Acid–Base Physiology I: The Bicarbonate Buffer System and Respiratory Compensation 6.5

Learning Objectives

- Define pH
- Explain why plasma pH is regulated within narrow limits
- Define alkalosis and acidosis
- List the three major systems for regulating plasma pH
- Define the association and dissociation constants for a chemical buffer
- List the major chemical buffers in plasma
- Describe the function of the chemical buffers
- Explain what is meant by the isohydric principle
- Describe the role of carbonic anhydrase in the bicarbonate buffer system
- Write the Henderson–Hasselbalch equation for the bicarbonate buffer system using P_{CO_2} for carbonic acid and with the appropriate constants
- Describe the consequences of hyper- or hypoventilation as a primary defect
- Describe the response of the respiratory system to metabolic acidosis or alkalosis
- Explain why respiratory compensation for pH disturbances cannot be complete

pH IS A MONOTONICALLY DECREASING FUNCTION OF $[H^+]$

Because the $[H^+]$ in solution can vary over many orders of magnitude, Sorenson devised the pH scale, originally named for the "potentz" (meaning "power" in German) of the $[H^+]$. The pH is *defined* as

$$[6.5.1] \qquad pH = -\log a_{H^+}$$

where P_{CO_2} is the **activity** of the H^+ ion. In Eqn [6.5.1], the logarithm is to the base 10. The activity is related to concentration by

$$[6.5.2] \qquad a_{H^+} = \gamma[H^+]$$

where γ is the **activity coefficient**. For dilute ideal solutions, $\gamma = 1$. In plasma, where $[H^+]$ is about 10^{-7} M, the assumption that $\gamma = 1.0$ is justified. In this case, we write:

$$[6.5.3] \qquad pH = -\log [H^+]$$

The $[H^+]$ in bodily fluids varies from a high of about 0.1 M in gastric juice to a low of about 2×10^{-9} M in the most alkaline pancreatic juice. The corresponding pH values are about pH 2 for the gastric juice and pH 8.8 in pancreatic juice.

PLASMA pH IS MAINTAINED WITHIN NARROW LIMITS

Failure to regulate $[H^+]$ within fairly narrow limits causes death. Below pH 6.9, a person slips into a coma and death follows. Above 7.8, death is accompanied by tetany and convulsions. These are the extremes of pH compatible with life. Normally arterial plasma pH is maintained within more narrow limits, between about pH 7.35 and 7.44. These normal limits (7.35 and 7.44) correspond to $[H^+]$ of 45×10^{-9} and 36×10^{-9} M. Regulation of plasma $[H^+]$ within this narrow range of low concentrations illustrates its importance. **Acidemia** refers to $[H^+]$ in the plasma below pH 7.35, the condition is called **acidosis**. Similarly, **alkalemia** refers to $[H^+]$ above pH 7.44, the condition is **alkalosis**.

The extreme sensitivity to $[H^+]$ is due to the binding (e.g., absorption and association) or unbinding (e.g., desorption and dissociation) of H^+ to or from ionizable groups on amino acids that make up proteins. These groups affect the local charge on the protein that affects the 3D structure of the proteins and therefore affects their function. Most enzymes, for example, have well-defined optimum pH and their activity falls off when pH is away from this optimum.

THE BODY USES *CHEMICAL BUFFERS*, THE *RESPIRATORY SYSTEM*, AND THE *RENAL SYSTEM* TO REGULATE pH

Chemical buffers respond rapidly and are the first line of defense in acid–base imbalances. This system resists changes in blood pH but cannot, in itself, restore acid or base excess. The respiratory system works by adjusting plasma P_{CO_2}. Increasing P_{CO_2} lowers the pH and decreasing P_{CO_2} raises it. The renal system works by adjusting plasma $[HCO_3^-]$. Increasing $[HCO_3^-]$ raises the pH and decreasing $[HCO_3^-]$ lowers the pH. How this works is described in more detail in Chapter 7.7.

