CHAPTER 42  BLOOD GAS ANALYSIS AND ACID-BASE DISORDERS

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Acid-base physiology is among the most complex topics in clinical medicine. Disturbances of this system are common in the critically ill, and important clinical decisions based on measured acid-base parameters occur on a daily, even hourly basis. Therefore, a sound understanding of acid-base physiology is mandatory for the intensivist.

The field is full of complicated concepts and equations that, at times, have only limited applicability to the practicing clinician due to the failure of any current model to faithfully and completely recapitulate the complex buffering process in vivo. The purpose of this chapter is to provide a conceptual introduction to the current approach to acid-base physiology, while de-emphasizing calculations and formulas. The goal is not to know how to derive the commonly used formulas, but rather to understand the meaning of measured and derived acid-base parameters that are used clinically, and how they may—or may not—help in answering three essential questions in the critically ill patient with an acid-base disturbance:

■ What acid-base disorder(s) is (are) present?
■ How severe is the disturbance?
■ What is the etiology underlying the derangements?

MAINTENANCE OF THE ARTERIAL pH AND ACID-BASE BALANCE: BUFFERING AND ACID EXCRETION

Buffering of acids is the first line of defense against perturbations in systemic pH. Recall that the pH is a logarithmic scale that is a function of the concentration of H$_2$O$^+$ species in solution (H$^+$ will be used interchangeably with H$_2$O$^+$ in this chapter). In neutral solution, [H$^+$] is $10^{-7}$ M and [OH$^-$] is $10^{-7}$ M; this satisfies the dissociation constant for water:

\[ \text{H}_2\text{O} \leftrightarrow \text{H}^+ + \text{OH}^- \quad K_{\text{eq}} = 10^{-14} \quad [1] \]

The pH, defined by Sörenson, is the negative log of the concentration of H$^+$. Therefore, in neutral solution, the pH is 7. This is a very small concentration of [H$^+$], and therefore, addition of small amounts of [H$^+$] to water will lead to significant fluctuations in pH. For example, we will consider an experiment performed by Jorgensen and Astrup [1] in which 1.25 mEq/L of HCl is added to hemolyzed human blood. Assuming that the blood contained no buffers (i.e., if the blood was imagined to be a container of water that starts at a neutral pH), the expected pH following such an infusion would be calculated by the following:

\[ 1.25 \times 10^{-3} \text{ moles (number of moles of H}^+ \text{ added)} + 1 \times 10^{-7} \text{ moles (number of moles of H}^+ \text{ in neutral water)} = 1.25 \times 10^{-3} \text{ moles/L}. \]

Taking the negative log yields a pH of 1.9; this would be the expected pH if there were not buffers available. However, following the infusion, the pH of the blood changed approximately 0.2 pH points. This means that less than 1/10,000th of the H$^+$ added remains unbound in the blood. This illustrates the tremendous buffering capacity of the blood. A buffer can be thought of as a substance that, when present in solution, takes up [H$^+$] and therefore resists change in pH when [H$^+$] is added. The overall buffering system of the body is complex and includes several components. These are listed in Table 42.1. The most important system is the carbon dioxide-bicarbonate system, which is the principal buffer in the extracellular fluid. This buffering system is also very important clinically since it is the only buffering system where the two components (acid and conjugate base) are readily measurable in the extracellular fluid (ECF). Buffers work by binding the free H$^+$ as the conjugate base, which is a weak acid.

Buffers allow the body to resist acute changes in pH; however, buffering capacity will eventually be depleted if acid is continually added. For example, in humans, the net fixed acid production is approximately 70 to 100 mmol/day. It is the excretion of the daily acid load that ultimately allows the body to maintain acid-base balance. The excretion of the daily acid load occurs through two distinct mechanisms: (a) the renal excretion of fixed acid and (b) the respiratory excretion of volatile acid (i.e., carbon dioxide). Through the interconversion of bicarbonate, carbonic acid, and carbon dioxide, fixed and volatile acids can be buffered until they can be excreted through the urine or respiration (Fig. 42.1). In the lung, CO$_2$ is released, which ultimately leads to more H$^+$ reacting with HCO$_3^-$ to generate water and more CO$_2$. In the kidneys, the entire filtered load of bicarbonate is—in order to avoid losing base—reabsorbed. When the kidney excretes one H$^+$ in the urine, one “new” HCO$_3^-$ is generated. These two processes are both important in the excretion of the acid load, and modulation of these processes is also important in compensating for acid-base disturbances.

Urinary Excretion of Fixed Acids

In the reabsorption of bicarbonate, the corresponding H$^+$ produced in the process must be excreted in the urine. As most bicarbonate reabsorption occurs in the proximal tubule, the renal
secretion of H⁺ is ten times greater in the proximal tubule—approximately 4,000 mmol/day—as compared with the distal tubule—approximately 400 mmol/day. However, in the distal tubule, there is a much higher luminal–intracellular H⁺ gradient than that seen in the proximal tubule—a ratio of approximately 500:1. This high gradient is due to active secretion of H⁺ into the tubule. If the excretion of acid occurred in the absence of buffers, the ability to excrete acid in the urine would be limited. In much the same way that the body can absorb large amounts of acid without much change in pH, the kidney accomplishes a similar task in the excretion of large amounts of fixed acid through the use of buffers in the urine with modestly acidic pH (approximately 5.5 under maximal conditions).

The excretion of H⁺ in the urine occurs with different conjugate bases, which are grouped as titratable acids—mostly phosphates—and nontitratable acids—ammonium. The excretion of titratable acid has a limit that is, for the most part, dependent on the filtered load of phosphate, as this is the main buffer for nontitratable acids. However, the kidney can generate its own buffer—ammonia; moreover, the renal capacity to generate ammonia and to excrete acid as ammonium under normal conditions is substantial. This capacity may be significantly up-regulated in the face of systemic acidosis. Ammonia is produced in the kidney, traverses the plasma membrane, and is “trapped” in the tubular lumen because the low pH drives the following reaction to the right, as the plasma membrane is much less permeable to the charged species ammonia.

\[
\text{NH}_4^+ + \text{H}^+ \rightarrow \text{NH}_3\text{H}^+
\]  

Therefore, ammonia–ammonium acts as a urinary buffer system, allowing the elimination of one H⁺ for nearly every ammonia produced. The buffering of acid in the urine, especially via ammonium, allows for substantial amounts of acid to be excreted without generating excessively acidic urine. Titratable acids make up a relatively small proportion of the acid excreted and do not increase to near the degree that non-titratable acidity (ammonium) increases in the face of systemic acidosis.

The kidney, through active secretion of H⁺ in the distal tubule, is able to achieve an H⁺ concentration gradient of approximately 100:1 between the urine and the intracellular space of the tubular epithelial cells. This corresponds to the maximally acidic urine of approximately pH 5. Without any buffers, it would require 7,000 liters of urine to excrete a daily load of 70 mEq of acid in buffer-free urine of pH 5.0! Therefore, urinary buffers are very important in allowing the body to excrete the daily fixed acid load. Chronic metabolic acidosis stimulates the renal production of ammonia as a physiologic response; this response reaches its maximum production after several days.

### Assessing Urinary Acid Excretion

In the presence of systemic acidosis, the kidney will compensate by increasing the excretion of fixed acids, mainly in the nontitratable form (i.e., ammonium). The increase in ammonium—which is a cation; recall that ammonia is predominantly in the form of NH₄⁺ at a pH of 7 or below—is excretion results in a perturbation in the electrolytes present in the urine. This manifests as a change in the urine anion gap where ammonium is the unmeasured anion. The urinary anion gap is a useful clinical test that can be used to gauge the amount of ammonium excreted in the urine without directly measuring it (2). It may be used to indirectly estimate the amount of ammonium in the urine and is calculated using the following formula:

\[
[\text{Na}^+ + [\text{K}^+]] - [\text{Cl}^-] = \text{urinary anion gap}
\]

The urine anion gap is assessed in patients with metabolic acidosis and is used to determine if the renal response to the systemic acidosis is appropriate. In other words, the urine anion gap answers the question, Are the kidneys excreting the acid load appropriately or are the kidneys part of the acid-base problem? If the kidneys are excreting the acid load appropriately, there must be a nonrenal source of the acidosis—for example, diarrhea. Because ammonium is not a measured cation in this equation, the presence of significant amounts of ammonium causes an abundance of chloride relative to the measured cationic constituents of the urine (sodium and potassium). Therefore, if there is a high level of ammonium in the urine, the urine anion gap will be negative. The relationship between the amount of ammonium in the urine and the urine anion gap is illustrated in Figure 42.2. As a general rule, a negative urinary anion gap suggests that the kidney is excreting ammonium in the urine. This is a continuous variable, and the more negative the value, the greater the renal response. In the face of systemic acidosis, if the renal response is appropriate, there will be a high amount of ammonium in the urine, and the urine anion gap will be highly negative. This is sometimes referred to as a negative net urinary charge; however, this is a bit misleading because the urine is, of course, electroneutral; it is simply because we are not considering the contribution of ammonium that the net urinary charge seems negative. A

### TABLE 42.1

<table>
<thead>
<tr>
<th>Acid</th>
<th>Conjugate base</th>
</tr>
</thead>
<tbody>
<tr>
<td>H₂CO₃</td>
<td>HCO₃⁻</td>
</tr>
<tr>
<td>Albumin-H</td>
<td>Albumin⁺⁺⁺</td>
</tr>
<tr>
<td>H₂PO₄</td>
<td>HPO₄⁻</td>
</tr>
<tr>
<td>High-H</td>
<td>High⁺⁺⁺⁺</td>
</tr>
</tbody>
</table>

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

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

\[\text{H}^+ + \text{HPO}_4^{2-} \rightarrow \text{H}_2\text{O} + \text{PO}_4^{3-}\]

\[\text{H}^+ + \text{HSO}_4^- \rightarrow \text{H}_2\text{O} + \text{SO}_4^{2-}\]

\[\text{H}^+ + \text{Non-titratable acid (NH}_4^+)\]

**FIGURE 42.1.** Normal acid-base homeostasis.
Chapter 42: Blood Gas Analysis and Acid-base Disorders

**RELATIONSHIP BETWEEN SYSTEMIC pH AND BUFFER CONCENTRATIONS: AN EVOLVING CONCEPT**

We have previously noted that, because of the presence of buffers, addition of—or conversely, removal of—[H+] to the body does not produce the expected change in pH that would occur in unbuffered solutions. In this section, we will address the question of the relationship between pH and the concentrations of buffers.

