pH is carried out by the body’s buffer systems.

BODY BUFFERING

Dilution

If one compares the effect of adding the daily nonvolatile $H^+$ load (i.e. 70 mmol $H^+$) to a 70 kg man and to an equal volume of non-buffered water, at the same temperature and pH (e.g. table 2), it is clear that dilution is a poor defense against pH changes.

Buffer systems

These are present in the extracellular fluid (ECF) and intracellular fluid (ICF). Their effectiveness, or capacity, is proportional to the amount of buffer, the
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pKa of the buffer, the pH of the carrying solutions and whether the buffer operates as an open or closed system.

Table 2. Effect of adding daily nonvolatile H⁺ load to man and to an equivalent volume of nonbuffered water

<table>
<thead>
<tr>
<th></th>
<th>Water volume (L)</th>
<th>pH (H⁺ mmol/L) Before</th>
<th>pH (H⁺ mmol/L) After</th>
</tr>
</thead>
<tbody>
<tr>
<td>70 kg man</td>
<td>42</td>
<td>7.4 (40)</td>
<td>7.39 (41)</td>
</tr>
<tr>
<td>Water</td>
<td>42</td>
<td>7.4 (40)</td>
<td>2.78 (1 666 666)</td>
</tr>
</tbody>
</table>

Buffer mechanisms

Any chemical reaction reaching an equilibrium can be expressed by the law of mass action. In the case of a weak acid:

\[ \text{HA} \rightleftharpoons \text{H}^+ + \text{A}^- \] (1)

at equilibrium the product of the concentrations of H⁺ and A⁻ is a constant fraction of the concentration of HA or:

\[ K = \frac{[\text{H}^+][\text{A}^-]}{[\text{HA}]} \] (2)

The value of K at equilibrium is always the same and independent of the concentrations of the reactants that are present initially. With the addition of another acid (i.e. H⁺ donor) to the system, the ionisation of the weak acid HA is reduced (to keep K constant). If a base is added, the reduction in the H⁺ ion concentration produces further ionisation of the acid, HA. Both reduce the change in H⁺ ion concentration (pH).

However, as the ionisation of a weak acid is small, only a small addition of H⁺ can be tolerated before the pH falls. By supplementing the ion A⁻ with the addition of a salt of a strong base (e.g. NaA), this acts as a reservoir of A⁻ for combining with the added H⁺.

Therefore, a buffer system can be produced by mixing a weak acid with the salt of that acid and a strong base. Equation (2) can be rearranged as:

\[ [\text{H}^+] = K \times \frac{[\text{HA}]}{[\text{A}^-]} \] (3) Henderson equation

The negative log of equation (3) is:

\[ \text{pH} = \text{pKa} + \log \frac{[\text{A}^-]}{[\text{HA}]} \] (4) Henderson-Hasselbalch equation

From equation (4) it can be seen that the pH of 1 L of a weak acid solution with a pKa of 7.0 which has a concentration of 5.5 mmol/L of [A⁻] and 5.5 mmol/L of HA, is 7.0. If 0.5 mmol of a strong acid is added to this solution, [A⁻] will combine with the free [H⁺] to form HA (i.e. the concentration of [A⁻] will decrease to 5 mmol/L and the concentration of HA will increase to 6 mmol/L) and the pH will decrease to 6.92. If 4.5 mmol of a strong acid are added to the solution, the concentration of [A⁻] will decrease to 1 mmol/L, the concentration of HA will increase to 10 mmol/L and the pH will fall to 6.0. However, addition of more acid reduces the pH dramatically (e.g. the addition of an extra 0.9 mmol of acid will decrease the pH to 5 and the addition of an extra 0.999 mmol of acid will decrease the pH to 3). So most (i.e. 80%) of the buffering occurs within ± 1 pH unit of the pKa value of the buffer system (Fig. 1), which occurs when,

\[ \log \frac{[\text{A}^-]}{[\text{HA}]} \text{ is } \pm 1 \text{ i.e., } \frac{\text{BASE}}{\text{ACID}} 1 \text{ or } 10 \]

The major body buffer systems involve bicarbonate, protein, haemoglobin and phosphate.