CHEMICAL BUFFERS ABSORB OR DESORB H^+ ACCORDING TO THE LAW OF MASS ACTION

The Bronsted–Lowry theory defines an acid as a proton donor, whereas a base is a proton acceptor; according to Lewis' definition, an acid is an electron acceptor,

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whereas a base is an electron donor. For our purposes, an acid is a chemical that dissociates in water to produce a hydrogen ion, H^+, and its conjugate base:

[6.5.4] $$HA \rightharpoonup H^+ + A^-$$

A base is any chemical that can remove H^+ from solution. In Eqn [6.5.4], the anion A^- is a base because the reverse reaction

[6.5.5] $$A^- + H^+ \rightharpoonup HA$$

removes H^+ from solution. The dissociation reaction (see Eqn [6.5.4]) and the association reaction (see Eqn [6.5.5]) occur simultaneously with forward and reverse rate constants, k_f and k_r. The reactions rates are given by

[6.5.6A] $$J_f = k_f[HA]$$

[6.5.6B] $$J_r = k_r[H^+][A^-]$$

where J_f is the rate of the forward reaction and J_r is the rate of the reverse reaction. Equilibrium occurs when the two rates are equal. When $J_f = J_r$, we can take the ratio of Eqn [6.5.6B] to Eqn [6.5.6A] to get

[6.5.7] $$\frac{k_f}{k_r} = K_D = \frac{[A^-][H^+]}{[HA]}$$

where K_D is the **dissociation constant**. In Eqn [6.5.7], the concentrations are not just any concentrations. The equation is true only for equilibrium concentrations. Although these can vary widely, setting any two determines the third uniquely. The equilibrium also can be written as the inverse:

[6.5.8] $$\frac{k_r}{k_f} = K_A = \frac{[HA]}{[A^-][H^+]}$$

where the equilibrium is equivalently described in terms of the **association constant**, $K_A = 1/K_D$. The units of K_D are M, and the units of K_A are M^{-1}. This nomenclature is sometimes confusing because chemists also refer to the dissociation constant as K_a, meaning the acid equilibrium constant.

Strong acids have large dissociation constants. When these compounds dissolve in water, almost all of the acid dissociates to H^+ and A^- and the equilibrium [HA] is small. Similarly, strong bases have small dissociation constants or large association constants. In water, strong bases bind nearly all of the available H^+ until all of the base is present as HA and the equilibrium $[A^-]$ is small. Physiological buffers are weak acids or weak bases, with a K_D close to physiological $[H^+]$. Any buffer has the property of releasing or absorbing H^+. Upon dissociation, the acid becomes a base. The acid and base of a buffer exist in a pair, and so we speak of an acid and its **conjugate** base, where the term "conjugate" means that they occur in pairs.

In chemistry, a pH buffer is a chemical compound that resists change in the pH of a solution when acid or base is added to it. Adding acid or base to pure water results in large pH changes. Addition of a buffer before adding the acid or base results in smaller pH changes, as shown in Figure 6.5.1. The buffer capacity of a solution is defined as the number of moles of strong acid or base that must be added per unit change in pH: $\Delta n/\Delta$pH. Large buffer capacities require more added strong acid or base for the same change in pH. The buffer capacity depends on the concentrations of [HA] and $[A^-]$; the greatest buffering capacity of a solution occurs when the $[H^+] = K_D$.

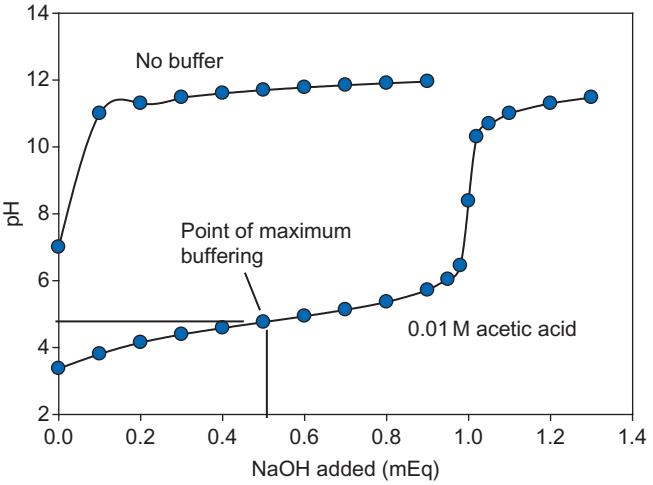

FIGURE 6.5.1 Adding a small amount (0.1 mEq) of NaOH to 100 mL of water at pH = 7.0 results in a large pH change. Adding NaOH to 100 mL of 0.01 M acetic acid produces a solution containing both undissociated acid and the Na acetate. The change in pH is buffered by combination with acetic acid. The pH change per unit NaOH is least at the point at which pH = pK (in this case, pK = 4.76). This is the point of highest buffer capacity.

