CHAPTER

50

Acid–Base Management

KEY CONCEPTS

1. The strong ion difference, P_{CO_2}, and total weak acid concentration best explain acid–base balance in physiological systems.
2. The bicarbonate buffer is effective against metabolic but not respiratory acid–base disturbances.
3. In contrast to the bicarbonate buffer, hemoglobin is capable of buffering both carbonic (CO_2) and noncarbonic (nonvolatile) acids.
4. As a general rule, P_{aCO_2} can be expected to increase 0.25–1 mm Hg for each 1 mEq/L increase in $[HCO_3^-]$.
5. The renal response to acidemia is 3-fold: (1) increased reabsorption of the filtered $[HCO_3^-]$, (2) increased excretion of titratable acids, and (3) increased production of ammonia.
6. During chronic respiratory acidosis, plasma $[HCO_3^-]$ increases approximately 4 mEq/L for each 10 mm Hg increase in P_{aCO_2} above 40 mm Hg.
7. Diarrhea is a common cause of hyperchloremic metabolic acidosis.
8. The distinction between acute and chronic respiratory alkalosis is not always made, because the compensatory response to chronic respiratory alkalosis is quite variable: plasma $[HCO_3^-]$ decreases 2–5 mEq/L for each 10 mm Hg decrease in P_{aCO_2} below 40 mm Hg.
9. Vomiting or continuous loss of gastric fluid by gastric drainage (nasogastric suctioning) can result in marked metabolic alkalosis, extracellular volume depletion, and hypokalemia.
10. The combination of alkalemia and hypokalemia can precipitate severe atrial and ventricular arrhythmias.
11. Changes in temperature affect P_{CO_2}, P_{O_2}, and pH. Both P_{CO_2} and P_{O_2} decrease during hypothermia, but pH increases because temperature does not appreciably alter $[HCO_3^-]$: P_{aCO_2} decreases, but $[HCO_3^-]$ is unchanged.

Nearly all biochemical reactions in the body are dependent on maintenance of a physiological hydrogen ion concentration. The latter is tightly regulated because alterations in hydrogen ion concentration are associated with widespread organ dysfunction. This regulation—often referred to as acid–base balance—is of prime importance to anesthesiologists. Changes in ventilation and perfusion and the infusion of electrolyte-containing solutions are common during anesthesia and can rapidly alter acid–base balance.

Our understanding of acid–base balance is evolving. In the past, we focused on the concentration

of hydrogen ions [H^+], CO_2 balance, and the base excess/deficit. We now understand that the strong ion difference (SID), P_{CO_2}, and total weak acid concentration (A_{TOT}) best explain acid–base balance in physiological systems.

This chapter examines acid–base physiology, common disturbances, and their anesthetic implications. Clinical measurements of blood gases and their interpretation are also reviewed.

Definitions

ACID–BASE CHEMISTRY

Hydrogen Ion Concentration & pH

In any aqueous solution, water molecules reversibly dissociate into hydrogen and hydroxide ions:

$$H_2O \leftrightarrow H^+ + OH^-$$

This process is described by the dissociation constant, K_W:

$$K_W = [H^+] + [OH^-] = 10^{-14}$$

The concentration of water is omitted from the denominator of this expression because it does not vary appreciably and is already included in the constant. Therefore, given [H^+] or [OH^-], the concentration of the other ion can be readily calculated.

Example: If [H^+] = 10^{-8} nEq/L, then [OH^-] = $10^{-14} \div 10^{-8} = 10^{-6}$ nEq/L.

Arterial [H^+] is normally 40 nEq/L, or 40 × 10^{-9} mol/L. Hydrogen ion concentration is more commonly expressed as pH, which is defined as the negative logarithm (base 10) of [H^+] (**Figure 50–1**). Normal arterial pH is therefore –log (40 × 10^{-9}) = 7.40. Hydrogen ion concentrations between 16 and 160 nEq/L (pH 6.8–7.8) are compatible with life.

Like most dissociation constants, K_W is affected by changes in temperature. Thus, the electroneutrality point for water occurs at a pH of 7.0 at 25°C, but at about a pH of 6.8 at 37°C; temperature-related changes may be important during hypothermia (see Chapter 22).

Because physiological fluids are complex aqueous solutions, other factors that affect the dissociation of water into H^+ and OH^- are the SID, the P_{CO_2}, and A_{TOT}.

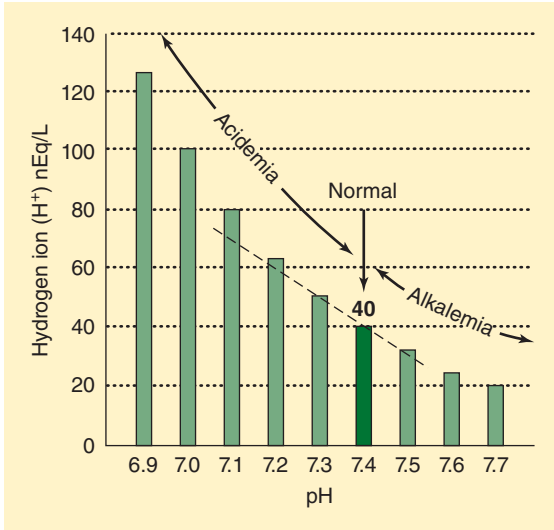

FIGURE 50–1 The relationship between pH and [H^+]. Note that between a pH of 7.10 and 7.50, the relationship between pH and [H^+] is nearly linear. (Reproduced, with permission, from Narins RG, Emmett M: Simple and mixed acid–base disorders: a practical approach. Medicine 1980;49:161.)

Acids & Bases

An acid is usually defined as a chemical species that can act as a proton (H^+) donor, whereas a base is a species that can act as a proton acceptor (Brönsted–Lowry definitions). In physiological solutions, it is probably better to use Arrhenius' definitions: An acid is a compound that contains hydrogen and reacts with water to form hydrogen ions. A base is a compound that produces hydroxide ions in water. Using these definitions, the SID becomes important, as other ions in solutions (cations and anions) will affect the dissociation constant for water, and, therefore, the hydrogen ion concentration. A *strong acid* is a substance that readily and almost irreversibly gives up an H^+ and increases [H^+], whereas a *strong base* avidly binds H^+ and decreases [H^+]. In contrast, *weak acids* reversibly donate H^+, whereas *weak bases* reversibly bind H^+; both weak acids and bases tend to have less of an effect on [H^+] (for a given concentration of the parent compound) than do strong acids and bases. Biological compounds are either weak acids or weak bases.

For a solution containing the weak acid HA, where

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

a dissociation constant, *K*, can be defined as follows:

$$K = \frac{[H^+][A^-]}{[HA]} \quad \text{or} \quad [H^+] = \frac{K[HA]}{[A^-]}$$

The negative logarithmic form of the latter equation is called the Henderson–Hasselbalch equation:

$$pH = pK + \log\left(\frac{[A^-]}{[HA]}\right)$$

From this equation, it is apparent that the pH of this solution is related to the ratio of the dissociated anion to the undissociated acid.

The problem with this approach is that it is phenomenological—measure the pH and bicarbonate, and then other variables can be manipulated mathematically. This approach works well with pure water—the concentration of $[H^+]$ must equal $[OH^-]$. But physiological solutions are far more complex. Even in such a complex solution, the $[H^+]$ can be predicted using three variables: the SID, the P_{CO_2}, and A_{TOT}.

Strong Ion Difference

The SID is the sum of all the strong, completely or almost completely dissociated, cations (Na^+, K^+, Ca^{2+}, Mg^{2+}) minus the strong anions (Cl^-, lactate$^-$, etc.) (**Figure 50–2**). Although we can calculate the SID, because the laws of electroneutrality must be observed, if there is a SID, other unmeasured ions must be present. P_{CO_2} is an independent variable, assuming ventilation is ongoing. The conjugate base of HA is A^- and is composed mostly of phosphates and proteins that do not change independent of the other two variables. A^- plus AH is an independent variable because its value is not determined by any other variable. Note that $[H^+]$ is not a strong ion (water does not completely dissociate), but it can, does, and must change in response to any change in SID, P_{CO_2}, or A_{TOT} to comply with the laws of electroneutrality and conservation of mass. Strong ions cannot be made to achieve electroneutrality, but hydrogen ions, H^+, are created or consumed based on changes in the dissociation of water.