**Traditional Paradigm**

One of the earliest observations in this field, and still very important clinically today, was the observation by Henderson that the concentration of H+ in the blood was dependent upon the concentration of CO2, HCO3-, and CO32-. The Henderson-Hasselbalch equation was later derived by using the Sorenson convention of expressing [H+] as pH. This relationship is usually expressed as:

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

As the [H2CO3] in plasma is related to the partial pressure of CO2, this relationship can be rewritten as:

\[ \text{pH} = 6.1 + \log \left( \frac{[\text{HCO}_3^-]}{0.3 \times PCO_2} \right) \]

This relationship became very meaningful clinically as the methodologies to measure the key variables pH, HCO3-, and PCO2 were developed. Now the concentration of the constituents of the principal buffering system could be related to the systemic pH. This allowed, among other things, a framework around which to understand how much alkali must be added in order to affect systemic pH in an acidic patient. However, it became apparent that the relationship between pH, HCO3-, and PCO2 failed to completely describe the relative contributions of fixed acids and volatile acids (the respiratory component) to acidosis. This is because PCO2 and HCO3- are not truly independent of each other, as changes in one will lead to changes in the other, as will be seen later, according to the relationship given in Eq. 31. Additionally, it was noted that no single value accurately quantifies the degree of fixed acids present during metabolic acidosis or alkalosis. The degree of acidemia could be considered as simply the pH, as the pH is ultimately a composite of the net respiratory and metabolic components of the acid-base disturbance. However, because of the buffering capacity of the body, a quantification of the fixed acid derangement is not explained by this relationship alone.

Historically, several theoretical frameworks have been developed in an attempt to overcome this lack of exactitude in the concepts of quantification and etiology. The first obstacle to accurate quantification is the reality that the HCO3- system was not the only quantitatively important buffering system to be considered. The erythrocyte membrane is permeable to H+, and therefore H+ can diffuse inside the cell and hemoglobin can act as an intracellular buffer. Other buffering systems, such as phosphate and circulating proteins, can act as clinically relevant buffers as well (Table 42.1). By quantitative chemistry, the pH of a system is dependent on the relative concentrations of the acids and conjugate bases of all of the buffering systems present. Clinically, we measure accurately the concentration of the acid (CO2) and conjugate base (HCO3-), of only one buffering system. Therefore, perturbations in the other buffering systems are not accounted for in the framework that only considers carbonate species.

Another major complicating factor is the fact that the human body is not a closed system. CO2 is both continually being generated in the tissues and continually excreted through the respiratory system. Therefore, changes in CO2 can, and frequently do, occur very rapidly in humans as the respiratory rate increases or decreases. Additionally, the kidney can modulate the production of HCO3-, to adjust the HCO3- concentration and, albeit at a much slower pace than respiratory effects, change the pH. If the rate of HCO3- production exceeds consumption of HCO3-, the serum bicarbonate increases; conversely, if it is below the rate of production, HCO3- will decrease. What this means is that the concentration of the measured parameters—HCO3- and PCO2—are not just dependent on the inciting insult—the disease process—that caused them to change, but also on the body's response to that change (i.e., compensation).
Base Excess and Standard Base Excess

The change in pH of a system is dependent on both the amount of base added and the buffer capacity. As acid is added to a buffered solution, the buffer capacity, one molecule of conjugate base of the buffer is consumed. Therefore, assessing changes in concentrations of the conjugate base is more helpful than the degree of change in the pH in quantifying the degree of fixed acids present. The difficulty in describing the buffering system of a patient is the inaccessibility for measurement of a fair proportion of the buffers (Table 42.1), especially intracellular buffers. Several expressions have been proposed to quantify the degree of acid loading based on the change in body buffers. The most commonly used concept in this regard is the base excess. Siggard-Andersen defined the base excess of blood as the number of mEq of acid (or base) needed to titrate 1 L of blood to a pH of 7.4 at 37°C with a PCO₂ of 40 mm Hg; note that this is an experimentally arrived upon value. The standard base excess is the base excess corrected for changes in hemoglobin, recalling that hemoglobin is an important intracellular buffer. The base excess can be considered as a measurement of the "metabolic" portion of an acid-base disturbance since the concentration of CO₂ is being held constant at a normal level. The base excess has become a widely used parameter to characterize acid-base disturbances. One major drawback of the base excess is that it is a measured parameter of whole blood. However, in vivo, the blood is circulating and comes into contact with other tissues that can serve to provide buffering capacity. In clinical practice, however, the base excess is not measured by titration; rather, it is calculated from a nomogram that assumes normal nonbicarbonate buffers. This simplification, while allowing the widespread application of the base excess, has, in one sense, the drawback of losing the actual measurement of nonbicarbonate buffers that occurs when blood is directly titrated. Despite potential drawbacks, the base excess is very useful in describing the magnitude of a metabolic disturbance on the concentration of buffers and has become a widely used parameter to assess the degree of a metabolic disturbance.

The Anion Gap

The anion gap is calculated by taking the difference between the concentrations of the measured cations and the measured anions; it takes on a value of approximately 8 to 12 mEq/L in healthy individuals [1-3]. The anion gap is an indirect estimation of the amount of "extra anions" in the circulation. The anion gap normally reflects the serum albumin (negatively charged at physiologic pH) [6], phosphate, and other minor anions [7]. The unmeasured anions that may, under pathologic situations, lead to an increased anion gap can be either endogenous substances normally found in lower levels such as lactate or α-hydroxybutyrate or exogenous substances such as salicylates. The anion gap is calculated using the following formula:

\[
\text{[Na}^+\text{]} - (\text{[Cl}^-\text{]} + \text{[HCO}_3^-\text{]}) \tag{5}
\]

Metabolic acidosis is subdivided into anion gap and non-anion gap metabolic acidosis based on the value of the anion gap. In general, metabolic acidosis is caused either by the loss of bicarbonate—as in gastrointestinal losses or impaired renal acid excretion—or by a gain of acid associated with an unmeasured anion. The gain of acid is usually associated with the presence of an unmeasured anion (e.g., lactic acid); an exception might be intake of HCl. The extra base present—again, using the example of lactate—leads to a greater difference between the measured anions and cations, and therefore a greater anion gap. There is a wide range for the normal anion gap (4) and, in our experience, a normal anion gap is approximately 8 to 10 mEq/L—slightly lower than the value referenced above—but this may vary with methodologies in various labs; thus, checking with the local laboratory is imperative (4,8). When interpreting the anion gap, caution must be exercised, as there is significant variation in the anion gap and it can be influenced by many conditions other than metabolic acidosis.

Hypoalbuminemia is the most common condition that affects the normal anion gap since albumin normally contributes to the net negative charge of the blood (9). For every 1 mg/dL fall in the plasma albumin concentration, the anion gap should decrease by approximately 3 mEq/L (3). In plasma cell dyscrasias, such as multiple myeloma, the presence of cationic proteins in the serum is a cause for falsely depressing the anion gap (10), which has been attributed to an increased net positive charge due to the presence of net cationic immunoglobulins (1). Conditions that have been noted to increase the anion gap in the absence of metabolic acidosis are renal failure, volume depletion, metabolic alkalosis (12), and some penicillins. The anion gap can be lowered by hypoalbuminemia, hypercalcemia, and hypoproteinemia (13). Because of the wide variation in the anion gap and the variety of conditions that can affect it, it is best to directly measure "unmeasured anions" such as lactate whenever feasible.