Eqn [6.5.7] can be written in terms of $[H^+]$ as

[6.5.9] $$[H^+] = K_D \frac{[HA]}{[A^-]}$$

Taking the logarithm of both sides gives us

[6.5.10] $$\log[H^+] = \log K_D + \log\frac{[HA]}{[A^-]}$$

Multiplying both sides of the equation by -1, we get

[6.5.11] $$-\log[H^+] = -\log K_D + -\log\frac{[HA]}{[A^-]}$$

Recognizing that $-\log[H^+] = $ pH and identifying $-\log K_D = $ pK, we write Eqn [6.5.11] as

[6.5.12] $$\text{pH} = \text{p}K + \log\frac{[A^-]}{[HA]}$$

This is the **Henderson–Hasselbalch equation**, which becomes very useful in dealing with problems of acid–base physiology.

There are a variety of buffers in plasma and within cells that absorb or desorb H^+ ions. Examples include protein buffers, phosphate buffer, and the bicarbonate buffer system. Proteins have ionizable groups such as $-$COOH that can release H^+ and have pKs in the range of 3.5–5.5; they also possess $-NH_2$ groups that can accept H^+ and have pKs in the alkaline range, 8–9.

Imidazole groups from histidine also buffer pH changes. For each ionizable group we can write

$$[6.5.13] \qquad H_nPROT^{-r} \rightleftharpoons H_{n-1}PROT^{-(r+1)} + H^+$$

and we can write a corresponding Henderson–Hasselbalch equation for each dissociation reaction. Because proteins usually contain a number of acidic and basic residues, proteins in general have a number of different p*K*s. This allows proteins to buffer pH changes over a wide range of pH.

Phosphate undergoes three ionizations:

$$[6.5.14] \quad \begin{aligned} H_3PO_4 &\rightleftharpoons H_2PO_4^- + H^+ : K_D = 7.5 \times 10^{-3}\ M \\ H_2PO_4^- &\rightleftharpoons HPO_4^{-2} + H^+ : K_D = 6.2 \times 10^{-8}\ M \\ HPO_4^{-2} &\rightleftharpoons PO_4^{-3} + H^+ : K_D = 4.8 \times 10^{-13}\ M \end{aligned}$$

According to the Henderson–Hasselbalch equation, at physiological pH of around 7.4, the first H^+ is completely dissociated and essentially no H_3PO_4 remains. Similarly, the last H^+ does not dissociate until the pH becomes far more alkaline. The only dissociation that contributes meaningfully to the chemical buffers at normal plasma pH is the second dissociation reaction with a p$K = 7.21$. Phosphate buffer amounts to about 1 mM in plasma, but there are multiple forms of organic phosphates (ATP, ADP, pyrophosphate, creatine phosphate, etc.) inside cells that contribute to the intracellular buffer capacity.

By far the most important buffer system in the body is the HCO_3^- buffer system. It is written as

$$[6.5.15] \qquad CO_2 + H_2O \rightleftharpoons H_2CO_3 \leftrightharpoons HCO_3^- + H^+$$

The hydration of CO_2 to form **carbonic acid**, H_2CO_3, occurs slowly. Many tissues contain the enzyme **carbonic anhydrase** (**CA**) a Zn-containing enzyme that converts CO_2 and H_2O to H^+ and HCO_3^-. This bypasses the carbonic acid. However, H^+ and HCO_3^- can rapidly equilibrate with H_2CO_3, so that effectively the enzyme equilibrates all components of the carbonic acid–bicarbonate system. There are multiple isoforms of carbonic anhydrase in human tissues, and all have large turnover numbers on the order of 10^3–10^6 completed reactions s^{-1}.

THE *ISOHYDRIC PRINCIPLE* STATES THAT ALL BUFFERS IN A SOLUTION ARE IN EQUILIBRIUM WITH THE SAME $[H^+]$

A Henderson–Hasselbalch equation can be written for each of the three buffer systems listed above. The three equations for the protein, phosphate, and bicarbonate buffers are as follows:

$$[6.5.16] \quad \begin{aligned} pH &= pK_{PROT} + \log\frac{[H_{n-1}PROT^{-(r+1)}]}{[H_nPROT^{-r}]} \\ pH &= pK_{Pi} + \log\frac{[HPO_4^{-2}]}{[H_2PO_4^-]} \\ pH &= pK + \log\frac{[HCO_3^-]}{[H_2CO_3]} \end{aligned}$$

where the pK for each reaction is different because the chemical environment for each H^+ binding site is different. All three of these reactions occur simultaneously in plasma, but there is only one $[H^+]$ and one pH in plasma. Thus all three of these chemical buffers are in equilibrium simultaneously with a single $[H^+]$. This is the **isohydric principle**, which states simply that all buffers in a solution are simultaneously in equilibrium with one $[H^+]$. All buffer systems are connected by virtue of their shared dependence on $[H^+]$. The consequence of this is that **adjustments of a single buffer system will adjust them all through changes in $[H^+]$**. This is what makes the bicarbonate buffer system so important: it is the one that is physiologically adjusted.