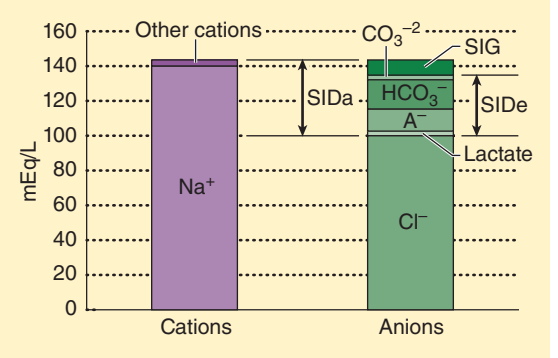

FIGURE 50–2 The strong ion difference (SID). SIDa, apparent strong ion difference. SIDe, effective strong ion difference. The strong ion gap (SIG) is the difference between SIDa and SIDe and represents the anion gap. (Reproduced, with permission, from Greenbaum J, Nirmalan M: Acid-base balance: Stewart's physiochemical approach, Curr Anaesth Crit Care June 2005;16(3):133-135.)

Conjugate Pairs & Buffers

As discussed above, when the weak acid HA is in solution, HA can act as an acid by donating an H^+, and A^- can act as a base by taking up H^+. A^- is therefore often referred to as the conjugate base of HA. A similar concept can be applied for weak bases. Consider the weak base B, where

$$B + H^+ \leftrightarrow BH^+$$

BH^+ is therefore the conjugate acid of B.

A buffer is a solution that contains a weak acid and its conjugate base or a weak base and its conjugate acid (conjugate pairs). Buffers minimize any change in $[H^+]$ by readily accepting or giving up hydrogen ions. It is readily apparent that buffers are most efficient in minimizing changes in the $[H^+]$ of a solution (ie, $[A^-] = [HA]$) when $pH = pK$. Moreover, the conjugate pair must be present in significant quantities in solution to act as an effective buffer.

CLINICAL DISORDERS

A clear understanding of acid–base disorders and compensatory physiological responses requires precise terminology (**Table 50–1**). The suffix "-osis" is used here to denote any pathological process that alters arterial pH. Thus, any disorder that tends to reduce pH to a less than normal value is an *acidosis*,

TABLE 50–1 Defining acid–base disorders.

Disorder	Primary Change	Compensatory Response
Respiratory		
Acidosis	↑ $Paco_2$	↑ HCO_3^-
Alkalosis	↓ $Paco_2$	↓ HCO_3^-
Metabolic		
Acidosis	↓ HCO_3^-	↓ $Paco_2$
Alkalosis	↑ HCO_3^-	↑ $Paco_2$

whereas one tending to increase pH is termed an *alkalosis*. If the disorder primarily affects [HCO_3^-], it is termed *metabolic*. If the disorder primarily affects $Paco_2$, it is termed *respiratory*. Secondary compensatory responses (see below) should be referred to as just that and not as an "-osis." One might therefore refer to a metabolic acidosis with respiratory compensation.

When only one pathological process occurs by itself, the acid–base disorder is considered to be simple. The presence of two or more primary processes indicates a *mixed* acid–base disorder.

The suffix "-emia" is used to denote the net effect of all primary processes and compensatory physiological responses (see below) on arterial blood pH. Because arterial blood pH is normally 7.35–7.45 in adults, the term *acidemia* signifies a pH <7.35, whereas *alkalemia* signifies a pH >7.45.

Compensatory Mechanisms

Physiological responses to changes in [H^+] are characterized by three phases: (1) immediate chemical buffering, (2) respiratory compensation (whenever possible), and (3) a slower but more effective renal compensatory response that may nearly normalize arterial pH even if the pathological process remains present.

BODY BUFFERS

Physiologically important buffers in humans include bicarbonate (H_2CO_3/HCO_3^-), hemoglobin (HbH/Hb^-), other intracellular proteins (PrH/Pr^-), phosphates ($H_2PO_4^-/HPO_4^{2-}$), and ammonia (NH_3/NH_4^+). The effectiveness of these buffers in the various fluid compartments is related to their concentration. Bicarbonate is the most important buffer in the extracellular fluid compartment. Hemoglobin, though restricted inside red blood cells, also functions as an important buffer in blood. Other proteins probably play a major role in buffering the intracellular fluid compartment. Phosphate and ammonium ions are important urinary buffers.

Buffering of the extracellular compartment can also be accomplished by the exchange of extracellular H^+ for Na^+ and Ca^{2+} ions from bone and by the exchange of extracellular H^+ for intracellular K^+. Acid loads can demineralize bone and release alkaline compounds ($CaCO_3$ and $CaHPO_4$). Alkaline loads ($NaHCO_3$) increase the deposition of carbonate in bone.

Buffering by plasma bicarbonate is almost immediate, whereas that due to interstitial bicarbonate requires 15–20 min. In contrast, buffering by intracellular proteins and bone is slower (2–4 h). Up to 50% to 60% of acid loads may ultimately be buffered by bone and intracellular buffers.

The Bicarbonate Buffer

Although in the strictest sense, the bicarbonate buffer consists of H_2CO_3 and HCO_3^-, CO_2 tension (Pco_2) may be substituted for H_2CO_3 because:

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

This hydration of CO_2 is catalyzed by carbonic anhydrase. If adjustments are made in the dissociation constant for the bicarbonate buffer and if the solubility coefficient for CO_2 (0.03 mEq/L) is taken into consideration, the Henderson–Hasselbalch equation for bicarbonate can be written as follows:

$$pH = pK' + \left(\frac{[HCO_3^-]}{0.03\ Paco_2} \right)$$

where $pK' = 6.1$.

Note that its pK' is well removed from the normal arterial pH of 7.40, which means that bicarbonate would not be expected to be an efficient extracellular buffer (see above). The bicarbonate system is, however, important for two reasons: (1) bicarbonate (HCO_3^-) is present in relatively high concentrations in extracellular fluid, and (2) more

TABLE 50–2 The relationship between pH and [H⁺].

pH	[H⁺] nEq/L
6.80	158
6.90	126
7.00	100
7.10	79
7.20	63
7.30	50
7.40	40
7.50	32
7.60	25
7.70	20

importantly—$Paco_2$ and plasma $[HCO_3^-]$ are closely regulated by the lungs and the kidneys, respectively. The ability of these two organs to alter the $[HCO_3^-]/Paco_2$ ratio allows them to exert important influences on arterial pH.

A simplified and more practical derivation of the Henderson–Hasselbalch equation for the bicarbonate buffer is as follows:

$$[H^+] = 24 \times \frac{Paco_2}{[HCO_3^-]}$$

This equation is very useful clinically because pH can be readily converted to $[H^+]$ (Table 50–2). Note that below 7.40, $[H^+]$ increases 1.25 nEq/L for each 0.01 decrease in pH; above 7.40, $[H^+]$ decreases 0.8 nEq/L for each 0.01 increase in pH.

Example: If arterial pH = 7.28 and $Paco_2$ = 24 mm Hg, what should the plasma $[HCO_3^-]$ be?

$$[H^+] = 40 + [(40 - 28) \times 1.25] = 55 \text{ nEq/L}$$

Therefore,

$$55 = 24 \times \frac{24}{[HCO_3^-]} \quad \text{and}$$

$$[HCO_3^-] = \frac{(24 \times 24)}{55} = 10.5 \text{ mEq/L}$$

2 It should be emphasized that the bicarbonate buffer is effective against metabolic but *not* respiratory acid–base disturbances. If 3 mEq/L of a strong nonvolatile acid, such as HCl, is added to extracellular fluid, the following reaction takes place:

$$3 \text{ mEq/L of } H^+ + 24 \text{ mEq/L of } HCO_3^- \rightarrow H_2CO_3 + H_2O + 3 \text{ mEq/L of } CO_2 + 21 \text{ mEq/L of } HCO_3^-$$

Note that HCO_3^- reacts with H^+ to produce CO_2. Moreover, the CO_2 generated is normally eliminated by the lungs such that $Paco_2$ does not change. Consequently, $[H^+] = 24 \times 40 \div 21 = 45.7$ nEq/L, and pH = 7.34. Furthermore, the decrease in $[HCO_3^-]$ reflects the amount of nonvolatile acid added.

In contrast, an increase in CO_2 tension (volatile acid) has a minimal effect on $[HCO_3]$. If, for example, $Paco_2$ increases from 40 to 80 mm Hg, the dissolved CO_2 increases only from 1.2 mEq/L to 2.2 mEq/L. Moreover, the equilibrium constant for the hydration of CO_2 is such that an increase of this magnitude minimally drives the reaction to the left:

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

If the valid assumption is made that $[HCO_3^-]$ does not appreciably change, then

$$[H^+] = \frac{(24 \times 80)}{24} = 80 \text{ nEq/L} \quad \text{and} \quad \text{pH} = 7.10$$

$[H^+]$ therefore increases by 40 nEq/L, and because HCO_3^- is produced in a 1:1 ratio with H^+, $[HCO_3^-]$ also increases by 40 nEq/L. Thus, extracellular $[HCO_3^-]$ increases negligibly, from 24 mEq/L to 24.000040 mEq/L. Therefore, the bicarbonate buffer is not effective against increases in $Paco_2$, and changes in $[HCO_3^-]$ do not reflect the severity of a respiratory acidosis.

