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Acid-Base Balance and Buffer Systems

Equilibrio ácido-base y sistemas buffer

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Objectives:

- Describe the physiological characteristics of acid-base balance
- Enumerate the buffering systems involved in acid-base disorders

INTRODUCTION

History and physiology of acid-base balance

Knowledge of acid–base balance is fundamental in medicine. Anesthesiologist Bjorn Ibsen and chemist Poul Astrup revolutionized medicine by using a newly invented pH electrode to demonstrate that patients were dying from acidemia (low blood pH) due to inadequate ventilation, not from alkalosis as previously believed. This discovery led to the creation of modern intensive care medicine, where blood gas analysis became a vital tool. Today, the evaluation of acid–base balance remains crucial, especially in critically ill patients. For example, lactate measurement is essential in the diagnosis of sepsis.

What are acidosis and alkalosis?

The normal blood pH is maintained within a narrow range of 7,35 to 7,45.

- Acidosis is defined as a pH below 7,35.
- Alkalosis is a pH above 7,45.

Although the concentration of hydrogen ions (H^+) is low compared with other ions, its balance is vital, as it affects the chemical reactions of many biological processes. For example, a low pH (acidosis) in muscles during intense exercise reduces contractile strength. A low pH also activates the Bohr effect, which shifts the hemoglobin–oxygen dissociation curve to the right, facilitating oxygen release to metabolically active tissues.

Mechanisms of pH regulation

The body produces large amounts of volatile acids (mainly CO_2) and nonvolatile acids daily, which must be eliminated. pH homeostasis is achieved through three mechanisms that act on different time scales:

1. Buffer systems: act within seconds or minutes to neutralize changes in pH. They consist of a weak acid and its conjugate base. Although they do not eliminate the acid, they neutralize it until other mechanisms can act. The bicarbonate/carbonic acid system is the most important, functioning as an “open buffer” that is adjusted through respiration.
2. Respiratory system: functions within minutes to hours. Respiration is the main mechanism for eliminating volatile acids. An increase in carbon dioxide pressure (PCO_2) or hydrogen ion (H^+) concentration stimulates the respiratory center, increasing ventilation to exhale excess CO_2.
3. Renal system: acts over hours to days. The kidneys are responsible for the excretion of nonvolatile acids. Their primary function is the reabsorption of filtered bicarbonate

and the excretion of H^+ in the urine, mainly bound to phosphate or ammonium.

These three mechanisms work together to maintain pH within a narrow physiological range, a critical factor for survival.

Acid-base disorders

The study of acid–base disorders in critically ill patients has evolved significantly over time, moving from partial approaches to more comprehensive models in order to avoid misdiagnoses and inadequate treatments.

- Early discoveries: the understanding of acid–base balance began with Arrhenius in 1884, who defined acids by their ability to produce hydrogen ions. In 1909, Sørensen introduced the term pH.
- Henderson–Hasselbalch model: in 1908, Henderson described the relationship between carbon dioxide (CO_2) and bicarbonate (HCO_3^-), which led to the Henderson-Hasselbalch equation associating pH, pCO_2, and HCO_3^-.
- Base excess: in the 1900s, Siggaard-Andersen proposed the concept of base excess, which was later formalized mathematically by Van Slyke. This concept helped in the diagnosis of metabolic acidosis.
- Stewart model: between 1970 and 1980, Stewart proposed a more advanced approach that separated the metabolic component from the respiratory one. This model focuses on the strong ion difference (SID), including ions such as sodium, potassium, calcium, magnesium, chloride, and lactate.
- Chloride/sodium ratio: more recently, in 2000, Durward and his team introduced the chloride/sodium ratio as a useful tool for diagnosing hyperchloremic metabolic acidosis.

These advances have allowed physicians to move from simple diagnoses to a comprehensive and precise approach, which is crucial for managing critically ill patients with multiple acid-base disorders.

What are acids and bases?

The definitions of acids and bases have varied throughout history.

- Arrhenius: at the end of the 19th century, Svante Arrhenius defined acids as compounds that release hydrogen ions (H^+) in an aqueous solution. Bases, on the other hand, were compounds that release hydroxide ions (OH^-).
- Brønsted and Lowry: in 1923, Johannes Brønsted and Thomas Lowry proposed a broader definition. An acid is any substance that can donate a hydrogen ion (a proton), while a base is any substance that can accept a hydrogen ion. This theory explains why some substances without OH^- ions can act as bases.

Acids are substances that, when dissolved in water, increase the concentration of hydrogen ions (H^+). Fruit juices and cola drinks are common examples of acidic solutions. Bases (or alkaline substances), on the other hand, reduce the concentration of H^+, usually by releasing hydroxide ions (OH^-) that combine with hydrogen ions. Examples of bases include sodium bicarbonate and soap.