Case Scenario #1: Use of Henderson-Hasselbalch Equation to Guide Ventilation

A 48-year-old morbidly obese patient is admitted to the hospital with shortness of breath and fever. In the emergency room, he is started on intravenous antibiotics. Over the next 5 hours, he becomes severely short of breath and develops a diminished level of consciousness. He is tachypneic and tachycardic with a need for mechanical ventilation. His past medical history is significant for diabetes mellitus and hypertension. Social history is significant for one pack per day tobacco abuse for 20 years. Current medications include amiodipine 5 mg PO daily, enalapril 5 mg PO bid, and hydrochlorothiazide 12.5 mg PO bid. Physical exam shows blood pressure of 156/88 mm Hg, pulse 76 beats/minute, and temperature 99°F. The patient is morbidly obese. Cardiovascular exam is normal. Lung exam reveals bilateral breath sounds with diffuse crackles on the right and egophony. The initial ventilator settings are synchronous intermittent mandatory ventilation (SIMV) with a rate of 20, tidal volume of 800 mL, and positive end-expiratory pressure (PEEP) of 5 cm H₂O, with an FiO₂ of 1.0. Thirty minutes after mechanical ventilation is initiated, the following labs are drawn:

<table>
<thead>
<tr>
<th>Test</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sodium (mEq/L)</td>
<td>141</td>
</tr>
<tr>
<td>Potassium (mEq/L)</td>
<td>4.2</td>
</tr>
<tr>
<td>Chloride (mEq/L)</td>
<td>100</td>
</tr>
<tr>
<td>Bicarbonate (mEq/L)</td>
<td>34</td>
</tr>
<tr>
<td>Blood urea nitrogen (BUN) (mg/dL)</td>
<td>13</td>
</tr>
<tr>
<td>Phosphorus (mg/dL)</td>
<td>3.8</td>
</tr>
<tr>
<td>Creatinine (mg/dL)</td>
<td>0.8</td>
</tr>
<tr>
<td>Albumin (g/dL)</td>
<td>3.8</td>
</tr>
<tr>
<td>Glucose (mg/dL)</td>
<td>152</td>
</tr>
</tbody>
</table>

Arterial blood gas

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>pH</td>
<td>7.67</td>
</tr>
<tr>
<td>PO₂ (mm Hg)</td>
<td>340</td>
</tr>
<tr>
<td>PCO₂ (mm Hg)</td>
<td>32</td>
</tr>
</tbody>
</table>
What acid-base disorder is present in this patient? This patient has an underlying respiratory acidosis with compensation (note elevated HCO\textsubscript{3}–). When a patient with chronic respiratory acidosis and appropriate renal compensation is placed on mechanical ventilation, he or she is at risk of developing severe alkalosis. This occurs because mechanical ventilation can remove PCO\textsubscript{2} from the blood quickly, hence increasing the pH precipitously. However, it takes time for the kidney to adapt to the change in blood pH. In time, the kidney can adapt by decreasing bicarbonate resorption, leading to loss of bicarbonate in the urine if the patient is not chloride depleted, but this does not happen in the acute setting. Following the start of mechanical ventilation in this patient, he has developed an intravascular alkalosis and a dangerously high arterial pH.

In order to correct the pH to 7.35, what goal CO\textsubscript{2} should be maintained?
The appropriate measure is to decrease the minute ventilation to allow the PCO\textsubscript{2} to rise to a level that would lead to a normal or slightly acidic pH. To determine the PCO\textsubscript{2} that corresponds to a pH of 7.35, use the Henderson-Hasselbalch relationship. In the acute setting, the HCO\textsubscript{3}– will not change since renal adjustments take several days to have full effect, and therefore the best way to change the pH is to adjust PCO\textsubscript{2}.

\[
7.35 = \log\left(\frac{34}{0.03\, \text{PCO}_2}\right)
\]
\[\text{PCO}_2 = 64\, \text{mm Hg}\]

Therefore, the ventilation rate should be decreased to maintain a PCO\textsubscript{2} of approximately 64 to achieve a pH of 7.35.

Newer Models of Acid-base Quantification: Stewart Approach

The assumptions made in the traditional model are that acids behave as Brønsted/Lowry acids—that is, proton donors—and that the degree of a metabolic disturbance causes a decrease in buffers, which is best approximated by the decrease in serum bicarbonate. Therefore, even more of H\textsuperscript{+} added results in a reciprocal decrease in the concentration of buffers. This decrease in buffer occurs proportionally as a decrease in serum bicarbonate, but other unmeasured buffers, such as Hgb-H, are also decreased during acidosis. An approach that is gaining popularity, especially among critical care physicians, is the Stewart model, a deviation from the traditional approach to acid-base quantification, which makes different assumptions about the definition of acids and bases. In essence, in the Stewart model, an acid is defined as any substance that raises the [H\textsuperscript{+}] of a solution, not necessarily limited to an H\textsuperscript{+}-donating species. Many excellent reviews have been written on this topic (14–17); discussion in this chapter will be limited to an introduction to the key derived parameters of the Stewart model so that they can be contrasted with the standard approach. The most strikingly different concept of the Stewart model is that the serum bicarbonate is not used as the measure of buffering capacity present. This model uses the strong ion difference as a fundamental measure of the presence of buffers.

The Strong Ion Difference

Strong ions are the ions in the blood that can be considered as completely dissociated in solution (18). The strong ion difference (SID) is analogous to the buffer base of a solution. The SID is calculated as:

\[
\text{SID} = ([\text{Na}^+] + [K^+]) - ([\text{Cl}^-] - [\text{lactate}])
\]

[6]

The remaining anions in solution are the buffers, which can be thought of as the bicarbonate plus the nonbicarbonate buffers, denoted [A\textsuperscript{−}]. [A\textsuperscript{−}] is the sum of negative charge (buffering capacity) of albumin and phosphate.

\[
\text{SID} = [\text{HCO}_3^-] + [A^-]
\]

[7]

SID in the Stewart model is considered more reflective of the concentrations of buffers and not the serum bicarbonate. In fact, the Stewart equation describes the pH in terms of three independent variables: The strong ion difference (SID), [A\textsubscript{tot}], and PCO\textsubscript{2}, where A\textsubscript{tot} is the concentration of weak acids. This is in contrast to the Henderson-Hasselbalch equation, which relates pH to [HCO\textsubscript{3}–] and PCO\textsubscript{2} (Eq. 4). In the Stewart model, bicarbonate concentration varies dependently on these other more fundamental parameters. The arguments for and against this claim are many, and are beyond the scope of this text. It can be stated, however, that the traditional approach to acid-base disturbances is still practiced most frequently, and the Stewart model has gained widest acceptance in the critical care field. This makes sense in that the Stewart model may have advantages in description of extreme acid-base conditions, especially when the assumption that nonbicarbonate buffers are constant may not be true, such as in critical illness. A high SID denotes metabolic alkalosis, and a low SID denotes metabolic acidosis. There are modifications of the standard model that attempt to take into account perturbations in nonbicarbonate species such as the correction of the anion gap for disturbances in serum albumin; this will be illustrated later in examples.

Expected and Apparent Strong Ion Difference. The SID under normal conditions can be thought of as the sum of the buffer anions (bicarbonate and nonbicarbonate buffer anions) and should be about 40 mEq/L. As noted above, when the SID deviates from this value, a metabolic acid-base disturbance should be suspected. As noted above, the SID is one of three independent variables that determines [H\textsuperscript{+}], and therefore, conversely, the SID can be related to the three fundamental values: pH\textsubscript{a}, PCO\textsubscript{2}, and A\textsubscript{tot} (in this case A\textsubscript{tot} is approximated based on the albumin and phosphate). This relationship is given below:

\[
\text{SID} = (1,000 \times 2.46 \times 10^{-11} \times \text{PCO}_2 \times 10^{-46}) + ([\text{albumin}] \times (0.123 \times \text{pH} - 0.631) + ([\text{phosphate}] \times (0.309 \times \text{pH} - 0.469))
\]

[8]

The apparent SID (SIDa) is the strong ion difference considering the concentrations of the strong ions that are normally present in the serum: Na\textsuperscript{+}, K\textsuperscript{+}, and Cl\textsuperscript{−}. This definition is given below:

\[
\text{SIDa} = ([\text{Na}^+] + [K^+] + [\text{Cl}^-])
\]

[9]

When the SIDs and SID differ, there is a strong anion gap, which is described below.

Strong Ion Gap

The strong ion gap (SIG) should be considered as an evaluation of unmeasured anions, analogous to the traditional anion gap. The strong anion gap is normally zero and is defined as:

\[
\text{SIG} = \text{anion gap} - [A^-]
\]

where A\textsuperscript{−} is the composite of nonbicarbonate buffers in the blood, [A\textsuperscript{−}] = 2.8 (albumin in mg/dL) + 0.6 (phosphate in mg/dL).
at a pH of 7.4.

\[
\text{SIG} = [\text{SID}_2] - [\text{SID}_1]
\]

When the strong ion gap exceeds zero, there is an unmeasured anion present. This is analogous to the traditional anion gap, with a correction factor for the presence of hyposalbuninemia (19). The traditional anion gap is rarely corrected for disturbances in phosphate, although, as can be seen in the above formula for \( \Delta^+ \), the contribution of deviations in phosphate is much smaller than that of albumin, reflecting that, quantitatively, albumin has much greater buffering capacity than phosphate.

The Stewart model has also been used to classify metabolic acid-base disorders based on the SID. An elevated SID is consistent with metabolic alkalosis, and a low SID is consistent with metabolic acidosis. The metabolic acid bases are further subdivided based on a high SIG (analogous in many ways to a high anion gap) and a low SIG (analogous to a low or normal anion gap). In this regard, the two approaches approximate each other. The use of the SIG may be advantageous over the use of the standard anion gap, given that the anion gap can have a wide range of values and is thus somewhat imprecise. This is especially true in settings where nonbicarbonate buffers deviate from normal—for example, the patient with acidosis, sepsis, and acute renal failure with serum albumin of 1.9, phosphorus of 7.0, and hemoglobin of 7.2 mg/dL. Clearly in this extreme, the assumption that only changes in serum bicarbonate species reflect the metabolic component of the acidosis may not hold true.