Hemoglobin as a Buffer

Hemoglobin is rich in histidine, which is an effective buffer from pH 5.7 to 7.7 (pK_a 6.8). Hemoglobin is the most important noncarbonic buffer in extracellular fluid. Simplistically, hemoglobin may be thought of as existing in red blood cells in

equilibrium as a weak acid (HHb) and a potassium salt (KHb). In contrast to the bicarbonate buffer, hemoglobin is capable of buffering both carbonic (CO_2) and noncarbonic (nonvolatile) acids:

$$H^+ + KHb \leftrightarrow HHb + K^+ \quad \text{and}$$

$$H_2CO_3 + KHb \leftrightarrow HHb + HCO_3^-$$

RESPIRATORY COMPENSATION

Changes in alveolar ventilation responsible for the respiratory compensation of $Paco_2$ are mediated by chemoreceptors within the brainstem (see Chapter 23). These receptors respond to changes in cerebrospinal spinal fluid pH. Minute ventilation increases 1–4 L/min for every (acute) 1 mm Hg increase in $Paco_2$. In fact, the lungs are responsible for eliminating the approximately 15 mEq of CO_2 produced every day as a byproduct of carbohydrate and fat metabolism. Respiratory compensatory responses are also important in defending against marked changes in pH during metabolic disturbances.

Respiratory Compensation During Metabolic Acidosis

Decreases in arterial blood pH stimulate medullary respiratory centers. The resulting increase in alveolar ventilation lowers $Paco_2$ and tends to restore arterial pH toward normal. The respiratory response to lower $Paco_2$ occurs rapidly but may not reach a predictably steady state until 12–24 hr; pH is never completely restored to normal. $Paco_2$ normally decreases 1–1.5 mm Hg below 40 mm Hg for every 1 mEq/L decrease in plasma [HCO_3^-].

Respiratory Compensation During Metabolic Alkalosis

Increases in arterial blood pH depress respiratory centers. The resulting alveolar hypoventilation tends to elevate $Paco_2$ and restore arterial pH toward normal. The respiratory response to metabolic alkalosis is generally less predictable than the respiratory response to metabolic acidosis. Hypoxemia, as a result of progressive hypoventilation, eventually activates oxygen-sensitive chemoreceptors; the latter stimulates ventilation and limits the compensatory respiratory response. Consequently, $Paco_2$ usually does not increase above 55 mm Hg in response to metabolic alkalosis. As a general rule, $Paco_2$ can be expected to increase 0.25–1 mm Hg for each 1 mEq/L increase in [HCO_3^-].

RENAL COMPENSATION

The ability of the kidneys to control the amount of HCO_3^- reabsorbed from filtered tubular fluid, form new HCO_3^-, and eliminate H^+ in the form of titratable acids and ammonium ions (see Chapter 29) allows them to exert a major influence on pH during both metabolic and respiratory acid–base disturbances. In fact, the kidneys are responsible for eliminating the approximately 1 mEq/kg per day of sulfuric acid, phosphoric acid, and incompletely oxidized organic acids that are normally produced by the metabolism of dietary and endogenous proteins, nucleoproteins, and organic phosphates (from phosphoproteins and phospholipids). Metabolism of nucleoproteins also produces uric acid. Incomplete combustion of fatty acids and glucose produces keto acids and lactic acid. Endogenous alkali are produced during the metabolism of some anionic amino acids (glutamate and aspartate) and other organic compounds (citrate, acetate, and lactate), but the quantity is insufficient to offset the endogenous acid production.

Renal Compensation During Acidosis

The renal response to acidemia is 3-fold: (1) increased reabsorption of the filtered HCO_3^-, (2) increased excretion of titratable acids, and (3) increased production of ammonia. Although these mechanisms are probably activated immediately, their effects are generally not appreciable for 12–24 hr and may not be maximal for up to 5 days.

A. Increased Reabsorption of HCO_3^-

Bicarbonate reabsorption is shown in Figure 50–3. CO_2 within renal tubular cells combines with water in the presence of carbonic anhydrase. The carbonic acid (H_2CO_3) formed rapidly dissociates into H^+ and HCO_3^-. Bicarbonate ion then enters the bloodstream while the H^+ is secreted into the renal tubule, where it reacts with filtered HCO_3^- to form H_2CO_3.

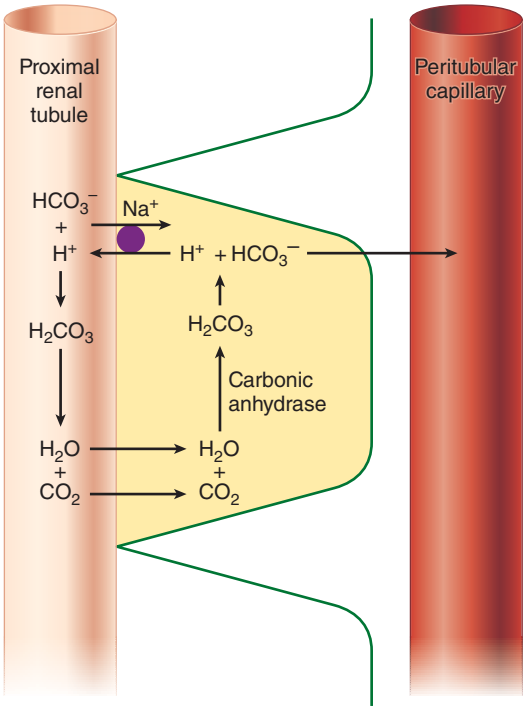

FIGURE 50–3 Reclamation of filtered HCO_3^- by the proximal renal tubules.

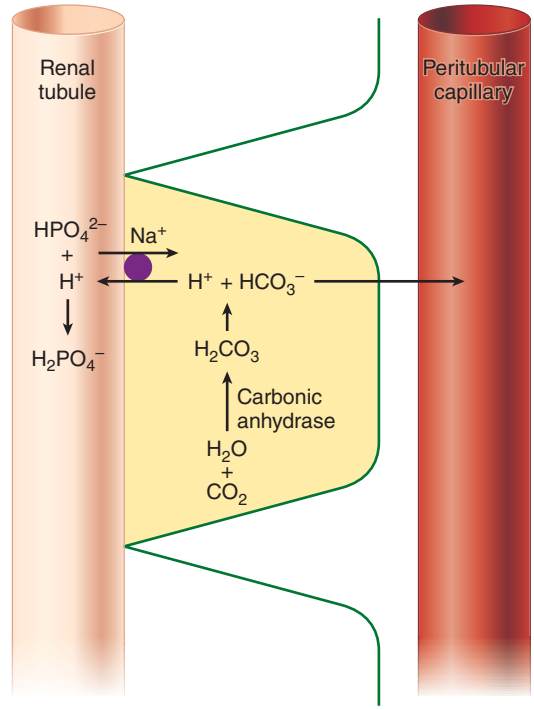

FIGURE 50–4 Formation of a titratable acid in urine.

Carbonic anhydrase associated with the luminal brush border catalyzes the dissociation of H_2CO_3 into CO_2 and H_2O. The CO_2 thus formed can diffuse back into the renal tubular cell to replace the CO_2 originally consumed. The proximal tubules normally reabsorb 80% to 90% of the filtered bicarbonate load along with sodium, whereas the distal tubules are responsible for the remaining 10% to 20%. Unlike the proximal H^+ pump, the H^+ pump in the distal tubule is not necessarily linked to sodium reabsorption and is capable of generating steep H^+ gradients between tubular fluid and tubular cells. Urinary pH can decrease to as low as 4.4 (compared with a pH of 7.40 in plasma).

B. Increased Excretion of Titratable Acids

After all of the HCO_3^- in tubular fluid is reclaimed, the H^+ secreted into the tubular lumen can combine with HPO_4^{2-} to form $H_2PO_4^-$ (Figure 50–4); the latter is not readily reabsorbed because of its charge and is eliminated in urine. The net result is that H^+ is excreted from the body as $H_2PO_4^-$, and the HCO_3^- that is generated in the process can enter the bloodstream. With a pK of 6.8, the $H_2PO_4^-/HPO_4^{2-}$ pair is normally an ideal urinary buffer. When urinary pH approaches 4.4, however, all of the phosphate reaching the distal tubule is in the $H_2PO_4^-$ form; HPO_4^{2-} ions are no longer available for eliminating H^+.