EXPRESSING $[H_2CO_3]$ IN TERMS OF P_{CO_2} MAKES THE HENDERSON–HASSELBALCH EQUATION MORE USEFUL

The Henderson–Hasselbalch equation for the dissociation of carbonic acid is given as

$$[6.5.17] \qquad pH = pK + \log\frac{[HCO_3^-]}{[H_2CO_3]}$$

The K_D for this reaction at 37°C is 3.38×10^{-7} M. This value for K_D can be used only if we know the concentrations of HCO_3^- and H_2CO_3. However, the H_2CO_3 concentration in plasma cannot be measured easily. Because of the action of carbonic anhydrase, $[H_2CO_3]$ is in equilibrium with the dissolved $[CO_2]$ and is proportional to it; the $[H_2CO_3]$ is 0.235% of the dissolved $[CO_2]$. From the definition of K_D [see Eqn [6.5.7]), we write for the reaction forming carbonic acid:

$$[6.5.18] \quad \begin{aligned} K_D &= \frac{[HCO_3^-][H^+]}{[H_2CO_3]} \\ &= \frac{[HCO_3^-][H^+]}{0.00235\,[CO_2]} \end{aligned}$$

We can define a new K'_D by substituting $[CO_2]$ for $[H_2CO_3]$:

$$[6.5.19] \qquad K'_D = 0.00235 \times K_D = 7.94 \times 10^{-10}\ M = \frac{[HCO_3^-][H^+]}{[CO_2]}$$

The Henderson–Hasselbalch equation then must be rewritten in terms of $[CO_2]$ instead of $[H_2CO_3]$. Eqn [6.5.17] becomes

$$[6.5.20] \qquad pH = 9.10 + \log\frac{[HCO_3^-]}{[CO_2]}$$

where the $9.10 = pK'_D = -\log K'_D$ when K'_D is in units of M. **When the $[HCO_3^-]$ is expressed in mM, then $pK'_D = 6.10$ at 37°C.** This equation still needs work because typically it is the P_{CO_2} that is measured and not the concentration of dissolved CO_2. The conversion

between the two is the solubility. According to Henry's Law, we write:

$$[6.5.21] \qquad [CO_2] = \alpha P_{CO_2}$$

When $[CO_2]$ is expressed in mL per dL of water, and P_{CO_2} is expressed in mmHg, the solubility coefficient, α, is 0.0747 mL dL^{-1} $mmHg^{-1}$ (see Table 6.3.3). This can be converted to the solubility in plasma by multiplying by 0.93, the percent of the plasma volume that is water. Thus the solubility in plasma is 0.0695 mL dL^{-1} $mmHg^{-1}$. The volume of gas dissolved is expressed as the volume at STPD. It is converted to molarity by dividing by the molar volume, which is 22.4 L mol^{-1} = 22,400 mL mol^{-1}. This gives a solubility coefficient of 3.08×10^{-6} when $[CO_2]$ is expressed in mol dL^{-1} and P_{CO_2} is in mmHg. Because $[HCO_3^-]$ is expressed in mM = 10^{-3} mol L^{-1}, the equation requires $[CO_2]$ in mM. Conversion of the solubility coefficient to give $[CO_2]$ in mM gives 3.08×10^{-6} mol dL^{-1} $mmHg^{-1} \times 10^3$ mmol mol^{-1} $\times$ 10 dL L^{-1} = 0.0308 mmol L^{-1} $mmHg^{-1}$. The final relation is

$$[6.5.22] \qquad [CO_2] = 0.0308 P_{CO_2}$$

when $[CO]_2$ is expressed in units of mM and P_{CO_2} is in mmHg. Inserting this result into Eqn [6.5.20] and using the value of pK appropriate for the units and the variables, we arrive at the useful form of the Henderson–Hasselbalch equation for the HCO_3^- buffer system:

$$[6.5.23] \qquad pH = 6.10 + \log \frac{[HCO_3^-]}{0.0308\ P_{CO_2}}$$

THE RESPIRATORY SYSTEM REGULATES pH BY ADJUSTING PLASMA P_{CO_2}

The HCO_3^- buffer system can be described by its chemical reaction and by the Henderson–Hasselbalch equation that derives from this reaction. These descriptions are reproduced below.