Stewart versus Traditional Approach

Despite the differences in these two approaches to acid-base quantification presented, it should be noted that they are quite similar. The advantage of the Stewart approach is that nonbicarbonate buffers considered in quantifying acid-base disturbances and, as noted before, this is most likely to be pivotal in critical illness. However, accurate quantification of acid-base status is only part of managing acid-base disturbances. Correctly diagnosing acid-base disorders and treating them appropriately is the ultimate goal; in this regard, we do not find considerable advantage of the Stewart approach over more traditional methodologies. It is important that the clinician understand the limitation of any of the acid-base models, such as understanding when perturbations in the anion gap are significant and when they are not. In the cases presented in this chapter, we have used a traditional approach to acid-base analysis, and we continue use this approach in our own practice.

Key Points

1. The buffering of acids allows the body to "absorb" large amounts of acid without significant disturbance in pH. It is through the excretion of the daily acid load, however, that the body is allowed to maintain acid-base balance. A highly negative urinary anion gap suggests that there is significant ammonium in the urine; in response to metabolic acidosis, this would indicate that the renal compensation is intact. A urinary anion gap that is near zero or positive suggests that there is little or no ammonium in the urine and, in the face of systemic acidosis, would indicate renal acid wasting.

2. Bicarbonate is the principal buffer in the body. However, other buffers play an important role in maintaining systemic pH, and disturbances in nonbicarbonate buffers may be more important in critical illness than in other settings.

Volatile Acidity

Up until now, we have dealt exclusively with fixed acids. Disturbances in fixed acids cause a change in available buffers and change in systemic pH. It is critical to note that volatile acidity plays a very important role in determining the systemic pH both in primary respiratory disturbances and in compensation to metabolic disturbances as will be discussed.

Carbon dioxide is soluble in water, and in solution, reacts with water molecules to form carbonic acid, which can then further react as the following:

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

\( \text{H}_2\text{CO}_3 \) is the acid portion of the bicarbonate buffer; however, its concentration is proportional to the partial pressure of \( \text{CO}_2 \), and therefore its direct measurement is not necessary. By the equilibrium expressions above, it can be seen that primary changes in \( \text{PCO}_2 \) will alter the amount of \( \text{H}_2\text{CO}_3 \), and a low \( \text{PCO}_2 \) will decrease the concentration of \( \text{H}_2\text{CO}_3 \). By quantitative chemistry, as you increase the concentration of the conjugate acid, the pH of a buffered solution will increase, and as you decrease concentration of conjugate acid, the opposite occurs. The \( \text{PCO}_2 \) in the circulation is the sum of its production and excretion. The production of \( \text{CO}_2 \) is not frequently altered; however, the excretion of \( \text{CO}_2 \)—occurring only through respiration—is variable based upon the minute ventilation.

Mechanisms of Compensation

The previous sections have detailed how buffering allows the body to absorb significant amounts of \( \text{H}^+ \) without large fluctuations in pH. These buffering systems allow pH to remain constant during physiologic changes in endogenous acid production, and they also form the first defense against an acid-base insult (Table 42.2.1). The buffering systems and respiratory compensation are very rapid, whereas renal compensation may take days to become fully effective (20). The capacity of the body's buffering system is substantial, and therefore significant amounts of acid can be absorbed before a relatively small change in systemic pH occurs. Buffers act immediately and are thus the first line of defense.

In response to systemic changes in pH, compensatory mechanisms act to counteract the primary disturbance. Figure 42.3 gives an overview of the compensatory responses to the primary acid-base disturbances. In response to metabolic acidosis, there is increased ventilation to decrease \( \text{PCO}_2 \); the kidney responds by increasing the excretion of \( \text{H}^+ \), thereby generating more \( \text{HCO}_3^- \) (Fig. 42.3A). The opposite response occurs during metabolic alkalosis, except that the kidneys are usually not able to respond to the increase in \( \text{HCO}_3^- \) appropriately, as failure of the kidney to respond to elevated \( \text{HCO}_3^- \) is necessary for the development of metabolic alkalosis (this is
Chapter 42: Blood Gas Analysis and Acid-base Disorders

637

Excess H⁺ (Metabolic Acidosis)  Excess HCO₃⁻ (Metabolic Alkalosis)

H⁺  HCO₃⁻

PCO₂ (ratio increased, pH decreases)  HCO₃⁻ (ratio decreased, pH increases)

HCO₃⁻  CO₂

Renal HCO₃⁻ production increases (equivalent to H⁺ excretion) days

H⁺  CO₂

PCO₂ (ratio decreased, pH increases)  HCO₃⁻ (ratio increased, pH decreases)

PCO₂  HCO₃⁻

Excess CO₂ (Respiratory Acidosis)  Decreased CO₂ (Respiratory Alkalosis)

↑ PCO₂  ↓ PCO₂

PCO₂ (ratio increased, pH decreases)  PCO₂ (ratio decreased, pH increases)

HCO₃⁻  CO₂

Renal HCO₃⁻ production (equivalent to H⁺ excretion) Increases days

H⁺  CO₂

PCO₂ (ratio decreased, pH increases)  PCO₂ (ratio increased, pH decreases)

PCO₂  HCO₃⁻

FIGURE 42.3. A: Primary metabolic acid-base disturbances and compensatory mechanisms. B: Primary respiratory acid-base disturbances and compensatory mechanisms.
Approach to the Critically Ill Patient with an Acid-base Disorder

The first step is to determine which acid-base disorder(s) are present, the cause of each disorder, and the degree of compensation. There are four important variables to look at when determining the acid-base status of a patient and these should be evaluated in all critically ill patients:

- **Arterial pH**: This is always the starting point. Avoid making judgments in the absence of a measured arterial pH. The pH is the negative logarithm of the concentration of $H^+$ and the physiologic range for this value is 7.38 to 7.44.

- **Arterial PCO$_2$**: Indicates the amount of volatile acidity. The PCO$_2$ generally reflects the respiratory response or contribution to the acid-base disorder.

- **Serum bicarbonate**: Indicative of the degree of fixed acids present (lower means more fixed acids present). Normal value is 24 mEq/L.

- **Serum anion gap ($=[Na^+] - ([Cl^-] + [HCO_3^-])$): A measure of conjugate bases (anions) present above what is expected under "normal" conditions. Has a wide variability, normal is usually between 8 and 12 mEq/L.

Determined Which Acid-Base Disturbances Are Present

A systematic approach is important in correctly diagnosing acid-base disorders in critically ill patients. Because it is common to have mixed acid-base disorders with two or even three disorders present, it is important to evaluate the available information thoroughly and avoid quick judgments based on an incomplete picture.

The approach to acid-base disorders is summarized in Figures 42.4 and 42.5. A key is to identify the primary disturbance. This is best accomplished by analyzing acid-base data in conjunction with a good history. The physical examination is rarely helpful in determining the etiology of an acid-base disorder. It is also important to note that the algorithm in Figure 42.5 is useful in the case of single acid-base disorders. Mixed disturbances are discussed later. Once the primary disturbance is identified, the next step is to assess the adequacy of compensation.
TABLE 42.2
COMPENSATIONS FOR ACID-BASE DISORDERS

<table>
<thead>
<tr>
<th>Metabolic acidosis</th>
<th>Metabolic alkalosis</th>
<th>Respiratory acidosis</th>
<th>Respiratory alkalosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>For every 1 mmol/L decrease in HCO$_3^-$ → 1 mm Hg decrease in PCO$_2$.</td>
<td>For every 1 mmol/L increase in HCO$_3^-$ → 0.7 mm Hg increase in PCO$_2$.</td>
<td>Acute: For 10 mm Hg increase in PCO$_2$ → 1 mmol/L increase in HCO$_3^-$.</td>
<td>Acute: For every 10 mm Hg decrease in PCO$_2$ → 2 mmol/L decrease in HCO$_3^-$.</td>
</tr>
<tr>
<td>Expected PCO$_2$ = 1.5 (HCO$_3^-$) + 8 ± 2.</td>
<td>Chronic: For 10 mm Hg increase in PCO$_2$ → 4 mmol/L increase in HCO$_3^-$.</td>
<td>Chronic: For 10 mm Hg increase in PCO$_2$ → 4 mmol/L increase in HCO$_3^-$.</td>
<td>Chronic: For every 10 mm Hg decrease in PCO$_2$ → 4 mmol/L decrease in HCO$_3^-$.</td>
</tr>
</tbody>
</table>

Table 42.2 gives the expected values of PCO$_2$ and HCO$_3^-$ following compensations for primary disturbances. In the setting of respiratory disorders, acute compensation occurs over hours, while the chronic compensation occurs over days. If there is only one disturbance, and the compensation is adequate, then a second disorder is present. Recall that a compensation will never normalize the pH or “compensate” past the point of neutrality (e.g., a primary metabolic acidosis as a single disorder cannot lead to a neutral or alkaline pH). In these cases, a mixed acid-base disorder is present. For this reason, it is good practice to calculate the anion gap in all critically ill patients.

CAUSES OF ACID-BASE DISORDERS

In determining the etiology, the clinician usually must rely on the history, clinical presentation, and, most importantly, laboratory data in order to determine the inciting disease state (Fig. 42.6).