C. Increased Formation of Ammonia

After complete reabsorption of HCO_3^- and consumption of the phosphate buffer, the NH_3/NH_4^+ pair becomes the most important urinary buffer (Figure 50–5). Deamination of glutamine within the mitochondria of proximal tubular cells is the principal source of NH_3 production in the kidneys. Acidemia markedly increases renal NH_3 production. The ammonia formed is then able to passively cross the cell's luminal membrane, enter the tubular fluid, and react with H^+ to form NH_4^+. Unlike NH_3, NH_4^+ does not readily penetrate the luminal membrane

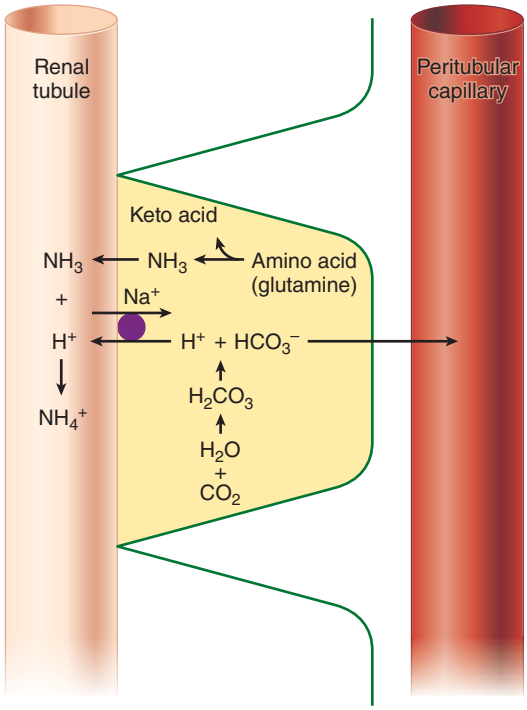

FIGURE 50–5 Formation of ammonia in urine.

and is therefore trapped within the tubules. Thus, excretion of NH_4^+ in urine effectively eliminates H^+.

Renal Compensation During Alkalosis

The tremendous amount of HCO_3^- normally filtered and subsequently reabsorbed allows the kidneys to rapidly excrete large amounts of bicarbonate, if necessary (see Chapter 49). As a result, the kidneys are highly effective in protecting against metabolic alkalosis, which therefore generally occurs only in association with concomitant sodium deficiency or mineralocorticoid excess. Sodium depletion decreases extracellular fluid volume and enhances Na^+ reabsorption in the proximal tubule. To maintain neutrality, the Na^+ ion is brought across with a Cl^- ion. As Cl^- ions decrease in number (<10 mEq/L of urine), HCO_3^- must be reabsorbed. Increased H^+ secretion in exchange for augmented Na^+ reabsorption favors HCO_3^- formation with metabolic alkalosis. Similarly, increased mineralocorticoid activity augments aldosterone-mediated Na^+ reabsorption in exchange for H^+ secretion in the distal tubules. The resulting increase in HCO_3^- formation can initiate or propagate metabolic alkalosis. Metabolic alkalosis is commonly associated with increased mineralocorticoid activity, even in the absence of sodium and chloride depletion.

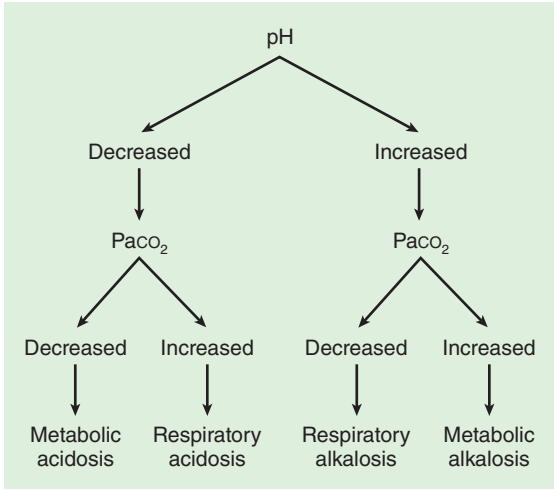

FIGURE 50–6 Diagnosis of simple acid–base disorders.

Base Excess

Base excess is the amount of acid or base (expressed in mEq/L) that must be added for blood pH to return to 7.40 and $PaCO_2$ to return to 40 mm Hg at full O_2 saturation and 37°C. Moreover, it adjusts for noncarbonic buffering in the blood. Simplistically, base excess represents the metabolic component of an acid–base disturbance. A positive value indicates metabolic alkalosis, whereas a negative value reveals metabolic acidosis. Base excess is usually derived graphically or electronically from a nomogram originally developed by Siggaard–Andersen and requires measurement of hemoglobin concentration (Figure 50–6).

Acidosis

PHYSIOLOGICAL EFFECTS OF ACIDEMIA

$[H^+]$ is strictly regulated in the nanomole/liter (36–43 nmol/L) range, as H^+ ions have high charge densities and "large" electric fields that can affect

the strength of hydrogen bonds that are present on most physiological molecules. Biochemical reactions are very sensitive to changes in $[H^+]$. The overall effects of acidemia seen in patients represent the balance between its direct biochemical effects and the effects of acidemia-induced sympathoadrenal activation. With severe acidosis (pH < 7.20), direct depressant effects predominate. Direct myocardial and smooth muscle depression reduces cardiac contractility and peripheral vascular resistance, resulting in progressive hypotension. Severe acidosis can lead to tissue hypoxia, despite a rightward shift in hemoglobin affinity for oxygen. Both cardiac and vascular smooth muscle become less responsive to endogenous and exogenous catecholamines, and the threshold for ventricular fibrillation is decreased. Progressive hyperkalemia as a result of the movement of K^+ out of cells in exchange for extracellular H^+ is also potentially lethal. Plasma $[K^+]$ increases approximately 0.6 mEq/L for each 0.10 decrease in pH.

Central nervous system depression is more prominent with respiratory acidosis than with metabolic acidosis. This effect is often termed **CO_2 narcosis**. Unlike CO_2, H^+ ions do not readily penetrate the blood–brain barrier.

RESPIRATORY ACIDOSIS

Respiratory acidosis is defined as a primary increase in $Paco_2$. This increase drives the reaction

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

to the right, leading to an increase in $[H^+]$ and a decrease in arterial pH. For the reasons described above, $[HCO_3^-]$ is minimally affected.

$Paco_2$ represents the balance between CO_2 production and CO_2 elimination:

$$Paco_2 = \frac{CO_2 \text{ production}}{\text{Alveolar ventilation}}$$

CO_2 is a byproduct of fat and carbohydrate metabolism. Muscle activity, body temperature, and thyroid hormone activity can all have major influences on CO_2 production. Because CO_2 production does not appreciably vary under most circumstances, respiratory acidosis is usually the result of alveolar hypoventilation (Table 50–3). In patients with a limited capacity to increase alveolar ventilation, however, increased CO_2 production can precipitate respiratory acidosis.

TABLE 50–3 Causes of respiratory acidosis.

Alveolar hypoventilation
Central nervous system depression
Drug-induced
Sleep disorders
Obesity hypoventilation (Pickwickian) syndrome
Cerebral ischemia
Cerebral trauma
Neuromuscular disorders
Myopathies
Neuropathies
Chest wall abnormalities
Flail chest
Kyphoscoliosis
Pleural abnormalities
Pneumothorax
Pleural effusion
Airway obstruction
Upper airway
Foreign body
Tumor
Laryngospasm
Sleep disorders
Lower airway
Severe asthma
Chronic obstructive pulmonary disease
Tumor
Parenchymal lung disease
Pulmonary edema
Cardiogenic
Noncardiogenic
Pulmonary emboli
Pneumonia
Aspiration
Interstitial lung disease
Ventilator malfunction
Increased CO_2 production
Large caloric loads
Malignant hyperthermia
Intensive shivering
Prolonged seizure activity
Thyroid storm
Extensive thermal injury (burns)

Acute Respiratory Acidosis

The compensatory response to acute (6–12 h) elevations in $Paco_2$ is limited. Buffering is primarily provided by hemoglobin and the exchange of extracellular H^+ for Na^+ and K^+ from bone and the

intracellular fluid compartment (see above). The renal response to retain more bicarbonate is acutely very limited. As a result, plasma [HCO_3^-] increases only about 1 mEq/L for each 10 mm Hg increase in $Paco_2$ above 40 mm Hg.

Chronic Respiratory Acidosis

"Full" renal compensation characterizes chronic respiratory acidosis. Renal compensation is appreciable only after 12–24 hr and may not peak until 3–5 days. During that time, the sustained increase in $Paco_2$ has been present long enough to permit maximal renal compensation. During chronic respiratory acidosis, plasma [HCO_3^-] increases approximately 4 mEq/L for each 10 mm Hg increase in $Paco_2$ above 40 mm Hg.