$$[6.5.15] \qquad CO_2 + H_2O \rightleftharpoons H_2CO_3 \rightleftharpoons HCO_3^- + H^+$$

$$[6.5.23] \qquad pH = 6.10 + \log \frac{[HCO_3^-]}{0.0308\ P_{CO_2}}$$

To adjust plasma pH, the respiratory system has only one response: it can change pulmonary ventilation, which in turn alters alveolar ventilation. Recall the alveolar ventilation equation that we derived in Chapter 6.3:

$$[6.3.22] \qquad P_{A_{CO_2}} = \frac{Q_{CO_2}}{Q_A}(P_B - 47)$$

where $P_{A_{CO_2}}$ is the alveolar P_{CO_2}, Q_{CO_2} is the rate of CO_2 production by the body, Q_A is the alveolar ventilation, and P_B is the ambient, barometric pressure. If the respiratory system lowers alveolar ventilation (given a constant rate of CO_2 production, Q_{CO_2}), alveolar P_{CO_2} will increase, and so will arterial P_{CO_2} which is brought into equilibrium with alveolar P_{CO_2} when the blood passes through the lungs. The body will reach a new steady state in which the elimination of CO_2 through the lungs will equal its production, but it will be accomplished with less ventilation and a higher P_{CO_2} in the expired air. The increased P_{CO_2} will increase dissolved $[CO_2]$ which will, by the law of mass action, increase $[H_2CO_3]$ and increase $[HCO_3^-]$ and $[H^+]$. The increased $[H^+]$ lowers the pH of the plasma and acidosis results. All of this can be seen by an application of mass action to Eqn [6.5.15]. It can also be seen by applying Eqn [6.5.23]. The logarithm is a monotonically increasing function of its argument. The argument is the ratio $[HCO_3^-]/0.03$ P_{CO_2}. If P_{CO_2} increases, the argument decreases and so does the logarithm of the argument. Thus the pH also decreases because it is the sum of a constant and the logarithm. The decreased pH is called an **acidosis**. Thus **hypoventilation causes respiratory acidosis**.

By the same line of reasoning, in reverse, **hyperventilation causes respiratory alkalosis**.

HYPOVENTILATION IN RESPONSE TO ALKALOSIS IS CALLED *RESPIRATORY COMPENSATION OF ALKALOSIS*

Alkalosis can be produced by a variety of conditions including **vomiting**, in which stomach acid is lost from the body, or by **alkali treatment** for peptic ulcers or indigestion. When plasma pH rises from some problem other than the lungs, the respiratory system can compensate by hypoventilating. This raises plasma P_{CO_2} and adjusts plasma pH back toward normal. The depression of ventilation results from chemosensors for pH that help control ventilatory drive (see Chapter 6.6). The respiratory compensation that results is rapid but incomplete; the pH remains only partly compensated. Full compensation requires the kidneys to adjust $[HCO_3^-]$.

HYPERVENTILATION IN RESPONSE TO ACIDOSIS IS CALLED *RESPIRATORY COMPENSATION OF ACIDOSIS*

Acidosis can be produced by a variety of conditions in which H^+ production is increased or in which H^+ is not excreted. These conditions include **diarrhea**, in which buffer HCO_3^- is lost; **diabetes mellitus**, in which metabolic acid production is increased; and **renal tubular acidosis**, in which the kidneys fail to excrete sufficient acid. When plasma pH falls from some problem other than with the lungs, the respiratory system can compensate by hyperventilating. This lowers plasma P_{CO_2} and adjusts plasma pH back toward normal. The increased ventilatory drive results from the stimulation of chemosensors for pH that help control ventilatory drive (see Chapter 6.6). The respiratory compensation that results is rapid but incomplete; the pH remains only partly compensated. Once again, full compensation requires the kidneys to adjust $[HCO_3^-]$.