Metabolic Acidosis

Causes of Anion Gap Acidosis

The common etiologies of elevated anion gap metabolic acidosis are listed in Table 42.3.

Diabetic Ketonacidosis. Insulin is secreted and mediates the metabolism of carbohydrates and the storage of fat during times of normal enteral intake. Under fasting conditions, insulin secretion decreases. Diabetic ketoacidosis occurs when a deficit of insulin activity leads to altered cellular metabolism and glucose utilization is impaired. The deficiency of insulin causes the liberation of fatty acids and pathophysiologic keto acid production. The degree of increase in the anion gap is related to the amount of retained ketones, and therefore diabetic ketoacidosis can be present with varying degrees of hyperchloremia (21). In addition to abnormal ketoacid production, diabetic ketoacidosis is typically also associated with hyperglycemia, a decrease in circulating volume, and, oftentimes, free water deficits as well, in addition to hypokalemia and hypophosphatemia. Even though total body potassium stores are decreased, the serum potassium concentration is frequently elevated on presentation due to the effects of insulin deficiency, hyperglycemia, and acidosis on potassium distribution. The treatment of diabetic ketoacidosis includes re-expansion of the extracellular fluid volume, administration of insulin to halt acid production, and correction of potassium and phosphorus deficits, with close monitoring of plasma electrolytes.

TABLE 42.3
COMMON CAUSES OF ELEVATED ANION GAP METABOLIC ACIDOSIS

| Lactic acidosis |
| Diabetic ketoacidosis |
| Renal failure |
| Infections |
| Methanol |
| Ethylene glycol |
| Paraldehydes |
| Salicylates |
Section IV: Essential Physiologic Concerns

Lactic Acidosis. There are two types of lactic acidosis: Type A lactic acidosis is due to tissue hypoxia and the formation of excess lactic acid, and constitutes the majority of cases of lactic acidosis. This is frequently seen in sepsis, profound anemia, shock, hypotension, and bowel and limb ischemia. Lactate is formed in tissues under hypoxic conditions as it is a by-product of anaerobic cellular metabolism. Type A lactic acidosis is often associated with poor outcomes if the cause is not quickly reversed, usually due to the severity of the underlying condition, such as septic shock or bowel infarction.

Type B lactic acidosis occurs when there is insufficient liver metabolism of lactate. The normal metabolism of lactate leads to the generation of bicarbonate and therefore when this pathway is less operative, there is decreased bicarbonate and systemic acidosis. This condition can be seen in severe liver disease and/or other conditions that interfere with liver metabolism. Several commonly used medications have been associated with lactic acidosis including propofol, metformin, the nonnucleotide reverse transcriptase inhibitors, stavudine, didanosine, and zidovudine. Carbon monoxide poisoning can present with nonspecific symptoms and lead to lactic acidosis by inhibiting oxygen utilization in the tissues.

Toxic Ingestions Associated With Elevated Anion Gap Acidosis. Ingestions are important causes of acidosis in the critical care setting (22). Common ingestions that often lead to elevated anion gap metabolic acidosis are listed in Table 42.3. The presence of ingested alcohols or other solvents can be inferred by measurement of the osmolal gap when an ingestion is suspected. The osmolal gap can be calculated using the following formula:

\[
\text{Osmolal gap} = 2 \times [Na^+] - (\text{urea} \text{mmol/L}) + 8
\]

where the calculated serum osmolality is obtained as follows:

\[
\text{Osmolality (mOsm/kg H}_2\text{O)} = \frac{2 \times [Na^+]}{0.18} + \text{Glucose (mg/dL)} + 1.8
\]

The osmolal gap is normally approximately 10 mOsm/kg H$_2$O. The normal osmolal gap is a reflection of substances normally present in the serum that exert oncotic forces. These are plasma proteins and ions found in smaller quantities, such as calcium and magnesium. An elevated osmolal gap is an indication that an unmeasured osmole is present in the serum; in the intensive care setting, this is commonly due to ethanol. The osmolal gap can also be used to quantify the level of ethylene glycol or methanol, although direct measurement of these toxins is indicated if their presence is suspected; however, therapy should not be delayed while waiting for confirmation.

Case Scenario #2: Salicylate Toxicity

A 68-year-old man presents to the emergency room following an intentional toxic ingestion. He was brought in by his son, who found him confused when he stopped by his (the patient’s) house. One month prior to admission, he suffered the loss of his wife and has felt hopeless since that time. Upon presentation, he is lethargic and weak. His past medical history is significant for hypertension and gout. Past surgical history is significant for an appendectomy 20 years ago and coronary artery bypass grafts (CABG) 2 years ago. He smokes one and a half packs of cigarettes a day and denies the use of alcohol or illicit drugs. Physical exam is significant for blood pressure of 116/80 mm Hg, pulse of 79 beats/minute, respiration of 18 breaths/minute, and temperature of 98.4°F. He is febrile, in moderate respiratory distress, and oriented only to place and person. Cardiovascular exam is normal, and there is no wheezing on chest exam. Laboratory data are given below:

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sodium (mEq/L)</td>
<td>141</td>
</tr>
<tr>
<td>Potassium (mEq/L)</td>
<td>1.9</td>
</tr>
<tr>
<td>Chloride (mEq/L)</td>
<td>105</td>
</tr>
<tr>
<td>Bicarbonate (mEq/L)</td>
<td>9</td>
</tr>
<tr>
<td>BUN (mg/dL)</td>
<td>21</td>
</tr>
<tr>
<td>Creatinine (mg/dL)</td>
<td>1.2</td>
</tr>
<tr>
<td>Glucose (mg/dL)</td>
<td>128</td>
</tr>
</tbody>
</table>

Arterial blood gas

pH | 7.40 |
PO$_2$ | 42 |
PACO$_2$ | 25 |

Salicylate toxicity is typically associated with an anion gap metabolic acidosis and respiratory alkalosis; this is the acid-base disorder present in this patient. In diagnosing the acid-base disturbance in this patient, the first step is to look at the serum pH. The pH is normal with low serum bicarbonate. This is the first clue that a complex disorder is present since a compensatory response to metabolic acidosis would not normalize the serum pH. We can determine that there is a metabolic acidosis present because of the elevated anion gap (anion gap = 27). Given the presence of a metabolic acidosis, we can then predict what the PACO$_2$ should be. Using the Winter formula, the expected PACO$_2$ is approximately 24 mm Hg (Table 42.2), and thus a respiratory alkalosis is present. This pattern is strongly suggestive of salicylate toxicity (23).

Case Scenario #3: Lactic Acidosis in the Setting of Abnormal Levels of Nonbicarbonate Buffers

A 44-year-old female with cirrhosis secondary to autoimmune hepatitis is admitted to the hospital for fever and abdominal pain. The patient is listed for an orthotopic liver transplantation and has been clinically stable for the past month. She noted abdominal pain and fever that have gotten progressively worse over the last 2 days. Her past medical history is otherwise nonsignificant. Current medications include simvastatin 100 mg PO bid, furosemide 80 mg PO bid, and lactulose 30 ml PO bid. Previous surgeries include the placement of a transjugular intrahepatic portosystemic shunt (TIPS) and a cholecystectomy. Physical exam is significant for blood pressure of 74/45 mm Hg, pulse of 72 beats/minute, temperature 100.8°F, and respiratory rate of 24 breaths/minute. She appears cachectic. Cardiovascular and chest exams are normal. Her abdomen is distended and there is diffuse tenderness. She has pitting edema in the lower extremities. Spontaneous bacterial peritonitis is suspected, and the patient is admitted to the hospital. Admission labs are given below:

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sodium (mEq/L)</td>
<td>128</td>
</tr>
<tr>
<td>Potassium (mEq/L)</td>
<td>3.1</td>
</tr>
<tr>
<td>Chloride (mEq/L)</td>
<td>106</td>
</tr>
<tr>
<td>Bicarbonate (mEq/L)</td>
<td>21</td>
</tr>
<tr>
<td>BUN (mg/dL)</td>
<td>20</td>
</tr>
<tr>
<td>Creatinine (mg/dL)</td>
<td>1.3</td>
</tr>
<tr>
<td>Phosphorus (mg/dL)</td>
<td>2.1</td>
</tr>
<tr>
<td>Albumin (g/L)</td>
<td>1.4</td>
</tr>
<tr>
<td>Glucose (mg/dL)</td>
<td>84</td>
</tr>
</tbody>
</table>

Arterial blood gas

pH | 7.23 |
PO$_2$ (mm Hg) | 78 |
PACO$_2$ (mm Hg) | 28 |

What is the best characterization of the acid-base disturbance in this patient?

The acid-base disorder is an anion gap metabolic acidosis, likely lactic acidosis. While the anion gap appears normal, the degree of hyperalbuminemia needs to be considered because the negative charge on albumin is a significant component of the normal...
Ureterointestinal diversions

Laxatives, cholestyramine

Severe diarrhea leads to non–anion gap metabolic acidosis. These disorders can lead to the exit of cells. Type 4 RTA is a clinical entity. Diarrhea

October 23, 2008 13:19

The kidneys have the capacity to excrete acids to renin to achieve normal serum pH. Again, caution should be used in interpreting the anion gap in these settings, if any suspicion exists for lactic acidosis, the serum lactate should be measured directly.