Treatment of Respiratory Acidosis

Respiratory acidosis is treated by reversing the imbalance between CO_2 production and alveolar ventilation. In most instances, this is accomplished by increasing alveolar ventilation. Measures aimed at reducing CO_2 production are useful only in specific instances (eg, dantrolene for malignant hyperthermia, muscle paralysis for tetanus, antithyroid medication for thyroid storm, and reduced caloric intake in patients receiving enteral or parenteral nutrition). Potential temporizing measures aimed at improving alveolar ventilation (in addition to controlled mechanical ventilation) include bronchodilation, reversal of narcosis, or improving lung compliance (diuresis). Severe acidosis (pH <7.20), CO_2 narcosis, and respiratory muscle fatigue are indications for mechanical ventilation. An increased inspired oxygen concentration is also usually necessary, as coexistent hypoxemia is common. Intravenous $NaHCO_3$ is rarely necessary, unless pH is <7.10 and HCO_3^- is <15 mEq/L. Sodium bicarbonate therapy will transiently increase $Paco_2$:

$$H^+ + HCO_3^- \leftrightarrow CO_2 + H_2O$$

Buffers that do not produce CO_2, such as Carbicarb™ or tromethamine (THAM), are theoretically attractive alternatives; however, there is almost no evidence showing that they have greater efficacy than bicarbonate. Carbicarb™ is a mixture of 0.3 M sodium bicarbonate and 0.3 M sodium carbonate; buffering by this mixture mainly produces sodium bicarbonate instead of CO_2. Tromethamine has the added advantage of lacking sodium and may be a more effective intracellular buffer.

Patients with a baseline chronic respiratory acidosis require special consideration. When such patients develop acute ventilatory failure, the goal of therapy should be to return $Paco_2$ to the patient's "normal" baseline. Normalizing the patient's $Paco_2$ to 40 mm Hg will produces the equivalent of a respiratory alkalosis (see below). Oxygen therapy must also be carefully controlled, because the respiratory drive in these patients may be dependent on hypoxemia, not $Paco_2$. "Normalization" of $Paco_2$ or relative hyperoxia can precipitate severe hypoventilation.

METABOLIC ACIDOSIS

Metabolic acidosis is defined as a primary decrease in [HCO_3^-]. Pathological processes can initiate metabolic acidosis by one of three mechanisms: (1) consumption of HCO_3^- by a strong nonvolatile acid, (2) renal or gastrointestinal wasting of bicarbonate, or (3) rapid dilution of the extracellular fluid compartment with a bicarbonate-free fluid.

A fall in plasma [HCO_3^-] without a proportionate reduction in $Paco_2$ decreases arterial pH. The pulmonary compensatory response in a simple metabolic acidosis (see above) characteristically does not reduce $Paco_2$ to a level that completely normalizes pH but can produce marked hyperventilation (Kussmaul's respiration).

Table 50–4 lists disorders that can cause metabolic acidosis. Note that differential diagnosis of metabolic acidosis may be facilitated by calculation of the anion gap.

The Anion Gap

The anion gap in plasma is most commonly defined as the difference between the major measured cations and the major measured anions:

$$\text{Anion gap} = \text{major plasma cations} - \text{major plasma anions}$$

Or

$$\text{Anion gap} = [Na^+] - ([Cl^-] + [HCO_3^-])$$

TABLE 50–4 Causes of metabolic acidosis.

Increased anion gap
Increased production of endogenous nonvolatile acids
Renal failure
Ketoacidosis
Diabetic
Starvation
Lactic acidosis
Mixed
Nonketotic hyperosmolar coma
Alcoholic
Inborn errors of metabolism
Ingestion of toxin
Salicylate
Methanol
Ethylene glycol
Paraldehyde
Toluene
Sulfur
Rhabdomyolysis
Normal anion gap (hyperchloremic)
Increased gastrointestinal losses of HCO_3^-
Diarrhea
Anion exchange resins (cholestyramine)
Ingestion of $CaCl_2$, $MgCl_2$
Fistulas (pancreatic, biliary, or small bowel)
Ureterosigmoidostomy or obstructed ileal loop
Increased renal losses of HCO_3^-
Renal tubular acidosis
Carbonic anhydrase inhibitors
Hypoaldosteronism
Dilutional
Large amount of bicarbonate-free fluids (eg, 0.9% NaCl)
Total parenteral nutrition (Cl^- salts of amino acids)
Increased intake of chloride-containing acids
Ammonium chloride
Lysine hydrochloride
Arginine hydrochloride

Some physicians include plasma K^+ in the calculation. Using normal values,

$$\text{Anion gap} = 140 - (104 + 24) = 12 \text{ mEq/L}$$
$$\times (\text{normal range} = 7 - 14 \text{ mEq/L})$$

In reality, an anion gap cannot exist because electroneutrality must be maintained in the body; the sum of all anions must equal the sum of all cations. Therefore,

$$\text{Anion gap} = \text{unmeasured anions} - \text{unmeasured cations}$$

"Unmeasured cations" include K^+, Ca^{2+}, and Mg^{2+}, whereas "unmeasured anions" include all organic anions (including plasma proteins), phosphates, and sulfates. Plasma albumin normally accounts for the largest fraction of the anion gap (about 11 mEq/L). The anion gap decreases by 2.5 mEq/L for every 1 g/dL reduction in plasma albumin concentration. **Any process that increases "unmeasured anions" or decreases "unmeasured cations" will increase the anion gap. Conversely, any process that decreases "unmeasured anions" or increases "unmeasured cations" will decrease the anion gap.**

Mild elevations of plasma anion gap up to 20 mEq/L may not be helpful diagnostically during acidosis, but values >30 mEq/L usually indicate the presence of a high anion gap acidosis (below). Metabolic alkalosis can also produce a high anion gap because of extracellular volume depletion, an increased charge on albumin, and a compensatory increase in lactate production. A low plasma anion gap may be encountered with hypoalbuminemia, bromide or lithium intoxication, and multiple myeloma.

High Anion Gap Metabolic Acidosis

Metabolic acidosis with an increased anion gap is characterized by an increase in relatively strong nonvolatile acids. These acids dissociate into H^+ and their respective anions; the H^+ consumes HCO_3^- to produce CO_2, whereas their anions (conjugate bases) accumulate and take the place of HCO_3^- in extracellular fluid (hence the anion gap increases). Nonvolatile acids can be endogenously produced or ingested.

A. Failure to Excrete Endogenous Nonvolatile Acids

Endogenously produced organic acids are normally eliminated by the kidneys in urine (above). Glomerular filtration rates below 20 mL/min (renal failure) typically result in progressive metabolic acidosis from the accumulation of these acids.

B. Increased Endogenous Nonvolatile Acid Production

Severe tissue hypoxia following hypoxemia, hypoperfusion (ischemia), or an inability to utilize oxygen (cyanide poisoning) can result in *lactic acidosis*. Lactic acid is the end product of the anaerobic

metabolism of glucose (glycolysis) and can rapidly accumulate under these conditions. Decreased utilization of lactate by the liver, and, to a lesser extent by the kidneys, is less commonly responsible for lactic acidosis; causes include hypoperfusion, alcoholism, and liver disease. Lactate levels can be readily measured and are normally 0.3–1.3 mEq/L. Acidosis resulting from D-lactic acid, which is not recognized by α-lactate dehydrogenase (and not measured by routine assays), may be encountered in patients with short bowel syndromes; D-lactic acid is formed by colonic bacteria from dietary glucose and starch and is absorbed systemically.

An absolute or relative lack of insulin can result in hyperglycemia and progressive *ketoacidosis* from the accumulation of β-hydroxybutyric and acetoacetic acids. Ketoacidosis may also be seen following starvation and alcoholic binges. The pathophysiology of the acidosis often associated with severe alcoholic intoxication and nonketotic hyperosmolar coma is complex and may represent a build-up of lactic, keto, or other unknown acids.

Some inborn errors of metabolism, such as maple syrup urine disease, methylmalonic aciduria, propionic acidemia, and isovaleric acidemia, produce a high anion gap metabolic acidosis as a result of accumulation of abnormal amino acids.

C. Ingestion of Exogenous Nonvolatile Acids

Ingestion of large amounts of salicylates frequently results in metabolic acidosis. Salicylic acid and other acid intermediates rapidly accumulate and produce a high anion gap acidosis. Because salicylates also produce direct respiratory stimulation, most adults develop mixed metabolic acidosis with superimposed respiratory alkalosis. Ingestion of methanol (methyl alcohol) frequently produces acidosis and visual disturbances (retinitis). Symptoms are typically delayed until the slow oxidation of methanol by alcohol dehydrogenase produces formic acid, which is highly toxic to the retina. The high anion gap represents the accumulation of many organic acids, including acetic acid. The toxicity of ethylene glycol is also the result of the action of alcohol dehydrogenase to produce glycolic acid. Glycolic acid, the principal cause of the acidosis, is further metabolized to form oxalic acid, which can be deposited in the renal tubules and result in renal failure.

