Physiology

Acid Base Balance and the pH of Blood
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While long term disturbances in the acid-base balance can disturb the normal growth and development, acute short term, but severe changes in pH, can also be drastic. The body’s acid base balance is maintained by different organ systems, including the lungs and the kidneys, along with the intracellular and extracellular buffer systems. A human body’s normal pH ranges from 7.35-7.45. pH and hydrogen ions concentration have an inverse relationship with each other. Changes in pH can force the hydrogen ions to combine with proteins, disturbing their function.

Review of [H$^+$] and pH

\[ \text{pH} = -\log_{10} [\text{H}^+] \]

Average arterial blood pH

- pH = 7.4
- [H$^+$] = 0.0000004

Thus, large changes in pH, such as in the GI system, require 10 fold changes in hydrogen concentration.

- pH = 1; [H$^+$] = 0.1
- pH = 8; [H$^+$] = 0.00000001
Example pH values of various fluids

<table>
<thead>
<tr>
<th>Compartment</th>
<th>pH</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastric secretions (under conditions of maximal acidity)</td>
<td>0.7</td>
<td>→ H⁺-K⁺-ATPase (proton pump) in parietal cells</td>
</tr>
<tr>
<td>Lysosome</td>
<td>5.5</td>
<td></td>
</tr>
<tr>
<td>Chromaffin granule</td>
<td>5.5</td>
<td></td>
</tr>
<tr>
<td>Neutral H₂O at 37°C</td>
<td>6.81</td>
<td></td>
</tr>
<tr>
<td>Cytosol of a typical cell</td>
<td>7.2</td>
<td>Range: 6.0—7.4 based in part on metabolism</td>
</tr>
<tr>
<td>Cerebrospinal fluid</td>
<td>7.3</td>
<td></td>
</tr>
<tr>
<td>Arterial blood plasma</td>
<td>7.4</td>
<td>Range: 7.35—7.45 highly regulated</td>
</tr>
<tr>
<td>Mitochondrial inner matrix</td>
<td>7.5</td>
<td></td>
</tr>
<tr>
<td>Secreted pancreatic fluid</td>
<td>8.1</td>
<td>→ HCO₃⁻ secretion ductal cells</td>
</tr>
</tbody>
</table>

Blood pH: Acidosis and Alkalosis

Arterial blood pH
Acids and Bases

Ionization, in chemistry and physics, is a process by which electrically neutral atoms or molecules are converted to electrically charged atoms or molecules (ions).

An acid is defined as a compound that dissociates in water and gives away hydrogen ions. Bases are compounds that can accept hydrogen ions.

Acid solutions contain hydrogen ions. The higher the concentration of hydrogen ions, the lower the pH. Hydrochloric acid is a strong acid and ethanoic acid is a weak acid. Strong acids are fully ionized but weak acids are only partly ionized in solution.

Similarly, a weak base is a chemical base that does not ionize fully in an aqueous solution.

Weak bases will have a higher H+ concentration (meaning lower pH) because they are less completely protonated than stronger bases and, therefore, more hydrogen ions remain in the solution. However, pH of bases is usually calculated using the OH− concentration to find the pOH first. This is done because the H+ concentration is not a part of the reaction, while the OH− concentration is.

Buffers

Buffers are chemical substances that minimize changes in pH when an acid or a base is added to a reaction. In the absence of buffers, a minor change in H+ ions concentration can lead to a dramatic change in the pH. Buffers actually avoid those large

\[
\text{pH} = -\log_{10}[H^+] \]

\[
\text{pOH} = -\log_{10}[OH^-] \]
changes in pH by reacting with the newly generated H\(^+\) ions and neutralizing them:

\[
A^- + H^+ \rightarrow HA
\]

Weak acids and bases that are 50 % dissociated (i.e. equally into HA and A\(^-\)) are known to be the best buffers. The pH at which these compounds are 50 % dissociated is called pK, or ionization constant. The best buffers for the human body are those which have a pK close to 7.40; these include the physiological buffers of the human body. If pH < pk of a buffer, HA > A\(^-\) and when pH > pk, A\(^-\) is more than HA.