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Pure water naturally self-ionizes, producing a small and equal amount of hydrogen ions (H+) and hydroxide ions (OH−). The concentration of these ions in pure water is 1 × 10−7 M (moles per liter), which defines a neutral pH.

The pH scale

The pH scale is used to measure the acidity or basicity of a solution. It is based on the negative logarithm of the hydrogen ion concentration, that is $pH=-\log_{10}[H^+]$, where:

- A pH of 7,0 is considered neutral.
- A pH below 7,0 indicates an acidic solution (higher concentration of H^+).
- A pH above 7,0 indicates a basic or alkaline solution (lower concentration of H^+).

The scale is logarithmic, so each change of one pH unit represents a tenfold change in hydrogen ion concentration. Solutions with very low pH (such as stomach acid) or very high pH are harmful to life, although some organisms, such as the human stomach, have special mechanisms to withstand them.

Strong acids ionize completely in water, while weak acids dissociate very little. Substances that can act as acids or bases are called amphoteric, such as water (H_2O).

Buffer solutions

Living organisms, including humans, need to maintain their pH within a very narrow range to function properly. For example, human blood pH must remain around 7,4. To achieve this, the body uses buffer solutions, which are mixtures of an acid and its conjugate base that resist drastic changes in pH.

Buffer solutions are solutions that resist sudden changes in pH. They are composed of a weak acid and its salt (its conjugate base). When small amounts of an acid or a base are added, the buffer solution neutralizes the change, maintaining a stable pH.

A key example of a buffer system in the blood is that of carbonic acid (H_2CO_3) and the bicarbonate ion (HCO_3^-). This system helps regulate pH by absorbing excess hydrogen ions when the solution becomes too acidic or by releasing them when the pH rises too high.

Without these buffers, pH fluctuations would be fatal.

The functions of buffers are vital for the survival of the organism. For example, in human blood, the carbonic acid (H_2CO_3) / bicarbonate (HCO_3^-) buffer system maintains the pH within a range of 7,4. The ability of buffer solutions to maintain pH within a specific range is crucial for biological and chemical processes.

Assessing acid-base balance remains fundamental in the management of critically ill patients.

The Henderson-Hasselbalch equation, which relates pH to the concentration of the weak acid and its conjugate base, is used to calculate the pH of a buffer solution.

What is acidosis and why is it relevant?

Key Definitions

- The normal pH of blood is 7,35 to 7,45; this corresponds to a hydrogen ion [H+] concentration of 35 to 45 n mol/L.
- Acidosis is defined as a pH below 7,35.
- A pH above 7,45 is alkalosis.

Although the concentration of hydrogen ions [H+] (in nmol L^{-1}) is about 1/1 000 000 that of other common ions ($Na^+ \approx 135$ mmol L^{-1}, $Cl^- \approx 105$ mmol L^{-1}), it has fundamental importance because the chemical reactions of many biological processes, enabled by enzymatic proteins, depend greatly on pH.

For example, during intense exercise, lactic acid accumulates in skeletal muscle. This acid is strong, with a pK_1 of 3,8, and rapidly dissociates into lactate and H^+ ions, which causes a reduction in intracellular pH. This decreases the concentration of free Ca^{2+} in the sarcomere available to bind to troponin, and reduces the number of actin-myosin interactions. In turn, this diminishes muscle contraction strength. In laboratory studies, a similar decrease in cardiac

muscle contractility has been observed; however, this is not replicated in all clinical studies and is thought to be due to the increase in catecholamines observed in acidotic states, which masks this effect.

The oxygen content of blood (CaO_2) can be quantified as:

$$CaO_2 = 1{,}34 \times Hb \times SaO_2 + (0{,}025 \times PO_2)\ ml\ L^{-1}\ (\approx 200\ ml\ L^{-1}\ of\ blood)$$

Balance between acid-base production and clearance

The body produces approximately 13 moles of acid per day. This consists of volatile acids derived from CO_2 production (13 000 mmol per day, or 0,5 kg for those interested in carbon offset calculations) and nonvolatile acids (80 mmol per day). Nonvolatile acids are further subdivided into organic acids (lactate, free fatty acids, and ß-hydroxybutyrate) and inorganic acids (sulfuric and phosphoric acid).

In normal homeostasis, there is a drive to eliminate acid from active tissues as soon as it is produced, and this is achieved through three main mechanisms whose effects vary across different time scales:

- Neutralization through buffer systems (seconds to minutes).
- Exhalation via the respiratory system (minutes to hours).
- Clearance by the renal system (hours to days).