Normal Anion Gap Metabolic Acidosis

Metabolic acidosis associated with a normal anion gap is typically characterized by hyperchloremia. Plasma [Cl^-] increases to take the place of the HCO_3^- ions that are lost. *Hyperchloremic metabolic acidosis* most commonly results from abnormal gastrointestinal or renal losses of HCO_3^-, or from excessive intravenous administration of 0.9% NaCl solution.

Calculation of the anion gap in urine can be helpful in diagnosing a normal anion gap acidosis.

$$\text{Urine anion gap} = ([Na^+] + [K^+]) - [Cl^-]$$

The urine anion gap is normally positive or close to zero. The principal unmeasured urinary cation is normally NH_4^+, which should increase (along with Cl^-) during a metabolic acidosis; the latter results in a negative urinary anion gap. Impairment of H^+ or NH_4^+ secretion, as occurs in renal failure or renal tubular acidosis (below), results in a positive urine anion gap in spite of systemic acidosis.

A. Increased Gastrointestinal Loss of HCO_3^-

7 Diarrhea is a common cause of hyperchloremic metabolic acidosis. Diarrheal fluid contains 20–50 mEq/L of HCO_3^-. Small bowel, biliary, and pancreatic fluids are all rich in HCO_3^-. Loss of large volumes of these fluids can lead to hyperchloremic metabolic acidosis. Patients with ureterosigmoidostomies and those with ileal loops that are too long or that become partially obstructed frequently develop hyperchloremic metabolic acidosis. The ingestion of chloride-containing anion-exchange resins (cholestyramine) or large amounts of calcium or magnesium chloride can result in increased absorption of chloride and loss of bicarbonate ions. These nonabsorbable resins bind bicarbonate ions, whereas calcium and magnesium combine with bicarbonate to form insoluble salts within the intestines.

B. Increased Renal Loss of HCO_3^-

Renal wasting of HCO_3^- can occur as a result of failure to reabsorb filtered HCO_3^- or to secrete adequate amounts of H^+ in the form of titratable acid or ammonium ion. These defects are encountered in patients taking carbonic anhydrase inhibitors, such as acetazolamide, and in those with renal tubular acidosis.

Renal tubular acidosis comprises a group of nonazotemic defects of H^+ secretion by the renal

tubules, resulting in a urinary pH that is too high for the systemic acidemia. These defects may be a result of a primary renal defect or may be secondary to a systemic disorder. The site of the H^+-secreting defect may be in the distal (type 1) or proximal (type 2) renal tubule. Hyporeninemic hypoaldosteronism is commonly referred to as type 4 renal tubular acidosis. With distal renal tubular acidosis, the defect occurs at a site after most of the filtered HCO_3^- has been reclaimed. As a result, there is a failure to acidify the urine, so that net acid excretion is less than the daily net acid production. This disorder is frequently associated with hypokalemia, demineralization of bone, nephrolithiasis, and nephrocalcinosis. Alkali ($NaHCO_3$) therapy (1–3 mEq/kg/d) is usually sufficient to reverse those side effects. With the less common proximal renal tubular acidosis, defective H^+ secretion in the proximal tubule results in massive wasting of HCO_3^-. Concomitant defects in tubular reabsorption of other substances, such as glucose, amino acids, or phosphates, are common. The hyperchloremic acidosis results in volume depletion and hypokalemia. Treatment involves giving alkali (as much as 10–25 mEq/kg per day) and potassium supplements.

C. Other Causes of Hyperchloremic Acidosis

A *dilutional hyperchloremic acidosis* can occur when extracellular volume is rapidly expanded with a bicarbonate-free fluid, such as normal saline. This is a reason to prefer balanced salt solutions over 0.9% saline for fluid resuscitation. The plasma HCO_3^- decreases in proportion to the amount of fluid infused as extracellular HCO_3^- is diluted. Amino acid infusions (parenteral hyperalimentation) contain organic cations in excess of organic anions and can produce hyperchloremic metabolic acidosis because chloride is commonly used as the anion for the cationic amino acids. Lastly, the administration of excessive quantities of chloride-containing acids, such as ammonium chloride or arginine hydrochloride (usually given to treat a metabolic alkalosis), can cause hyperchloremic metabolic acidosis.

Treatment of Metabolic Acidosis

Several general measures can be undertaken to control the severity of acidemia until the underlying processes are corrected. Any respiratory component of the acidemia should be corrected. Respiration should be controlled, if necessary; a $Paco_2$ in the low 30s may be desirable to partially return pH to normal. If arterial blood pH remains below 7.20, alkali therapy, usually in the form of $NaHCO_3$ (usually a 7.5% solution), may be necessary. $Paco_2$ may transiently rise as HCO_3^- is consumed by acids (emphasizing the need to control ventilation in severe acidemia). The amount of $NaHCO_3$ given is decided empirically as a fixed dose (1 mEq/kg) or is derived from the base excess and the calculated bicarbonate space (see below). In either case, serial blood gas measurements are mandatory to avoid complications (eg, overshoot alkalosis and sodium overload) and to guide further therapy. Raising arterial pH to >7.25 is usually sufficient to overcome the adverse physiological effects of the acidemia. Profound or refractory acidemia may require acute hemodialysis with a bicarbonate dialysate.

The routine use of large amounts of $NaHCO_3$ in treating cardiac arrest and low flow states is not recommended. Paradoxical intracellular acidosis may occur, particularly when CO_2 elimination is impaired, because the CO_2 formed readily enters cells, but the bicarbonate ion does not. Alternate buffers that do not produce CO_2, such as Carbicarb™ or tromethamine (THAM), may be theoretically preferable, but are unproven clinically.

Specific therapy for diabetic ketoacidosis includes replacement of the existing fluid deficit (as a result of a hyperglycemic osmotic diuresis) first, as well as insulin, potassium, phosphate, and magnesium. The treatment of lactic acidosis should be directed first at restoring adequate oxygenation and tissue perfusion. Alkalinization of the urine with $NaHCO_3$ to a pH greater than 7.0 increases elimination of salicylate following salicylate poisoning. Treatment options for ethanol or ethylene glycol intoxication include ethanol infusion or fomepizole administration, which competitively inhibit alcohol dehydrogenase and hemodialysis or hemofiltration.

Bicarbonate Space

The bicarbonate space is defined as the volume to which HCO_3^- will distribute when it is given intravenously. Although this theoretically should equal the extracellular fluid space (approximately 25% of body

weight), in reality, it ranges anywhere between 25% and 60% of body weight, depending on the severity and duration of the acidosis. This variation is at least partly related to the amount of intracellular and bone buffering that has taken place.

Example: Calculate the amount of $NaHCO_3$ necessary to correct a base deficit (BD) of –10 mEq/L for a 70-kg man with an estimated HCO_3^- space of 30%:

$$NaHCO_3 = BD \times 30\% \times \text{body weight in L}$$
$$NaHCO_3 = -10\ \text{mEq/L} \times 30\% \times 70\ \text{L} = 210\ \text{mEq}$$

In practice, only 50% of the calculated dose (105 mEq) is usually given, after which another blood gas is measured.

ANESTHETIC CONSIDERATIONS IN PATIENTS WITH ACIDOSIS

Acidemia can potentiate the depressant effects of most sedatives and anesthetic agents on the central nervous and circulatory systems. Because most opioids are weak bases, acidosis can increase the fraction of the drug in the nonionized form and facilitate penetration of the opioid into the brain. Increased sedation and depression of airway reflexes may predispose to pulmonary aspiration. The circulatory depressant effects of both volatile and intravenous anesthetics can also be exaggerated. Moreover, any agent that rapidly decreases sympathetic tone can potentially allow unopposed circulatory depression in the setting of acidosis. Halothane is more arrhythmogenic in the presence of acidosis. Succinylcholine should generally be avoided in acidotic patients with hyperkalemia to prevent further increases in plasma $[K^+]$.

Alkalosis

PHYSIOLOGICAL EFFECTS OF ALKALOSIS

Alkalosis increases the affinity of hemoglobin for oxygen and shifts the oxygen dissociation curve to the left, making it more difficult for hemoglobin to give up oxygen to tissues. Movement of H^+ out of cells in exchange for the movement of extracellular K^+ into cells can produce hypokalemia. Alkalosis increases the number of anionic binding sites for Ca^{2+} on plasma proteins and can therefore decrease ionized plasma $[Ca^{2+}]$, leading to circulatory depression and neuromuscular irritability. Respiratory alkalosis reduces cerebral blood flow, increases systemic vascular resistance, and may precipitate coronary vasospasm. In the lungs, respiratory alkalosis increases bronchial smooth muscle tone (bronchoconstriction), but decreases pulmonary vascular resistance.