RESPIRATORY ACIDOSIS AND RESPIRATORY ALKALOSIS

Hypoventilation in the absence of alkalosis to inhibit ventilatory drive is a primary respiratory problem. This can result from **CNS depression** caused by trauma or by some drugs that inhibit respiratory drive such as barbiturates. Hypoventilation increases P_{CO_2} and leads to acidosis. There can be no respiratory compensation for a primary respiratory problem. In addition, anything that interferes with gas exchange can also cause respiratory acidosis. These conditions include **emphysema** or **asthma**. Interference with airflow as in asthma or reduction of the area of exchange as in emphysema can both increase P_{CO_2} and cause respiratory acidosis.

In the absence of acidosis to stimulate ventilatory drive, hyperventilation is a primary respiratory problem. This can result from excess CNS stimulation caused by anxiety or other psychogenic phenomena or by voluntary hyperventilation prior to holding one's breath under water, for example. Hyperventilation decreases P_{CO_2} and leads to alkalosis. There can be no respiratory compensation for a primary respiratory problem.

THE pH – HCO_3^- DIAGRAM DEPICTS ACID–BASE BALANCE GRAPHICALLY

There are a variety of graphical techniques that have been developed to simplify the analysis of acid–base physiology. Two common graphs are the pH – HCO_3^- diagram, sometimes also called the Davenport diagram, and the pH–log P_{CO_2} diagram, also called the Siggaard–Anderson nomogram. We will discuss only the pH – HCO_3^- diagram here.

The Henderson–Hasselbalch equation describes the relationship between P_{CO_2} and HCO_3^- at a given pH:

$$[6.5.23] \qquad pH = 6.10 + \log \frac{[HCO_3^-]}{0.0308\ P_{CO_2}}$$

In the pH – HCO_3^- diagram, the pH is plotted on the abscissa and $[HCO_3^-]$ is plotted on the ordinate. Because the values of pH, $[HCO_3^-]$, and P_{CO_2} are related according to Eqn [6.5.23], any two values determine the third. If we set $P_{CO_2} = 40$ mmHg, as an example, we can determine the set of all points whose values of pH and $[HCO_3^-]$ satisfy the Henderson–Hasselbalch equation. All points in the set define a P_{CO_2}**isobar**, meaning "same pressure." P_{CO_2} isobars at 20, 40, 60, and 80 mmHg are shown in Figure 6.5.2.

The P_{CO_2} isobars describe how pH and $[HCO_3^-]$ change at constant P_{CO_2}. The **plasma buffer line** describes how pH and $[HCO_3^-]$ change when the blood is equilibrated with various P_{CO_2}. It is called the buffer line because adding or removing CO_2 is equivalent to adding or removing acid as would occur in a titration. Because the red blood cells contain hemoglobin, which is a powerful pH buffer, the buffering power of plasma depends on both plasma proteins and hemoglobin, and therefore the slope of the buffer line depends on the hemoglobin concentration of blood. Figure 6.5.3 shows the plasma buffer line as a function of [Hb].

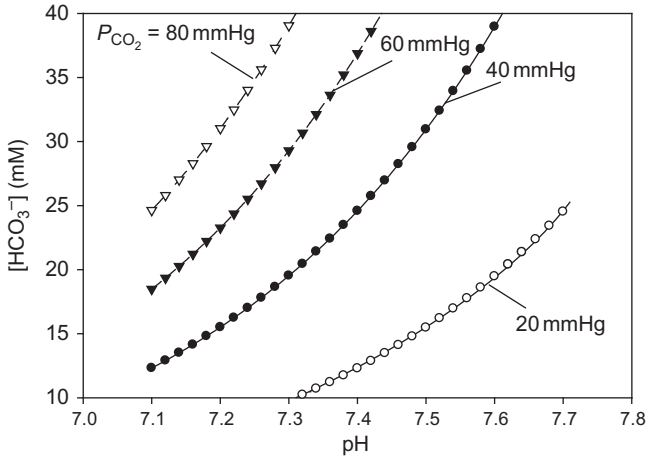

FIGURE 6.5.2 The pH – HCO_3^- diagram showing the variation of pH and $[HCO_3^-]$ at constant P_{CO_2}. The lines of equal P_{CO_2} are called isobars. *Adapted from H.W. Davenport,* The ABC of Acid–Base Chemistry, *6th edition, University of Chicago Press, 1974.*