Bicarbonate-carbonic acid buffer pair. The arterial H⁺ ion activity can be represented by the Henderson equation:

\[ [\text{H}^+] = 24 \times \frac{\text{PaCO}_2}{[\text{HCO}_3^-]} \]

or the Henderson-Hasselbalch equation:

\[ \text{pH} = 6.1 + \log \frac{[\text{HCO}_3^-]}{\text{PaCO}_2 \times 0.03} \]

Where:

- 24 = the numerical value of the solubility coefficient of carbon dioxide and the dissociation constant of carbonic acid.
- \text{PaCO}_2 = arterial blood partial pressure in mmHg
- [HCO₃⁻] = arterial blood bicarbonate concentration in mmol/L
- [H⁺] = arterial blood H⁺ ion concentration in mmol/L
0.03 = solubility coefficient of carbon dioxide
6.1 = negative logarithm of the dissociation constant of carbonic acid

This system is quantitatively the most important ECF buffer, and functions better as a physiological (or open) buffer than chemical (or closed) buffer. Its pKa is 6.1, therefore its chemical buffering capacity at a pH of 7.4 is poor (see position x in figure 1).

The benefit of an open, rather than closed, buffer system can be demonstrated if both systems are subjected to a pH change of 0.3 units by the addition of an acid. If one considers the Henderson-Hasselbalch equation under normal conditions, when pH 7.4, PaCO₂ 40 mmHg, HCO₃⁻ 24 mmol/L, then:

\[7.4 = 6.1 + \log \frac{24}{1.2}\]

However, addition of an acid to decrease the pH by 0.3 units, will produce different effects in the closed system when compared to the open system. For example,

\[
\begin{align*}
\text{A closed buffer system} & \quad 7.1 = 6.1 + \log \frac{22.9}{2.29} \\
\text{An open buffer system} & \quad 7.1 = 6.1 + \log \frac{12}{1.2}
\end{align*}
\]

In both systems the ratio of H₂CO₃ to HCO₃⁻ remains constant. In the closed system the total amount of H₂CO₃ and HCO₃⁻ remains constant (i.e. 25.2 mmol/L). In the open system, the denominator only is kept constant at 1.2 mmol/L, by increasing the ventilation and keeping the PaCO₂ at 40 mmHg (40 x 0.03 = 1.2). The buffer anion in the closed system falls from 24 to 22.9 whereas in the open system it falls from 24 to 12, thereby buffering more H⁺.

The bicarbonate/carbonic acid system also has the added advantage of a further carbon dioxide change with respiratory compensation, reducing even further the pH defect. These responses are shown, in stages, in figure 2.

The utility of this buffer system can be fully appreciated when it is realised that it is ‘open ended’ for both the numerator and the denominator. The PaCO₂ can be modified by a change in ventilation, and the HCO₃⁻ concentration can be regulated by renal mech-anisms. All other buffer systems in the body adjust accordingly to alterations in this pair, an interrelation-ship which is termed the isohydric principle.

**Haemoglobin, protein and phosphate buffers.**

Proteins have a series of titratable groups within their molecular structure with the ability to buffer pH changes. The buffering characteristic of haemoglobin is almost entirely dependent upon the imidazole group of histidine, which dissociates less when haemoglobin is in the oxygenated form compared with the deoxygenated form. Thus, deoxygenated blood is a better buffer than oxygenated blood; the haemoglobin molecule accommodates 0.7 mmol of H⁺ for each mmol of oxygen released, without any change in pH. As the respiratory quotient is normally 0.8, a slight reduction in pH usually occurs when blood travels from the arterial to the venous system.

The haemoglobin buffer is an important one, as it is involved in handling the largest daily acid load of the body, i.e. carbonic acid. Gram for gram, plasma proteins have one-third the buffering capacity of haemoglobin; however, as haemoglobin has twice the concentration of plasma protein, it has six times the capacity to buffer H⁺.

The phosphate buffer system has a pKa of 6.8 and so is a better chemical (or closed) buffer system than the bicarbonate buffer system. However, in plasma it has one-twentieth the concentration of bicarbonate, and also operates only as a closed system, so its capacity is far less than that of the bicarbonate-carbonic acid buffer. In the ICF and in urine, the phosphate buffer system assumes greater importance.