RESPIRATORY ALKALOSIS

Respiratory alkalosis is defined as a primary decrease in $Paco_2$. The mechanism is usually an inappropriate increase in alveolar ventilation relative to CO_2 production. Table 50–5 lists the most common causes of respiratory alkalosis. Plasma $[HCO_3^-]$ usually

TABLE 50–5 Causes of respiratory alkalosis.

Central stimulation
Pain
Anxiety
Ischemia
Stroke
Tumor
Infection
Fever
Drug-induced
Salicylates
Progesterone (pregnancy)
Analeptics (doxapram)
Peripheral stimulation
Hypoxemia
High altitude
Pulmonary disease
Congestive heart failure
Noncardiogenic pulmonary edema
Asthma
Pulmonary embolism
Severe anemia
Unknown mechanism
Sepsis
Metabolic encephalopathies
Iatrogenic
Ventilator-induced

decreases 2 mEq/L for each 10 mm Hg acute decrease in $Paco_2$ below 40 mm Hg. The distinction between acute and chronic respiratory alkalosis is not always made, because the compensatory response to chronic respiratory alkalosis is quite variable: plasma [HCO_3^-] decreases 2–5 mEq/L for each 10 mm Hg decrease in $Paco_2$ below 40 mm Hg.

Treatment of Respiratory Alkalosis

Correction of the underlying process is the only treatment for respiratory alkalosis. For severe alkalemia (arterial pH >7.60), intravenous hydrochloric acid, arginine chloride, or ammonium chloride may be indicated (see below).

METABOLIC ALKALOSIS

Metabolic alkalosis is defined as a primary increase in plasma [HCO_3^-]. Most cases of metabolic alkalosis can be divided into (1) those associated with NaCl deficiency and extracellular fluid depletion, often described as chloride sensitive, and (2) those associated with enhanced mineralocorticoid activity, commonly referred to as chloride-resistant (Table 50–6).

TABLE 50–6 Causes of metabolic alkalosis.

Chloride-sensitive
Gastrointestinal
Vomiting
Gastric drainage
Chloride diarrhea
Villous adenoma
Renal
Diuretics
Posthypercapnic
Low chloride intake
Sweat
Cystic fibrosis
Chloride-resistant
Increased mineralocorticoid activity
Primary hyperaldosteronism
Edematous disorders (secondary hyperaldosteronism)
Cushing's syndrome
Licorice ingestion
Bartter's syndrome
Severe hypokalemia
Miscellaneous
Massive blood transfusion
Acetate-containing colloid solutions
Alkaline administration with renal insufficiency
Alkali therapy
Combined antacid and cation-exchange resin therapy
Hypercalcemia
Milk-alkali syndrome
Bone metastases
Sodium penicillins
Glucose feeding after starvation

Chloride-Sensitive Metabolic Alkalosis

Depletion of extracellular fluid causes the renal tubules to avidly reabsorb Na^+. Because not enough Cl^- is available to accompany all of the Na^+ ions reabsorbed, increased H^+ secretion must take place to maintain electroneutrality. In effect, HCO_3^- ions that might otherwise have been excreted are reabsorbed, resulting in metabolic alkalosis. Physiologically, maintenance of extracellular fluid volume is therefore given priority over acid–base balance. Because secretion of K^+ ion can also maintain electroneutrality, potassium secretion is also enhanced. Moreover, hypokalemia augments H^+ secretion (and HCO_3^- reabsorption) and will also propagate metabolic alkalosis. Indeed, severe hypokalemia alone can cause alkalosis. Urinary chloride concentrations during a chloride-sensitive metabolic alkalosis are characteristically low (<10 mEq/L).

Diuretic therapy is the most common cause of chloride-sensitive metabolic alkalosis. Diuretics, such as furosemide, ethacrynic acid, and thiazides, increase Na^+, Cl^-, and K^+ excretion, resulting in NaCl depletion, hypokalemia, and usually mild metabolic alkalosis. Loss of gastric fluid is also a common cause of chloride-sensitive metabolic alkalosis. Gastric secretions contain 25–100 mEq/L of H^+, 40–160 mEq/L of Na^+, about 15 mEq/L of K^+, and about 200 mEq/L of Cl^-. Vomiting or continuous loss of gastric fluid by gastric drainage (nasogastric suctioning) can result in marked metabolic alkalosis, extracellular volume depletion, and hypokalemia. Rapid normalization of $Paco_2$ after plasma [HCO_3^-] has risen in chronic respiratory acidosis results in metabolic alkalosis (posthypercapnic alkalosis; see above). Infants being fed formulas containing Na^+ without chloride readily develop metabolic alkalosis because of the increased H^+ (or K^+) secretion that must accompany sodium absorption.

Chloride-Resistant Metabolic Alkalosis

Increased mineralocorticoid activity commonly results in metabolic alkalosis, even when it is not associated with extracellular volume depletion. Inappropriate increases in mineralocorticoid activity cause sodium retention and expansion of extracellular fluid volume. Increased H^+ and K^+ secretion takes place to balance enhanced mineralocorticoid-mediated sodium reabsorption, resulting in metabolic alkalosis and hypokalemia. Urinary chloride concentrations are typically greater than 20 mEq/L in such cases.

Other Causes of Metabolic Alkalosis

Metabolic alkalosis is rarely encountered in patients given even large doses of $NaHCO_3$ unless renal excretion of HCO_3^- is impaired. The administration of large amounts of blood products and some plasma protein-containing colloid solution frequently results in metabolic alkalosis. The citrate, lactate, and acetate contained in these fluids are converted by the liver into HCO_3^-. Patients receiving high doses of sodium penicillin (particularly carbenicillin) can develop metabolic alkalosis. Because penicillins act as nonabsorbable anions in the renal tubules, increased H^+ (or K^+) secretion must accompany sodium absorption. For reasons that are not clear, hypercalcemia that results from nonparathyroid causes (milk-alkali syndrome and bone metastases) is also often associated with metabolic alkalosis. The pathophysiology of alkalosis following refeeding is also unknown.

Treatment of Metabolic Alkalosis

As with other acid–base disorders, correction of metabolic alkalosis is never complete until the underlying disorder is treated. When ventilation is controlled, any respiratory component contributing to alkalemia should be corrected by decreasing minute ventilation to normalize $Paco_2$. The treatment of choice for chloride-sensitive metabolic alkalosis is administration of intravenous saline (NaCl) and potassium (KCl). H_2-blocker therapy is useful when excessive loss of gastric fluid is a factor. Acetazolamide may also be useful in edematous patients. Alkalosis associated with primary increases in mineralocorticoid activity readily responds to aldosterone antagonists (spironolactone). When arterial blood pH is greater than 7.60, treatment with intravenous hydrochloric acid (0.1 mol/L), ammonium chloride (0.1 mol/L), arginine hydrochloride, or hemodialysis should be considered.

ANESTHETIC CONSIDERATIONS IN PATIENTS WITH ALKALEMIA

Respiratory alkalosis seems to prolong the duration of opioid-induced respiratory depression; this effect may result from increased protein binding of opioids. Cerebral ischemia can occur from marked reduction in cerebral blood flow during respiratory alkalosis, particularly during hypotension. The combination of alkalemia and hypokalemia can precipitate severe atrial and ventricular arrhythmias. Potentiation of nondepolarizing neuromuscular blockade is reported with alkalemia, but may be more directly related to concomitant hypokalemia.

DIAGNOSIS OF ACID–BASE DISORDERS

Interpretation of acid–base status from analysis of blood gases requires a systematic approach. A recommended approach follows (Figure 50–6):

1. Examine arterial pH: Is acidemia or alkalemia present?
2. Examine $Paco_2$: Is the change in $Paco_2$ consistent with a respiratory component?
3. If the change in $Paco_2$ does not explain the change in arterial pH, does the change in $[HCO_3^-]$ indicate a metabolic component?
4. Make a tentative diagnosis (see Table 50–1).
5. Compare the change in $[HCO_3^-]$ with the change in $Paco_2$. Does a compensatory response exist (Table 50–7)? Because arterial pH is related to the ratio of $Paco_2$ to $[HCO_3^-]$, both respiratory and renal compensatory mechanisms are always such that $Paco_2$ and $[HCO_3^-]$ change in the same direction.

TABLE 50–7 Normal compensatory responses in acid–base disturbances.