Non–Anion Gap Acidosis

In a non–anion gap/hyperchloremic acidosis, there is a primary decrease in the serum bicarbonate and an associated increase in the serum chloride. The serum bicarbonate decreases because of renal or extrarenal, gastrointestinal losses (Table 42.4). One of the key etiologic questions to be answered in the approach to a patient with a non–anion gap acidosis is whether or not the kidney is appropriately responding to the acidosis by excreting the acid load or if the cause of the acidosis is improper acid excretion by the kidney. This allows one to differentiate renal from nonrenal causes of the acidosis. The urine anion gap, which is calculated using Eq. 3, is a convenient methodology to assess urinary acid excretion. If the urine anion gap is positive or close to zero, this suggests that (a) there is very little ammonium in the urine and (b) the kidney is not appropriately excreting acids. If the urine anion gap is highly negative, this suggests that (a) there is a large amount of ammonium in the urine and (b) the kidney is excreting acids appropriately (Fig. 42.2).

Causes of Non–Anion Gap Metabolic Acidosis

Diarrhea. Severe diarrhea leads to non–anion gap metabolic acidosis through loss of bicarbonate, and it is typically associated with volume depletion and hypokalemia. In very severe cases, circulatory collapse can occur, and an anion gap (lactic acidosis) may supervene upon the non–anion gap acidosis. Patients who chronically abuse laxatives may develop metabolic acidosis and hypokalemia. However, frequently, these patients also abuse diuretics and therefore can have an associated metabolic alkalosis. In order to determine if the renal response to the acidosis is normal, the urine anion gap should be measured.

Ureterointestinal Diversions. In a ureterointestinal diversion, urine in the intestine leads to reabsorption of chloride and water. Consequently, the absorption of chloride can induce secretion of bicarbonate into the intestine. Additionally, urease-positive bacteria in the intestine metabolize the urea in the urine to form ammonium, which, when absorbed, liberates excess acid after it is metabolized in the liver. Also, chronic pyelonephritis is common in the diverted kidney, and a superimposed distal renal tubular acidosis (RTA) may occur.

Renal Tubular Acidosis. Renal tubular acidosis is a heterogeneous mix of disorders that is characterized by defects in urinary acid excretion in the setting of intact renal function. Proximal (type 2) RTA is caused by a decrease in proximal bicarbonate reabsorption, whereas in distal (type 1) RTA, the primary defect is impairment of distal acidification (24,35). The net result is that the urine pH is not maximally acidified. The lack of acidification—in other words, secretion of $H^+$—leads to less ammonium trapping in the urine and therefore to an anion gap that is either positive or near zero. In the intensive care unit, renal tubular acidosis often presents with profound acidosis and hypokalemia. It is important to treat the hypokalemia first with potassium chloride before correcting the acidosis, as administration of bicarbonate in the setting of severe potassium depletion can lead to fatal hypokalemia as potassium is taken up by cells when $H^+$ exits the cells. Type 4 RTA is a clinical syndrome of hyperkalemia and hyperchloremic metabolic acidosis (26) caused by a lack of aldosterone effect on the kidney and is seen most commonly in the following settings: diabetes, advanced age, acquired immunodeficiency syndrome (AIDS), interstitial nephritis, obstructive uropathy, postrenal transplant status, use of angiotensin-converting enzyme inhibitors and heparin (both of which impair aldosterone production), and use of cyclosporine.

RTA should be suspected if the renal response to systemic acidemia is impaired as evidenced by a positive urine anion gap. The next step is to determine the type. The most practical starting point is to differentiate a proximal from a distal RTA. To understand this, some physiology must be discussed. Recall that bicarbonate is reabsorbed predominantly in the proximal tubule. Proximal RTA develops because of impaired reabsorption of bicarbonate. The lack of bicarbonate reabsorption in patients with normal serum bicarbonate leads to wasting of bicarbonate in the urine until a steady state is reached in which the serum bicarbonate drops to a level at which the reabsorptive capacity of the proximal tubule is no longer overwhelmed. At this point, there is no longer any bicarbonate in the urine. For this reason, in a patient with proximal RTA, the serum bicarbonate will be low; however, the urine pH will be low—this is because the distal acidification mechanisms are functional. If such a patient is given an alkali load, serum bicarbonate is temporarily increased, and bicarbonate “spills” into the urine because the filtered load of bicarbonate exceeds the reabsorptive threshold, which leads to an increase in the urine pH. Once the alkali load is stopped, serum bicarbonate drops, bicarbonate no longer appears in the urine, and the urine pH can now drop to its maximally acidic level of approximately 5.5. This is the basis for the provocative testing to demonstrate a proximal RTA, and also explains why these patients often have to take a tremendous amount of alkali in order to achieve normal serum pH.

Renal Failure. The kidneys have the capacity to excrete acids to such a degree that acid–base balance is maintained until kidney function deteriorates to below a glomerular filtration rate of approximately 20 mL/min. The resulting acidosis is of a mixed type and it is generally, but not universally, associated with an elevated anion gap. Chronic metabolic acidosis should be treated to prevent bone demineralization, which may occur with time. The goal of treatment is to maintain normal acid–base status.

Pancrætic or Biliary Fistula. These disorders can lead to the loss of bicarbonate-rich solutions through the gastrointestinal

<table>
<thead>
<tr>
<th>TABLE 42.4</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ETIOLOGIES OF NON–ANION GAP METABOLIC ACIDOSIS</strong></td>
</tr>
<tr>
<td>Extrarenal source</td>
</tr>
<tr>
<td>---</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
</tr>
<tr>
<td>Diarrhea</td>
</tr>
<tr>
<td>Pancreatic and biliary fistula</td>
</tr>
<tr>
<td>Laxatives, cholestyramine</td>
</tr>
<tr>
<td>Ureterointestinal diversions (ileal conduit)</td>
</tr>
</tbody>
</table>

unmeasured anions. For every 1 g/dL decrease in the serum albumin, the expected anion gap decreases by 2.5 mEq/L. Thus, in this patient, consider her anion gap at a normal level, it should not exceed approximately 5 to 6 mEq/L. Again, caution should be used in interpreting the anion gap in these settings.
tract and result in systemic acidosis. If correction of the underlying factor is not possible, treatment with alkali salts can be helpful.

Hypoadosteronism. Similar to type 4 RTA acidosis, hypoad-
sertone activity in the kidney leads to hypokalemia and metabolic acidosis; conversely, lack of this activity decreases aldosterone secretion and leads to hyperkalemia and metabolic acidosis.

Case Scenario #4: Non–Anion Gap Metabolic Acidosis: Assessing Urinary Acid Excretion
A 66-year-old man is seen in the emergency room. He has had 8 days of severe diarrhea, abdominal pain, and decreased food intake, but adequate intake of liquids. He believes that he became sick after babysitting his grandson who had similar symptoms. His medical history is significant for diabetes and hypertension. Surgical history only consists of coronary artery bypass grafting 3 years ago. His medications include metformin 1 g PO bid, aspirin 81 mg PO daily, enalapril 20 mg PO daily, hydrochlorothiazide 25 mg PO daily, and metformin 1 g PO bid. He has a family history of diabetes and premature coronary artery disease. He does not smoke or use drugs, and drinks alcohol occasionally. Physical exam is significant for blood pressure of 105/70 mm Hg and a pulse of 72 beats/minute; temperature is 98.8 °F, and respiratory rate is 12 breaths/minute. There is a small amount of occult blood in the stool. Labs are given below:

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum sodium (mEq/L)</td>
<td>136</td>
</tr>
<tr>
<td>Potassium (mEq/L)</td>
<td>3.9</td>
</tr>
<tr>
<td>Chloride (mEq/L)</td>
<td>114</td>
</tr>
<tr>
<td>Bicarbonate (mEq/L)</td>
<td>13</td>
</tr>
<tr>
<td>BUN (mg/dL)</td>
<td>21</td>
</tr>
<tr>
<td>Creatinine (mg/dL)</td>
<td>1.2</td>
</tr>
<tr>
<td>Albumin (g/dL)</td>
<td>4.0</td>
</tr>
<tr>
<td>Glucose (mg/dL)</td>
<td>128</td>
</tr>
<tr>
<td>Urine pH</td>
<td>6.27</td>
</tr>
<tr>
<td>Sodium (mEq/L)</td>
<td>32</td>
</tr>
<tr>
<td>Potassium (mEq/L)</td>
<td>21</td>
</tr>
<tr>
<td>Chloride (mEq/L)</td>
<td>80</td>
</tr>
<tr>
<td>Arterial blood gas pH</td>
<td>7.27</td>
</tr>
</tbody>
</table>

Which acid-base disorder is present and what is the likely etiology?

This patient has a non–anion gap metabolic acidosis from a renal origin. The low pH and decreased serum bicarbonate indicate the presence of metabolic acidosis. Respiratory compensation is adequate, and therefore there is no complex acid–base disorder present. The serum anion gap is not elevated. The urine electrolytes and the calculation of the urine anion gap are useful to distinguish between a renal source and a gastrointestinal (GI) source of the acidosis. If gastrointestinal losses are the cause of the acidosis and the renal response to the acidosis is normal, a significant amount of ammonium will be present in the urine. The presence (or absence) of ammonium can be inferred by calculating the urine anion gap. The formula for the urine anion gap is as follows: [K⁺] + [Na⁺] − [HCO₃⁻]. If there is an unmeasured anion present, then [Cl⁻] exceeds [K⁺] + [Na⁺] and the urine anion gap is significantly negative. When there is little or no unmeasured anion present, the urine anion gap will take on a positive value. In this case, the urine anion gap is 21 mEq/L, and therefore there is a significant amount of ammonium (NH₄⁺) in the urine, which implies a normal renal response to the systemic acidosis—thereby designating an extrarenal cause of the acidosis.