**Physiologic Buffers**

These include bicarbonate and non-bicarbonate buffers which are actually protective for the body against abnormal changes in the pH. While managing patients, doctors routinely monitor the bicarbonate buffer system. In this system, bicarbonate picks up surplus H\(^+\) ions from the system, producing carbon dioxide (CO\(_2\)) and water.

Similarly, when H\(^+\) ion concentration decreases in the system, carbon dioxide combines with water to release hydrogen and bicarbonate ions. The pK of this reaction is 6.1. The Henderson-Hasselbalch equation expresses the relationship among pH, pk, and the concentrations of an acid and its conjugate base which is valid for any buffer. The Henderson-Hasselbalch equation for bicarbonate and carbon dioxide is as follows:

\[
\text{pH} = 6.1 + \log \left( \frac{[\text{HCO}_3^-]}{[\text{CO}_2]} \right)
\]

The Henderson-Hasselbalch equation contains 3 variables; if any two of these are known, the third can be calculated. CO\(_2\) is taken clinically as mm Hg and multiplied by its solubility constant, 0.03 mmol/L/mm Hg.

**The non-bicarbonate buffers**

The non-bicarbonate buffers include proteins and phosphates. Protein buffers include the extracellular proteins (albumin) and intracellular proteins (hemoglobin). Because of the amino acid histidine in the proteins, this can bind or release hydrogen ions. Proteins are very effective buffers. On the basis of its position in the protein molecule, its pK can vary; the average pK is about 6.5.

Hemoglobin and albumin both have histidine 34 and 16, respectively.

**Phosphate buffers**

Phosphates can bind 3 H\(^+\). They can exist as PO\(_4\)\(^{3-}\), HPO\(_4\)\(^{2-}\), H\(_2\)PO\(_4\)\(^{1-}\), or H\(_3\)PO\(_4\)\(^{-}\); Mostly they exist as HPO\(_4\)\(^{2-}\) or H\(_2\)PO\(_4\)\(^{1-}\).

\[
\text{H}_2\text{PO}_4\text{ }^{1-} \rightarrow \text{H}^+ + \text{HPO}_4\text{ }^{2-}
\]

As the pK of this reaction is 6.8, it is also a very good buffer. It is of lesser significance than albumin because concentration of PO\(_4\) in the ECF is relatively low, but it is found in a higher concentration in the urine, where it is an important buffer.

**Extracellular pH and Intracellular pH**

It is actually the intracellular pH that affects the cell function. Any change in the intracellular pH also changes the extracellular pH in one way or another. Although
intracellular pH is more important, we only measure the extracellular pH clinically while managing patients. Still, the intracellular buffer system is more active and efficient in managing major pH changes.

**Normal Acid Base Balance**

Of the three buffer systems, the bicarbonate buffer system is arguably the most important as it is the only one that is coupled to the respiratory system.

**Two major organs are involved in the normal acid and base balance:**

1. **Lungs excrete CO₂ from the system out into the environment and maintain a Pco₂ in the blood.** Central ventilation control in the CNS regulates the rate of breathing in order to maintain Pco₂ between 35—45 mmHg. When the ventilation rate increases, Pco₂ decreases and when the rate of ventilation decreases, Pco₂ increases.

2. **Kidneys remove endogenous acids from the body through the urine.** On average 1—2 mEq/kg/24 hr of H⁺ ions are produced in the body in adults, whereas, in children, 2—3 mEq/kg/24 hr of H⁺ ions are produced. Main sources include dietary protein metabolism, incomplete metabolism of carbohydrates and fat, and stool losses of bicarbonate. This shows that acid production depends on the amount of protein intake in the diet and the rate of catabolic activity.

No H⁺ ions are produced after complete carbohydrate and fat metabolism; instead, the end products of metabolism are water and CO₂ and CO₂ is exhaled by the lungs. **Incomplete catabolism of carbohydrates and fats produces lactic acid and keto acids,** like β-hydroxybutyric acid and acetoacetic acid. Normally, this occurs in small amounts but, in various pathologic conditions, like lactic acidosis and diabetic ketoacidosis, endogenous acid production is abnormally increased.