Buffer systems

A buffer is a system that resists changes in pH. It consists of a solution of a weak acid and its conjugate base. Although buffers do not add or remove acid, they act to neutralize the harmful effects of an increase in $[H^+]$, while other mechanisms operate.

$$H^+ + A^- \rightleftharpoons HA$$

The predominant acid produced is carbonic acid, a byproduct of aerobic respiration during the breakdown of carbohydrates within the mitochondria:

$$C_6H_{12}O_6 + 6O_2 \Rightarrow 6CO_2 + 6H_2O \text{ with ATP production.}$$

Although approximately 10 % of CO_2 is transported to the lungs dissolved in plasma, most is carried as bicarbonate (approximately 60 %) or carbamino compounds (approximately 30 %).

$$CO_2 + H_2O \leftrightharpoons H_2CO_3 \leftrightharpoons HCO_3^- + H^+$$

When CO_2 combines with water, it forms carbonic acid. This reaction is slow, with an equilibrium time of several minutes, but the catalytic enzyme carbonic anhydrase (CA) reduces it to a fraction of a second. Although this enzyme is not present in plasma, it is distributed throughout the body, particularly in red blood cells, the nephron, and the gastrointestinal tract. Dissolved CO_2 rapidly diffuses into red blood cells and reacts with H_2O, producing carbonic acid, which, due to its low pK_1, dissociates quickly.

The bicarbonate/carbonic acid system $H_2CO_3 \leftrightharpoons HCO_3^- + H^+$

The pK_a of this reaction is 6,1, the pH at which the ratio of HCO_3^- to H_2CO_3 is 1:1. This is the pH at which the system has the greatest capacity to resist a change caused by an additional acid or base. From the buffer titration curve, it is observed that this value is well below the physiological pH; at pH 7,4, the ratio of HCO_3^- to H_2CO_3 is 5000:1. Theoretically, this is the weakest point of the buffer, located in the flat portion of the sigmoidal curve.

The bicarbonate system is important for two reasons. Firstly, it is the most abundant buffer in the body. Secondly, it functions as an open buffering system.

The classical buffer describes a closed system, in which the acid and its conjugate base depend solely on each other, without being affected by other reactions. However, the bicarbonate buffer acts as part of an open equilibrium. The respiratory system can remove CO_2 from the body, adjusting the equilibrium toward carbonic acid and eliminating a greater amount of H^+.

$$CO_2 + H_2O \leftrightharpoons H_2CO_3 \leftrightharpoons HCO_3^- + H^+$$

Now let us consider an open system. If a change of 2 mmol·L^{-1} in CO_2 were to occur, a corresponding decrease in HCO_3^- would result. However, in reality, the respiratory system would adjust, and the additional CO_2 would be exhaled, reducing it to about 1,2 mmol·L^{-1}. Therefore, the ratio $[HCO_3^-]/[CO_2]$ would be 22/1,2, and the pH would be 7,36.

Carbamino Compounds

Carbamino compounds are formed through the combination of CO_2 with the terminal amino groups of proteins. This reaction occurs with both intracellular and extracellular proteins, the most significant being hemoglobin. Both hemoglobin and oxyhemoglobin can bind to CO_2. Hemoglobin is less acidic than oxyhemoglobin and can bind more H^+ (with an affinity 3,5 times greater). This is known as the Haldane effect.

Effect of Acid-Base Control on Respiration

Carbon dioxide is released and exhaled in the lungs. According to the law of mass action, the clearance of H^+ coincides with that of CO_2. The partial pressure of CO_2 or the concentration of H^+ in the blood has an indirect effect on the respiratory center of the brainstem through signals originating from the chemosensitive area on the ventral surface of the medulla oblongata. This area lies within the blood–brain barrier (BBB). Under normal conditions, H^+ cannot cross the BBB, but CO_2 can.

Paradoxically, the effect of CO_2 on respiration is likely due to alterations in the concentration of H^+. The buffering effect of cerebrospinal fluid (CSF) is weaker than that of plasma, so the CO_2 that crosses the blood–brain barrier (BBB) reacts rapidly with H_2O to form H^+ and HCO_3^-. The H^+ then triggers the response of the chemosensitive area.

There is a marked linear respiratory response to an increase in PCO_2 across the entire normal physiological range (PCO_2 4–13 kPa). Alveolar ventilation increases by 1–2 L·min^{-1} for every 0,1 kPa rise in PCO_2. In contrast, the response to a change within the normal pH range of 7,3–7,5 is only one-tenth as great. Respiratory adaptation is a continuous process, not limited to diseases. Any metabolic activity, such as exercise, is associated with an increase in CO_2 production, and this enhances ventilation.

Renal Regulation of Acid-Base Control

The kidneys are responsible for the excretion of nonvolatile acids. These are produced through amino acid metabolism. A normal dietary intake of 70 g/day generates 190 mmol of acids: hydrochloric acid (HCl), derived from the breakdown of arginine, lysine, and histidine; and sulfuric acid (H_2SO_4), derived from methionine and cystine. Most of this acid is utilized in the breakdown and recycling of organic anions (glutamate, aspartate, and lactate), and the remaining 40–80 mmol/day must be excreted by the kidneys.