Disturbance	Response	Expected Change
Respiratory acidosis		
Acute	↑ $[HCO_3^-]$	1 mEq/L/10 mm Hg increase in $Paco_2$
Chronic	↑ $[HCO_3^-]$	4 mEq/L/10 mm Hg increase in $Paco_2$
Respiratory alkalosis		
Acute	↓ $[HCO_3^-]$	2 mEq/L/10 mm Hg decrease in $Paco_2$
Chronic	↓ $[HCO_3^-]$	4 mEq/L/10 mm Hg decrease in $Paco_2$
Metabolic acidosis	↓ $Paco_2$	1.2 × the decrease in $[HCO_3^-]$
Metabolic alkalosis	↑ $Paco_2$	0.7 × the increase in $[HCO_3^-]$

A change in opposite directions implies a mixed acid–base disorder.

6. If the compensatory response is more or less than expected, by definition, a mixed acid–base disorder exists.
7. Calculate the plasma anion gap in the case of metabolic acidosis.
8. Measure urinary chloride concentration in the case of metabolic alkalosis.

An alternative approach that is rapid, but perhaps less precise, is to correlate changes in pH with changes in CO_2 or HCO_3. For a respiratory disturbance, every 10 mm Hg change in CO_2 should change arterial pH by approximately 0.08 U in the opposite direction. During metabolic disturbances, every 6 mEq change in HCO_3 also changes arterial pH by 0.1 in the same direction. If the change in pH exceeds or is less than predicated, a mixed acid–base disorder is likely to be present.

MEASUREMENT OF BLOOD GAS TENSIONS & pH

Values obtained by routine blood gas measurement include oxygen and carbon dioxide tensions (Po_2 and Pco_2), pH, $[HCO_3^-]$, base excess, hemoglobin, and the percentage oxygen saturation of hemoglobin. As a rule, only Po_2, Pco_2, and pH are measured. Hemoglobin and percentage oxygen saturation are measured with a cooximeter. $[HCO_3^-]$ is derived using the Henderson–Hasselbalch equation and base excess from the Siggaard–Andersen nomogram.

Sample Source & Collection

Arterial blood samples are most commonly utilized clinically, though capillary or venous blood can be used if the limitations of such samples are recognized. Oxygen tension in venous blood (normally 40 mm Hg) reflects tissue extraction, not pulmonary function. Venous Pco_2 is usually 4–6 mm Hg higher than $Paco_2$. Consequently, venous blood pH is usually 0.05 U lower than arterial blood pH. Despite these limitations, venous blood is often useful in determining acid–base status. Capillary blood represents a mixture of arterial and venous blood, and the values obtained reflect this fact. Samples are usually collected in heparin-coated syringes and should be analyzed as soon as possible. Air bubbles should be eliminated, and the sample should be capped and placed on ice to prevent significant uptake of gas from blood cells or loss of gases to the atmosphere. Although heparin is highly acidic, excessive amounts of heparin in the sample syringe usually lower pH only minimally, but decrease Pco_2 in direct proportion to percentage dilution and have a variable effect on Po_2.

Temperature Correction

11 Changes in temperature affect Pco_2, Po_2, and pH. Decreases in temperature lower the partial pressure of a gas in solution—even though the total gas content does not change—because gas solubility is inversely proportionate to temperature. Both Pco_2 and Po_2 therefore decrease during hypothermia, but pH increases because temperature does not appreciably alter $[HCO_3^-]$: $Paco_2$ decreases, but $[HCO_3^-]$ is unchanged. Because blood gas tensions and pH are always measured at 37°C, controversy exists over whether to correct the measured values to the patient's actual temperature. "Normal" values at temperatures other than 37°C are not known. Many clinicians use the measurements at 37°C directly ("α-stat"), regardless of the patient's actual temperature (see Chapter 22).

CASE DISCUSSION

A Complex Acid–Base Disturbance

A 1-month-old male infant with an anorectal malformation undergoes anoplasty. Postoperatively, he is found to be in congestive heart failure resulting from coarctation of the aorta. He is noted to have tachypnea, decreased urinary output, poor peripheral perfusion, hepatomegaly, and cardiomegaly. Following tracheal intubation, the infant is placed on a ventilator (pressure support ventilation, fraction of inspired oxygen [F_{IO_2}] = 1.0). Initial arterial blood gas, hemoglobin, and electrolyte measurements are as follows:

P_{aCO_2} = 11 mm
pH = 7.47
P_{aO_2} = 209 mm Hg
Calculated [HCO_3^-] = 7.7 mEq/L
BD = –14.6 mEq/L
Hb = 9.5 g/Dl
[Na^+] = 135 mEq/L
[Cl^-] = 95 mEq/L
[K^+] = 5.5 mEq/L
[Total CO_2] = 8 mEq/L

Note that the [total CO_2] normally measured with electrolytes includes both plasma [HCO_3^-] and dissolved CO_2 in plasma.

What is the acid–base disturbance?

Using the approach described above, the patient clearly has an alkalosis (pH >7.45), which is at least partly respiratory in origin (P_{aCO_2} <40 mm Hg). Because P_{aCO_2} has decreased by nearly 30 mm Hg, we would expect [HCO_3^-] to be 18 mEq/L:

$$(40 - 10) \times \frac{2 \text{ mEq/L}}{10} = 6 \text{ mEq/L below 24 mEq/L}$$

In fact, the patient's [HCO_3^-] is nearly 10 mEq/L less than that! The patient therefore also has a mixed acid–base disturbance: primary respiratory alkalosis and primary metabolic acidosis. Note that the difference between the patient's [HCO_3^-] and the [HCO_3^-] expected for a pure respiratory alkalosis roughly corresponds to the base excess.

What are likely causes of these disturbances?

The respiratory alkalosis is probably the result of congestive heart failure, whereas the metabolic acidosis results from lactic acidosis secondary to poor perfusion. The latter is suggested by the calculated plasma anion gap:

$$\text{Anion gap} = 135 - (95 + 8) = 32 \text{ mEq/L}$$

The lactate level was in fact measured and found to be elevated at 14.4 mEq/L. It is probable that fluid overload precipitated the congestive heart failure.

What treatment is indicated?

Treatment should be directed at the primary process, (ie, the congestive heart failure). The patient was treated with diuresis and inotropes.

Following diuresis, the patient's tachypnea has improved, but perfusion still seems to be poor. Repeat laboratory measurements are as follows (F_{IO_2} = 0.5):

P_{aCO_2} = 23 mm Hg
pH = 7.52
P_{aO_2} = 136 mm Hg
Calculated [HCO_3^-] = 18 mEq/L
BD = –3.0 mEq/L
Hb = 10.3 g/dL
[Na^+] = 137 mEq/L
[Cl^-] = 92 mEq/L
[K^+] = 3.9 mEq/L
[Total CO_2] = 18.5 mEq/L

What is the acid–base disturbance?

Respiratory alkalosis is still present, whereas the BD seems to have improved. Note that the hemoglobin concentration has increased slightly, but [K^+] has decreased as a result of the diuresis. With the new P_{aCO_2}, the expected [HCO_3^-] should be 20.6 mEq/L:

$$(40 - 10) \times \frac{2 \text{ mEq/L}}{10} = 3.4 \text{ mEq/L below 24 mEq/L}$$

Therefore, the patient still has metabolic acidosis because the [HCO_3^-] is 2 mEq/L less. Note again

that this difference is close to the given BD and that the anion gap is still high:

$$\text{Anion gap} = 137 - (92 + 18) = 27$$

The repeat lactate measurement is now 13.2 mEq/L.

The high anion gap and lactate level explain why the patient is still not doing well and indicate that a new process is masking the severity of the metabolic acidosis (which is essentially unchanged).

Given the clinical course, it is likely that the patient now has a triple acid–base disorder: respiratory alkalosis, metabolic acidosis, and now metabolic alkalosis. The latter probably resulted from hypovolemia secondary to excessive diuresis (chloride-sensitive metabolic alkalosis). Note also that the metabolic alkalosis is nearly equal in magnitude to the metabolic acidosis.

The patient was subsequently given packed red blood cells in saline, and within 24 hr all three disorders began to improve:

$Paco_2 = 35$ mm Hg
pH = 7.51
$Pao_2 = 124$ mm Hg
Calculated $[HCO_3^-] = 26.8$ mEq/L
Base excess = +5.0 mEq/L
Hb = 15 g/dL
$[Na^+] = 136$ mEq/L
$[Cl^-] = 91$ mEq/L
$[K^+] = 3.2$ mEq/L
[Total CO_2] = 27 mEq/L
Lactate = 2.7 mEq/L

Outcome

The respiratory alkalosis and the metabolic acidosis have now resolved, and the metabolic alkalosis is now most prominent.

Intravenous KCl replacement and a small amount of saline were judiciously given, followed by complete resolution of metabolic alkalosis. The patient subsequently underwent surgical correction of the coarctation.

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