Stool loss of bicarbonate also contributes to the overall acid production in the body. The stomach mainly produces H⁺ ions, and the rest of the GI tract produces bicarbonate with an overall loss of bicarbonate from the body into the GI tract and out through the stools. **To produce bicarbonate into the GI tract, H⁺ ions are released into the blood stream,** at the rate of one H⁺ ion for each bicarbonate. This amount of acid production is also not much in the body, but it is dramatically increased in a patient with watery diarrhea.

**Only the lungs can regulate the CO₂ concentration, and only the kidneys can regulate the bicarbonate and H⁺ concentration.**

Excess H⁺ ions with endogenous acid producing mechanisms in the body are neutralized by bicarbonate, leading to a decrease in its concentration. This bicarbonate deficiency is restored by the kidneys by increasing the secretion of hydrogen ions. The lungs cannot regenerate bicarbonate, although the loss of carbon dioxide also lowers the hydrogen ion concentration:

\[
\text{H}^+ + \text{HCO}_3^- \rightarrow \text{CO}_2 + \text{H}_2\text{O}
\]

During metabolic acidosis, an increased ventilation rate lowers the CO₂ concentration in the blood, moving this reaction towards the right and decreasing H⁺ ion concentration, increasing the pH. This is a rapid compensation that does not last, as eventually the respiratory centers adapt to the continuing overproduction of CO₂. When metabolic acidosis still persists in the body, the kidneys assume the major compensatory role, usually after three days.
The following reaction is occurring in the body:

$$\text{H}^+ + \text{HCO}_3^- \rightarrow \text{CO}_2 + \text{H}_2\text{O}$$

Due to metabolic activity, raised H$^+$ ion concentration promotes the forward reaction increasing the CO$_2$ concentration and decreasing the hydrogen ion concentration. In respiratory acidosis, renal compensation by tubular reabsorption of bicarbonate and increased excretion of H$^+$ restores the pH toward normal. Both the lungs and the kidneys can affect the hydrogen ion concentration, hence the pH. Only the lungs can regulate CO$_2$ concentration, and only the kidneys can regulate bicarbonate and H$^+$ concentration.

**Henderson-Hasselbalch-Examples**

$$\text{pH} = 6.1 + \log \left( \frac{\text{HCO}_3^-}{0.03 \times \text{P}_{\text{CO}_2}} \right)$$

<table>
<thead>
<tr>
<th>Normal arterial blood gas</th>
<th>Acidic arterial blood gas</th>
<th>Alkalotic arterial blood gas</th>
</tr>
</thead>
<tbody>
<tr>
<td>HCO$_3^-$ = 24 mM</td>
<td>HCO$_3^-$ = 26 mM</td>
<td>HCO$_3^-$ = 22 mM</td>
</tr>
<tr>
<td>PaCO$_2$ = 40 mmHg</td>
<td>PaCO$_2$ = 60 mmHg</td>
<td>PaCO$_2$ = 20 mmHg</td>
</tr>
<tr>
<td>pH = 7.40</td>
<td>pH = 7.26</td>
<td>pH = 7.66</td>
</tr>
</tbody>
</table>

**Renal Handling of Acids and Bases**

After reclaiming filtered bicarbonate, the renal acid-base handling mechanism allows the excretion of acid formed by endogenous acid production (explained earlier). It occurs in the collecting ducts and distal tubule. As the hydrogen pumps in the collecting ducts cannot lower the urine pH below 4.5, excretion of endogenous acids need the presence of urinary buffers.

The two main urinary buffers are

1. **Phosphate buffer**
2. **Ammonia buffer**

The concentration of phosphates in the urine depends on the amount of dietary intake and the amount filtered and later reabsorbed in the proximal tubules. The serum level of phosphates is much lower than the concentration of urinary phosphates. These phosphates serve as an effective buffer through:

$$\text{H}^+ + \text{HPO}_4^{2-} \rightarrow \text{H}_2\text{PO}_4^- \quad \text{pK} = 6.8$$

As the urine pH decreases from 7.0 to 5.0 within the collecting duct, phosphate buffers are very effective, but the buffering capacity of this reaction is limited by its concentration. Urinary phosphate concentration cannot be modified by any mechanism.