**Treatment of Metabolic Acidosis**

Treatment of Anion Gap Metabolic Acidosis. The treatment of an anion gap metabolic acidosis is focused on reversing the pathogenesis of the endogenous acid production and eliminating excess acid. By far the most important aspect of treatment is to identify the source of the acidosis if it is not already apparent, such as in diabetic ketoacidosis or septic shock. Treatment of an anion gap acidosis with bicarbonate replacement therapy remains controversial, especially in lactic acidosis. It has been argued that bicarbonate may be used as a bridge until homeostatic mechanisms reverse the condition through the metabolism of endogenous bases, such as lactate and ketone bodies, and therefore bicarbonate regeneration. This approach of using alkali therapy assumes that there is a detrimental effect on the organism, which is beyond the harm caused by the underlying condition. However, evidence from animal models argues that bicarbonate therapy may have deleterious effects on the organism, which is beyond the harm caused by the underlying condition. Therefore, evidence from animal models argues that bicarbonate therapy may have deleterious effects on the pH, serum lactate levels, and cardiac function (27–29). Bicarbonate leads to the generation of CO₂ during buffering and, as CO₂ readily diffuses across cell membranes, intracellular acidosis has been shown to worsen during bicarbonate therapy. Worsening of cardiac function, which has been associated with lactic acidosis, is the proposed mechanism for worsening of lactic acidosis following the administration of bicarbonate during lactic acidosis (30). Hemodialysis rapidly corrects acidosis and is typically necessary to treat acidosis in the setting of renal failure.

Treatment of Non–Anion Gap Metabolic Acidosis. Bicarbonate therapy is generally indicated in non–anion gap acidosis since the primary disturbance is a decrease in bicarbonate. The treatment of anion gap acidosis where correction of the underlying cause is the primary concern. Oral bicarbonate or oral citrate solutions are agents for chronic therapy for non–anion gap acidosis. For acute presentations, especially in patients who may not be able to tolerate prolonged hyperventilation, intravenous bicarbonate therapy may be used.

**Medications and Metabolic Acidosis**

Medications are an increasingly important cause of severe acidosis and can be life threatening in many cases. Lactic acidosis has been reported with all nonnucleoside reverse transcriptase inhibitors used to treat human immunodeficiency virus (HIV); this effect is related to the drug's inhibition of mitochondrial function, with resultant anaerobic metabolism (31–34). The newer-generation anticonvulsant topiramate has also been associated with lactic acidosis (34). Metformin is also well known to lead to lactic acidosis, which can be treated with hemodialysis (35). The propofol infusion syndrome is a dangerous complication sometimes seen with the use of this drug; it is associated with head injury, use of propofol for more than 48 hours, use in children, and concomitant use of catecholamines and steroids (36–38).

Case Scenario #5: Propofol Infusion Syndrome
A 25-year-old male is in the intensive care unit following a cranio-
surgery for a traumatic head injury. He had suffered a depressed skull fracture to the left frontotemporal bone associated with intracranial hemorrhage. He has no known medical problems and takes no medi-
cations. Family members state that he occasionally uses intravenous
cocaine and smokes cigarettes. Intraoperatively, he is given intra-
venous ephedrine and phenylephrine. It is now postoperative day 2,
and he is currently receiving propofol infusion at 8 g/kg/minute.
Blood pressure is 153/90 mm Hg, pulse 80 beats/minute, temper-
ature 97.4°F, and respiratory rate 12 breaths/minute. He is cur-
rently mechanically ventilated on SIMV mode with bilateral breath
sounds. He has a normal cardiac exam, and there is no peripheral edema. Laboratory data are as follows:

TABLE 42.5

<table>
<thead>
<tr>
<th>Day 3</th>
<th>Day 6</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sodium (mEq/L)</td>
<td>136</td>
</tr>
<tr>
<td>Potassium (mEq/L)</td>
<td>3.9</td>
</tr>
<tr>
<td>Chloride (mEq/L)</td>
<td>104</td>
</tr>
<tr>
<td>Bicarbonate (mEq/L)</td>
<td>20</td>
</tr>
<tr>
<td>Creatinine (mg/dL)</td>
<td>18</td>
</tr>
<tr>
<td>Alanine (mmol/L)</td>
<td>4.0</td>
</tr>
<tr>
<td>Blood glucose (mg/dL)</td>
<td>128</td>
</tr>
<tr>
<td>pH</td>
<td>7.37</td>
</tr>
<tr>
<td>PCO₂</td>
<td>38</td>
</tr>
</tbody>
</table>

What is the likely cause of the acidosis in this patient?

Propofol infusion syndrome is an important entry in the inten-
sive care unit [37,39,40]. The patients who appear to be at the
greatest risk for the condition are those receiving prolonged in-
fusions after suffering brain injury. Treatment for the condition
appears to be discontinuation of propofol; hemofiltration has
been used successfully [41,42]. It is important to note that many
fatalities have occurred when the condition is not recognized
promptly, and thus early recognition is critical.

**Key Points**

1. Bicarbonate therapy is indicated for non–anion gap acidosis.
2. The primary concern in an anion gap acidosis is correction of the underlying cause.

**Metabolic Alkalosis**

Metabolic alkalosis occurs when there is an excess of buffers present, raising the systemic pH. In metabolic alkalosis, there is
a primary elevation in the serum bicarbonate. This condition is
common in the intensive care setting and can have severe complications. As the primary problem is an increase in bicar-
bonate, metabolic alkalosis can be readily corrected by renal bi-
carbonate excretion. Under normal circumstances the potential
for bicarbonate excretion is tremendous, and thus, alterations
in the renal handling of bicarbonate must occur to maintain
the alkalosis. Without an impairment of the renal capacity to
excrete bicarbonate, the kidneys would simply excrete the bi-
carbonate load. The most common reason for impairment of
renal excretion of bicarbonate is chloride deficiency and renal
failure. In general, metabolic alkaleses are generated by either
bicarbonate intake in excess of loss or by the primary loss of
H⁺ (Table 42.5).

**Chloride-sensitive Metabolic Alkalosis**

Nasogastric suction, vomiting, and diuretics are very frequent
causes of metabolic alkalosis. Hyperkalemia develops in the set-
ting of vomiting or nasogastric suction not due to gastrointesti-
nal losses, as the stomach contents are not rich in potassium;
rather, the losses of potassium are renal losses due to potassium
bicarbonate excretion and secondary hyperaldosteronism. In
these settings, renal losses of sodium and potassium are oblig-
tory in order to excrete bicarbonate. In this situation, the
urinary chloride (not the urinary sodium) better reflects the
effective blood volume of the patient. Similar to the loss of
gastrointestinal secretions, diuretic-induced extracellular fluid volume
depletion stimulates aldosterone secretion. The action of al-
dosterone stimulates sodium reabsorption in the distal tubule,
which is coupled with secretion of potassium and H⁺. There-
fore, a urine that is paradoxically acidic is generated. Other
causes of metabolic alkalosis that are sensitive to the admin-
istration of chloride include those occurring after hyperventila-
tion and diuretic use.

As noted above, in order to maintain the alkalosis, renal bicarbonate excretion must be impaired in some way. In the
setting of chloride depletion, the kidney is unable to excrete the excess bicarbonate, and therefore the alkalosis is main-
tained [43,44] (Table 42.6). Among patients with normal renal

**TABLE 42.6**

CLASSIFICATION OF METABOLIC ALKALOSIS BY CHLORIDE HANDLING

<table>
<thead>
<tr>
<th>Chloride sensitive (urine Cl⁻ less than 20 mEq/L)</th>
<th>Chloride resistant (urine Cl⁻ greater than 40 mEq/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastrointestinal acid losses</td>
<td>Hypertensive</td>
</tr>
<tr>
<td>- Nasogastric suction, vomiting</td>
<td>- Renovascular hypertension</td>
</tr>
<tr>
<td>- Congenital Cl⁻ losses in stool?</td>
<td>- Hyperaldosteronism</td>
</tr>
<tr>
<td>- Renal adenaoma</td>
<td>- Liddle syndrome</td>
</tr>
<tr>
<td>- Penicillins, citrate</td>
<td>- Glycyrrhizic acid</td>
</tr>
<tr>
<td>- Postdiuretic</td>
<td>- Normotensive</td>
</tr>
<tr>
<td>- Posthypercapnic</td>
<td>- Diuretics</td>
</tr>
<tr>
<td>- Bartter and Gitelman syndromes</td>
<td>- Bartter and Gitelman syndromes</td>
</tr>
<tr>
<td>- Administration of alkali</td>
<td>- Administration of alkali</td>
</tr>
</tbody>
</table>

**Chapter 42:** Blood Gas Analysis and Acid-base Disorders
function and normal chloride status, attempting to raise the serum bicarbonate concentration 2 to 3 mEq/L above the normal value is virtually impossible because the kidneys can easily excrete the excess bicarbonate. The chloride-insensitive metabolic alkalosis commonly encountered in the critical care setting is that occurring after the use of loop diuretics. The loss of large amounts of bicarbonate-free fluid in a patient with expanded ECF space—such as during therapy with a loop diuretic—is thought to lead to a reduction in the ECF space, with relative conservation of bicarbonate concentration. This has been termed contraction alkalosis. Other causes of chloride-insensitive metabolic alkalosis are hyperaldosteronism—both primary and secondary—such as might be seen with renovascular disease (Table 42.6). Rare causes of chloride-insensitive metabolic alkalosis are Bartter and Gitelman syndromes.