**Total Body Buffering**

The contributions of ICF and ECF buffers vary depending upon the nature, severity and duration of the
acid or base disturbance. In dogs in which respiratory or metabolic acid-base defects were produced, the respiratory pH changes were buffered mainly by ICF buffers, whereas metabolic pH changes had a greater ECF buffering component (Figure 3). Preferential utilisation of extracellular buffers occurs in the initial phase of a metabolic acidosis with the contribution of ICF buffers becoming greater as the acidosis increases in severity.

RESPIRATORY RESPONSE

It is clear when considering the Henderson equation [Equation (1)], that variations in PCO$_2$ alter the pH. The effect is rapid and influences both the ICF and ECF. Arterial PCO$_2$ varies inversely with alveolar ventilation and directly with carbon dioxide production. Normal carbon dioxide production is 13,000 mmol per day; if pulmonary ventilation ceased in man for 20 min, PaCO$_2$ would rise to 110 mmHg (13.3 kPa) and pH would fall to 7.03. If renal function ceased for a similar period, no change in arterial pH would occur.

Regulation of ventilation involves a complex interplay between mechanical and chemical stimuli. Any change in arterial HCO$_3^-$, PCO$_2$, pH, PO$_2$ or stimuli from pulmonary mechanoreceptors alter ventilation and thus PaCO$_2$ and pH. The respiratory response to a metabolic pH change follows peripheral chemoreceptor stimulation, and provides the compensatory response to metabolic pH change.

RENAL RESPONSE

This determines the final outcome to the acid or base load, by altering the denominator of the Henderson equation (i.e. [HCO$_3^-$]). The response is slow and the maximum excretory capacity of 300 mmol H$^+$ can only be reached after 7-10 days.

Unlike all other ions, HCO$_3^-$ has no permanence. It may be generated from carbon dioxide and water or lost with carbon dioxide excretion. The accompanying H$^+$ generated or lost is dealt with by the body’s buffers. The kidney uses the HCO$_3^-$ ion for alkali reserve and as an anion for sodium reabsorption or excretion when maintaining the ECF volume; the lungs use the HCO$_3^-$ ion for carbon dioxide transport and excretion.

Renal regulation of H$^+$ balance is due to reabsorption or excretion of filtered HCO$_3^-$, excretion of titratable acidity (TA) and excretion of ammonia. Tubular H$^+$ secretion usually involves Na$^+$ reabsorption, maintaining electrical neutrality.

Reabsorption (reclaiming) filtered HCO$_3^-$

About 85-90% of the filtered HCO$_3^-$ is reclaimed by the proximal tubule. Further reabsorption occurs in the distal nephron, with the luminal fluid being free of HCO$_3^-$ at a luminal pH of 6.2. The amount of HCO$_3^-$
reaching the distal nephron is influenced by the filtered load of \( \text{HCO}_3^- \) (i.e. with a metabolic acidosis, the total proximal \( H^+ \) secretion is less than normal) and the functional ECF volume.\(^\text{26}\) The mechanism of proximal tubular \( \text{HCO}_3^- \) reabsorption relies upon \( H^+ \) secretion.

Cellular carbonic anhydrase (CA) supplies \( H^+ \) for the hydrogen pump and the brush border CA facilitates the combination of \( \text{HCO}_3^- \) with \( H^+ \). In the absence of the brush border carbonic anhydrase, a disequilibrium pH of 0.85 - 1.0 occurs, and proximal \( H^+ \) secretion is inhibited.

**Formation of titratable acidity**

At a pH of 7.4, four fifths (80\%) of the circulating phosphate is in the monohydrogen form and one fifth (20\%) is in the dihydrogen form. The majority of the urinary titratable acidity (TA) is formed with the conversion of monohydrogen phosphate to dihydrogen phosphate, which occurs throughout the nephron.\(^\text{25}\) The pKa of this system is 6.8, and at maximum urinary acidity (i.e. pH 4.5) almost all (99\%) of the filtered phosphate is in the dihydrogen form. At this urinary pH, 74\% of the filtered creatinine (pKa 4.97) and 92\% of the uric acid (pKa 5.8) are in the nonionised mode, and may account for 25\% of the urinary TA at maximum urinary acidity.