Quantitatively, of greatest importance to the body is the reabsorption of HCO_3^-. Each day, more than 4000 mmol are filtered into the glomerular lumen, of which 80–90 % are reabsorbed in the proximal convoluted tubule (PCT). HCO_3^- is not readily reabsorbed across the cell membrane; however, PCT cells secrete H^+ into the lumen (via a Na^+/H^+ cotransporter), where,

under the action of a membrane-bound carbonic anhydrase, they react to form CO_2 and H_2O. Driven by a concentration gradient, CO_2 easily crosses the cell membrane through aquaporins, where the reaction is reversed. H^+ is recycled back into the lumen, while HCO_3^- is transported into the interstitial fluid by a Na^+/HCO_3^- cotransporter and returns to the blood.

The remaining HCO_3^- passes through the loop of Henle into the distal convoluted tubule (DCT), where most of it is reabsorbed. Here, cellular excretion of H^+ is driven by the H^+/K^+-ATPase and a Na^+/H^+ exchange mechanism dependent on aldosterone.

The body can adjust urine pH from 8 to 4,5. However, even with maximal acidification (0,003 $mmol \cdot L^{-1}$ H^+), only a small fraction of H^+ can be eliminated in its free form; the remainder is excreted bound to titratable acids (phosphoric acid ≈ 80 %, uric acid ≈ 20 %, and citric acid) or to ammonium.

$HPO_4^{2-} + H^+ \leftrightharpoons H_2PO_4^-$
$NH^3 + H^+ \leftrightharpoons NH_4^+$

Phosphate is filtered into the glomerular lumen; it is reabsorbed to a lesser extent than H_2O in the proximal convoluted tubule (PCT) and becomes concentrated. Tubular fluid tends to be acidic due to phosphate, with a pK_a of 6,8, and it plays a more significant buffering role than in plasma. Once formed, $H_2PO_4^-$ is excreted as a sodium salt. In general, between 5 % and 10 % of the filtered phosphate is excreted in this way, representing between 30 and 40 mEq of H^+ excretion. The presence of titratable acids in the filtrate binds free H^+ and maintains the H^+ concentration gradient across the cell membrane, thereby allowing greater production of HCO_3^- and its return to the body.

Ammonium is responsible for the remaining clearance of nonvolatile acid, approximately 40–50 mmol per day. NH_3/NH_4^+ is not an effective buffer because its pK_a = 9,2 lies too far from the physiological pH. Instead, there is a combined role of the kidney and the liver. Through amino acid metabolism from a normal dietary protein intake, approximately 700–1000 mmol of NH_4^+ are produced. About 95 % of NH_4^+ combines in equal amounts with HCO_3^- to form urea, which is excreted in the urine without any net acid–base effect. The activity of the hepatic urea cycle depends on the amino acid load of the diet.

The proportion of NH_3 (not combined with HCO_3^-) in urea formation is used to influence acid–base balance. Free ammonium ions are toxic at high concentrations, so they combine with glutamate in the liver to form glutamine; this incorporates one NH_3 ion without consuming an HCO_3^- ion. Glutamine passes to the kidneys, specifically to the cells of the proximal convoluted tubule (PCT); here it is first cleaved by mitochondrial glutaminase, and then by cytosolic glutamate dehydrogenase, releasing 2 NH_4^+ and α-ketoglutarate. The latter is converted into glucose within the cell and returned to the body. The conversion to glucose requires one H^+, so the net effect is 1 H^+ (as NH_4^+) per molecule of glutamine. NH_4^+ moves into the tubular fluid, cotransported directly with Na^+, or dissociates into NH_3 and H^+. NH_3 can diffuse across the cell membrane down its concentration gradient, while H^+ is cotransported with Na^+.

Once in the tubular fluid, NH_4^+ is reformed and moves toward the loop of Henle. In the interstitium, significant reabsorption and concentration of NH_4^+ occur. This contributes to the hyperosmolarity of the renal medulla. However, in the collecting tubule, H^+ ions are actively pumped into the tubular fluid and recombine with NH_3, moving by passive diffusion to reform NH_4^+, and thereby be eliminated from the body.

The consumption and clearance of NH_4^+ through the urea cycle or the glutamate/glutamine system are regulated by feedback mechanisms influenced by pH. One to two days after the onset of metabolic acidosis, hepatic production of glutamine increases (at the expense of urea production), along with renal glutaminase activity, allowing NH_4^+ clearance to triple. Therefore, the liver exerts a direct effect on the acid–base balance of the body.

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