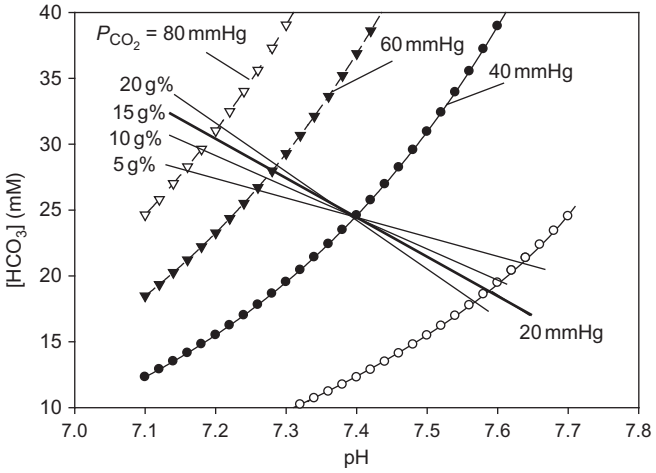

FIGURE 6.5.3 The pH – HCO_3^- diagram showing the buffer lines of blood that contains 5, 10, 15, and 20 g hemoglobin per dL whole blood. Increasing [Hb] increases the buffer capacity of blood. The buffer line at the normal hemoglobin concentration (15 g%) is the normal buffer line and is indicated in the figure by the darker line.

Disturbances of acid–base balance can be depicted graphically on the pH – HCO_3^- diagram as illustrated in Figure 6.5.4. The isobars at 20, 40, 60, and 80 mmHg P_{CO_2} are shown here along with the normal buffer line. The normal situation occurs at point A in the figure, where the pH is 7.4, $[HCO_3^-]$ is 24 mM, and P_{CO_2} is 40 mmHg. Pure respiratory alkalosis corresponds to a decrease in P_{CO_2} with no change other than by mass action to changes in HCO_3^-; this occurs at point B. Respiratory acidosis moves the point describing acid–base in the opposite direction: P_{CO_2} increases and the point describing the acid–base balance moves along the normal buffer line toward the higher P_{CO_2} isobar (point C).

EXAMPLE 6.5.1 Normal Acid–Base Conditions

The normal pH of arterial blood is 7.4. From previous discussion (see Chapter 6.4), the arterial $P_{a_{CO_2}}$ is 40 mmHg. What is the normal $[HCO_3^-]$?

Here we use the Henderson–Hasselbalch equation:

$$pH = 6.1 + \log[HCO_3^-]/0.0308\ P_{a_{CO_2}}$$

where pH = 7.4 and $P_{a_{CO_2}}$ = 40 mmHg. The constant, 0.0308, is designed for $[HCO_3^-]$ in mM and $P_{a_{CO_2}}$ in mmHg. Therefore, we have

$$7.4 - 6.1 = \log[HCO_3^-]/1.232; \quad 1.3 = \log[HCO_3^-]/1.232$$

The log here is log base 10. Thus we have

$$10^{1.3} \times 1.232 = [HCO_3^-] = \mathbf{24.6\ mM}$$

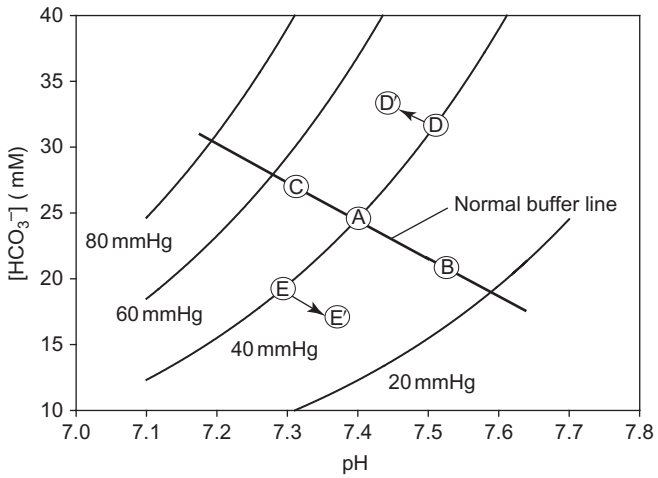

FIGURE 6.5.4 The pH – HCO_3^- diagram with acid–base status identified. The normal situation is at point A. P_{CO_2} is normal, pH is normal, and $[HCO_3^-]$ is normal. Respiratory alkalosis occurs at point B, where P_{CO_2} is reduced by hyperventilation. Point C corresponds to respiratory acidosis, in which P_{CO_2} is elevated as the primary problem. Uncompensated metabolic alkalosis occurs at point D; respiratory compensation rapidly moves the body from point D to D′, returning pH to near normal but with elevated $[HCO_3^-]$. Point E is uncompensated metabolic acidosis; respiratory compensation moves the body from E to E′ by hyperventilation.