**Renal Mechanisms in Acid-Base Balance**

The major mechanism by which the kidneys maintain pH is the regulation of serum bicarbonate concentration by promoting bicarbonate reabsorption and H$^+$ excretion in the urine. This is a two-step process.

1. **Proximal tubules reabsorb bicarbonate** filtered from the blood; then
2. **Distal Tubular secretion of hydrogen ions** occurs
Excretion of $H^+$ into the urine leaves behind the $HCO_3^-$ ions which neutralize the endogenous acid production. The renal acid excretion occurs throughout the nephron directly or indirectly, but is dominant in the distal tubules. Urinary buffers maintain the pH and allow the excretion or neutralization of endogenous acids.

Bicarbonate re-absorption occurs in the proximal tubules.

**Ammonia: $NH_3$ & $NH_4^+$**

Ammonia production can be modified, allowing for the regulation of acid excretion. The buffering capacity of ammonia is based on the reaction:

$$NH_3 + H^+ \rightarrow NH_4^+$$

Proximal tubular cells excrete ammonia, a byproduct of the catabolism of the amino acid glutamine:

$$Glutamine \rightarrow NH_4^+ + \text{glutamate}^-$$

$$Glutamine^- \rightarrow NH_4^+ + \text{ketoglutarate}^-$$

One glutamine produces two $NH_4^+$ ions. Later, the metabolism of $\alpha$-ketoglutarate also produces two bicarbonate ions. Ammonium ions go into the tubular lumen and bicarbonate ions exit the proximal tubule cells via a $Na^+, 3 HCO_3^-$ co-transporter. **Cells of the thick ascending limb of the loop of Henle re-absorb the ammonium ions which later moves into the blood neutralizing the bicarbonate ion produced earlier in the proximal tubules.** These ammonium ions are actually the sources of $H^+$ ions, making the cells of collecting ducts a crucial place in the excretion of $H^+$ in the form of $NH_4^+$ ions.

Cells of collecting ducts secrete $H^+$ ions and regenerate bicarbonate, which moves into the bloodstream and neutralizes the endogenous acid production. Renal buffers phosphate and ammonia buffer the $H^+$ secreted. Ammonia is present in a higher concentration in the renal interstitium and, due to free permeability in the collecting ducts, it diffuses into the lumen and neutralizes the $H^+$ ions responsible for the low urine pH; effectively buffering the pH.

Renal $H^+$ ion excretion is regulated according to the body’s physiologic requirements. When more acid production occurs, ammonia production is also upregulated in the proximal tubules to serve as a buffer in the collecting ducts i.e. $NH_4^+$ excretion may rise up to 10-folds over the baseline values.

**Extracellular pH: Regulator of Renal Acid Excretion**

Extracellular pH is the most important regulator of renal acid excretion. A fall in extracellular pH because of respiratory or metabolic imbalances promotes renal acid excretion. **Through the renin-angiotensin system, aldosterone also stimulates $H^+$ ion excretion in the collecting ducts, with the resultant increase in serum $HCO_3^-$ concentration.** Hypokalemia also increases acid secretion by promoting ammonia production in the proximal tubule and increasing $H^+$ ion secretion in the collecting duct, leading to metabolic alkalosis. Opposite effects occur in hyperkalemia leading to metabolic acidosis.

In case of alkalosis, bicarbonate resorption in the proximal tubule is decreased and bicarbonate is lost in the urine. In contrast, secretion into the lumen of $H^+$ ions by the
cells of collecting duct is reduced. As an end result, bicarbonate is lost in the urine and H⁺
ions move into the blood, compensating the body’s alkalosis.

References

Disorders

Acid-Base Balance: pH, Buffers, Acids, and Bases via courses.lumenlearning.com

Renal handling of acid-base balance via ld99.com

Acid-Base Balance and Renal Acid Excretion via med.unc.edu

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