Normally, 20 - 30 mmol of \( H^+ \) /day are excreted as TA, and this is proportional to the amount of buffer excreted, the pKa of the buffer, and the pH of the urine. In diabetic ketoacidosis the rate of excretion of unionised betahydroxybutyrate (pKa 4.8) with maximum urinary acidity is 66\%; so, in this condition it forms a large component (e.g. up to 250 mmol \( H^+ \) /day) of urinary TA. Acetoacetic acid has a pKa value of 3.8 and therefore only 17\% is excreted at maximum urinary acidity, although as the beta-hydroxybutyrate:acetate-acetate ratio is usually 3:1 (which may increase up to 9:1 with reduced redox states) almost all of the urinary ketone excretion is in the form of betahydroxybutyric acid. Only 20\% of lactic acid (pKa 3.9) remains in the nonionised state at maximum urinary acidity, therefore excretion of unionised lactic acid in lactic acidosis is also low.

Normally, urinary excretion of phosphate is determined by the need to maintain phosphate balance rather than acid-base homeostasis. Thus TA appears to play a supportive, rather than an active, role in \( H^+ \) balance.

**Formation of ammonia**

The major site for ammonia (NH\(_3\)) production is in the proximal convoluted tubule epithelium although it can be formed in tubular epithelia throughout the nephron.\(^\text{27}\) Deamidation and deamination of glutamine accounts for 60\% of the urinary NH\(_3\) whereas 30 - 35\% comes from free arterial NH\(_3\). The NH\(_3\) diffuses into the renal tubular lumen where it binds a \( H^+ \) ion to form a non diffusible ammonium ion (NH\(_4^+\)) which is subsequently excreted.\(^\text{28}\) This process permits Na\(^+\)/H\(^+\) exchange to occur without further change in urinary pH, although an acidic urine allows a greater sink into which free NH\(_3\) can diffuse and is therefore one of the determinants of urinary NH\(_4^+\) excretion.

Renal tubular synthesis of NH\(_3\) is coupled to renal glucoseoneogenesis which in turn is attuned to the body’s acid-base requirements. Systemic acidosis, hypokalaemia and mineralocorticoids increase ammonia production.\(^\text{27}\) Normally 30 - 50 mmol of H\(^+\)/day are excreted as NH\(_4^+\), which may increase to 300 mmol/day in severe acidosis.

**Mechanisms of proximal and distal \( H^+ \) secretion**

**Proximal \( H^+ \) secretion**

This is a low-gradient (minimal luminal pH achievable is 7.0), high-capacity (its \( H^+ \) secretion is responsible for reabsorbing most of the filtered \( \text{HCO}_3^- \), i.e. 4000 - 5000 mmol/day) system. The proximal \( H^+ \) secretion is increased with hypokalaemia, hypercapnia, increased luminal \( \text{HCO}_3^- \), increased tubular Na\(^+\) reabsorption, the presence of nonreabsorbable anions (e.g. SO\(_4^{2-}\), NO\(_3^-\), penicillin anion) and increase in carbonic anhydrase activity. In the presence of a functional ECF depletion, nonreabsorbable anion or metabolic alkalosis, the Na\(^+\)/H\(^+\) exchange mechanism is exaggerated, maintaining the ECF volume at the expense of pH homeostasis. Thus the maximum \( \text{HCO}_3^- \) reabsorption capacity of the kidney (i.e. \( Tm \text{HCO}_3^- \)) is not a fixed value and varies in response to the above factors.\(^\text{26}\)

**Distal \( H^+ \) secretion**

This is a high-gradient (minimal luminal pH achievable is 4.5), low-capacity (\( H^+ \) secretion ranges from 0 - 300 mmol/day) system. Unlike the proximal tubule the distal nephron is influenced by mineralocorticoid activity. In hyperaldosteronism, distal Na\(^+\) reabsorption and excretion of \( H^+ \) and K\(^+\) are enhanced. In the presence of hypokalaemia, \( H^+ \) loss is augmented due to electroneutrality requirements for some of the distal Na\(^+\) reabsorbed. In secondary hyperaldosteronism, the K\(^+\) and \( H^+ \) losses may be less than in primary hyperaldosterone states, due to a reduction in distal luminal flow induced by avid proximal Na\(^+\) reabsorption. Thus an increase in distal \( H^+ \) or K\(^+\) urinary secretion may only become evident when distal Na\(^+\) delivery is increased, for example with the use of diuretics or the administration of a sodium salt of a non reabsorbable anion.
REFERENCES