Changes in acid–base status parallel to the normal P_{CO_2} isobar correspond to **uncompensated metabolic alkalosis** or **uncompensated metabolic acidosis**. These states correspond to points D and E in Figure 6.5.4. Respiratory compensation for metabolic alkalosis consists of hypoventilation to raise P_{CO_2} to help bring pH toward normal. This corresponds to position D′ in Figure 6.5.4. Note that the respiratory compensation here cannot be complete because there must be some residual alkalosis to continue to inhibit respiratory drive to maintain the hypoventilation. Also, respiratory compensation for metabolic alkalosis does not return us to point A, the normal acid–base situation. This must be accomplished by lowering $[HCO_3^-]$. This job is performed by the kidneys.

On the other hand, respiratory compensation for metabolic acidosis consists of hyperventilation and reduction in P_{CO_2}. This moves the acid–base status from point E to E′ in Figure 6.5.4. Here again respiratory compensation cannot be complete because there must be a continual stimulation of hyperventilation to maintain the lower P_{CO_2}. Respiratory compensation cannot return the acid–base status to normal at point A. This requires addition of $[HCO_3^-]$. This final task of adjusting plasma pH is accomplished by the kidneys.

SUMMARY

The plasma pH is defined as $-\log [H^+]$; when $[H^+]$ increases, the pH decreases. The condition of high plasma pH is called alkalosis; low plasma pH is acidosis. The body has three lines of defense against departures from normal plasma pH: the chemical buffers, the respiratory system, and the renal system. The chemical buffers passively resist changes in pH by absorbing excess H^+ when pH falls or by releasing H^+ ions when pH rises. Chemical buffers include proteins, phosphate, and bicarbonate buffers. All of these equilibrate with a single $[H^+]$, and so the buffer systems are linked. This is the isohydric principle. Because of this link, adjustment of the bicarbonate buffer system controls all buffer systems. The bicarbonate buffer system has two components: plasma $[CO_2]$ and $[HCO_3^-]$. The respiratory system controls plasma pH by adjusting the $[CO_2]$; the renal system adjusts $[HCO_3^-]$.

Each buffer system can be described by its Henderson–Hasselbalch equation:

$$pH = pK + \log[A]/[HA]$$

where the $pK = -\log K_D$ and K_D is the dissociation constant that varies with the chemical nature of each buffer. The acid in the bicarbonate buffer system is H_2CO_3. The equilibrium between dissolved CO_2 and H_2CO_3 is accelerated by carbonic anhydrase. Because this equilibrium is established so quickly, we can transform the Henderson–Hasselbalch equation for the bicarbonate buffer system to

$$pH = 6.1 + \log[HCO_3]/0.0308 \times P_{CO_2}$$

where $[HCO_3^-]$ is in mM and P_{CO_2} is in units of mmHg. The respiratory system can increase P_{CO_2} by hypoventilation. This increases $[H^+]$ by adding acid as H_2CO_3 and decreases the pH. Respiratory acidosis is caused by hypoventilation as the primary disturbance. Hypoventilation also forms the respiratory response to metabolic alkalosis. The respiratory system can also decrease P_{CO_2} by hyperventilating. This decreases $[H^+]$

and causes an alkalosis. Respiratory alkalosis results from hyperventilation as the primary disturbance. Hyperventilation also forms the respiratory compensation of metabolic acidosis. Respiratory compensation for either acidosis or alkalosis is incomplete because some residual pH disturbance must remain to maintain the hyperventilation or hypoventilation. Complete compensation of pH disturbances requires the kidney to change plasma [HCO_3^-].

REVIEW QUESTIONS

1. Why is the bicarbonate buffer system so important when its p*K* is not very close to the normal pH of blood?
2. In the Henderson–Hasselbalch equation, what units are necessary for [HCO_3^-]? For P_{CO_2}? If different units were used, would the value for p*K* remain the same?
3. Draw the pH – HCO_3^- diagram. Label the axes. Draw the isobar for the normal P_{CO_2} of 40 mmHg. Draw the normal buffer line. Indicate the normal position of acid–base balance.
4. Describe the three systems for acid–base regulation, their relative speeds of operation, and their ability to compensate for imbalances.
5. Write the alveolar ventilation equation and predict the effect of changes in Q_A on $P_{a_{CO_2}}$ and $P_{a_{O_2}}$.