**Renal and Extrarenal Compensation**

Immediately following the generation of metabolic alkalosis, buffering systems begin to decrease the effects of the alkaline load. Respiratory compensation for a metabolic alkalosis involves respiratory suppression and an increase in the PCO₂ (Fig. 42.3A, Table 42.2). Respiratory compensation for severe metabolic alkalosis has practical limits, as respirations can be suppressed only to a certain degree. Without the effect of mitigating factors such as volume depletion, the kidney will respond to metabolic alkalosis through increasing the renal excretion of bicarbonate. Severe chloride depletion can theoretically inhibit this exchange and therefore inhibit bicarbonate secretion. Finally, hyperaldosteronism secondary to diuretic use stimulates the tubular secretion of potassium and H⁺. The net effect is an acute urine that also helps to maintain the alkalosis. In patients with low urinary chloride, chloride replacement is indicated to allow bicarbonate excretion.

**Treatment of Metabolic Alkalosis**

The metabolic alkalosis seen in the intensive care unit often develops as a complication rather than a presenting disorder. H₂ blockers and proton pump inhibitors can be used as a measure to decrease losses of H⁺ in patients with prolonged gastric aspiration or chronic vomiting, which may help prevent the development of metabolic alkalosis. In patients with chloride-sensitive metabolic alkalosis, treatment usually consists of replacement of the chloride deficit—usually with normal saline since volume depletion is also often present. Potassium chloride is almost always indicated when hypokalemia is also present, although potassium concentrations may increase as the alkalosis is corrected. In severe, symptomatic metabolic alkalosis—a pH greater than 7.6—hemodialysis may be indicated and can be used to correct alkalemia, especially when associated with renal failure (43). The use of acidic solutions is rarely indicated (Table 42.7).

### TABLE 42.7

<table>
<thead>
<tr>
<th>Type of Acidosis</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chloride sensitive</td>
<td>IV normal saline volume expansion</td>
</tr>
<tr>
<td>Chloride resistant</td>
<td>Remove offending agent</td>
</tr>
<tr>
<td>Extreme alkalosis</td>
<td>Replace potassium if deficient</td>
</tr>
</tbody>
</table>

The chloride-insensitive metabolic alkalosis commonly encountered in the critical care setting is that occurring after the use of loop diuretics. The loss of large amounts of bicarbonate-free fluid in a patient with expanded ECF space—such as during therapy with a loop diuretic—is thought to lead to a reduction in the ECF space, with relative conservation of bicarbonate concentration. This has been termed contraction alkalosis. Other causes of chloride-insensitive metabolic alkalosis are hyperaldosteronism—both primary and secondary—such as might be seen with renovascular disease (Table 42.6). Rare causes of chloride-insensitive metabolic alkalosis are Bartter and Gitelman syndromes.

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### Case Scenario #6: Diabetic Ketoacidosis with Concomitant Metabolic Alkalosis

A 21-year-old male presents to the emergency room with severely diminished mental status. He states that he has felt nauseated for the last few days and has been unable to eat well. This morning, he vomited several times and was brought to the emergency room by his girlfriend. His past medical history is negative for any chronic medical problems. He had a tonsillectomy as a child but no other surgeries. Physical exam is significant for blood pressure of 122/77 mm Hg, pulse of 105 beats/minute, respiratory rate of 28 breaths/minute, and temperature of 99.3 °F. He is thin and non-tender. Stool is negative for occult blood. In the emergency room, the patient begins to vomit large amounts, and he aspirates a significant amount of stomach contents and develops respiratory failure. He is intubated and started on mechanical ventilation. After 1 hour of mechanical ventilation, the following laboratory values are recorded:

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>pH</td>
<td>7.41</td>
</tr>
<tr>
<td>pCO₂</td>
<td>27</td>
</tr>
<tr>
<td>Bicarbonate</td>
<td>16</td>
</tr>
<tr>
<td>Potassium</td>
<td>91</td>
</tr>
<tr>
<td>Chloride</td>
<td>31</td>
</tr>
<tr>
<td>Sodium</td>
<td>138</td>
</tr>
</tbody>
</table>

**What is the acid-base disturbance present in this patient?**

This patient has a mixed acid-base disorder, metabolic acidosis/metabolic alkalosis. The patient presents with diabetic ketoacidosis. The anion gap is 31, which signifies a large degree of ketoacid production. Because of the nausea and vomiting, he also has developed a metabolic alkalosis, and thus the bicarbonate level is higher than one would expect with this degree of acid production. This can be formalized by calculating the delta-delta anion gap. Another method of conceptualizing what is occurring is to take the difference of the anion gap and a normal anion gap. To illustrate how this works, we define the normal anion gap as 12 mEq/L. In this case, the difference between the patient's anion gap and the normal anion gap is 31 – 12 = 19 mEq/L. This difference is often referred to as the delta-delta anion gap. If this number is added to the patient's bicarbonate, the result is 35. This significantly exceeds the normal bicarbonate of 24, which indicates that a metabolic alkalosis is present. What this tells us is that all of the unmeasured anions—which are potentially bicarbonate—are converted back to bicarbonate, the patient would be considered to have a metabolic alkalosis.

### Key Points

1. Metabolic alkalosis is often accompanied by a decrease in chloride such that the decrease offsets the incremental increase in bicarbonate.
2. Metabolic alkalosis is caused by excessive bicarbonate intake or loss of H⁺.
3. Vomiting, nasogastric suction, and diuretics are the most frequent causes of metabolic alkalosis in the intensive care unit setting.

4. In patients with metabolic alkalosis and low urinary chloride, normal saline is indicated to expand the extracellular space.

**Respiratory Acid-base Disorders**

Under normal conditions, through endogenous metabolism, approximately 15,000 mmol/day of CO$_2$ is produced. Carbon dioxide enters the plasma and forms carbonic acid, which subsequently dissociates to bicarbonate and H$^+$. The majority of this CO$_2$ generated is transported to the lungs in the form of bicarbonate. The H$^+$ produced in the process is exchanged across the erythrocyte membrane and is buffered intracellularly. In the alveoli, this process is reversed and the bicarbonate combines with H$^+$, liberating CO$_2$, which is then excreted through respiration. Carbon dioxide is the main stimulus for respiration, which is activated by small elevations in the PCO$_2$. Hypoxia is a minor stimulus for respiration and is typically effective when the PO$_2$ is in the range of 50 to 55 mm Hg. Derangements in respiratory CO$_2$ excretion lead to alterations in the ratio of PCO$_2$ to bicarbonate in the serum and therefore alter systemic pH (recall the Henderson-Hasselbalch relationship, Eq. 4).

**Respiratory Acidosis**

Respiratory acidosis results from the primary retention of carbon dioxide; a variety of disorders that reduce ventilation can lead to respiratory acidosis. The common etiologies of respiratory acidosis seen in intensive care unit patients are listed in Table 42.8.

The increase in the plasma PCO$_2$ decreases the pH by formation of carbonic acid (Eq. 11). The principal compensatory defense mechanisms against respiratory acidosis are buffering and renal compensation. Recalling the Henderson-Hasselbalch relationship (Eq. 4), the pH of the blood is dependent on the relative concentrations of CO$_2$ and bicarbonate. Therefore, when there is an increase in PCO$_2$, the renal response to increase HCO$_3^-$ is an action to normalize this relationship (Fig. 42.1B). In respiratory acidosis, the extracellular buffering capacity is severely limited because bicarbonate cannot buffer carbonic acid. Intracellular buffers—hemoglobin and other intracellular proteins—serve as the protection against acute rises in PCO$_2$. In circulating erythrocytes, the H$^+$ that is produced as carbonic acid is formed from CO$_2$ that is buffered by hemoglobin; bicarbonate then leaves the cell in exchange for chloride. The buffering response to an elevation of CO$_2$ occurs within 10 to 15 minutes.

Renal compensation occurs in response to chronic respiratory acidosis. Hypercapnia stimulates secretion of protons in the distal nephron. Additionally, the urinary pH decreases and urinary ammonium excretion is increased, as is titratable acid excretion and excretion of chloride. The net effect is enhanced reabsorption of bicarbonate. The kidney’s response to an acute increase in PCO$_2$ through compensation takes 3 to 4 days to reach completion (Table 42.2). Aside from the compensatory mechanisms mentioned above, an increase in alveolar ventilation is ultimately required in order to eliminate excess CO$_2$ and therefore to re-establish equilibrium. If ventilation inceases quickly during the acute period, the decrease in PCO$_2$ re-establishes equilibrium. However, following sustained hypercapnia that has elicited an appropriate renal response (i.e., a compensatory increase in serum bicarbonate), bicarbonaturia accompanies the return of the PCO$_2$ to normal. However, in order for this to occur, the chloride intake must be sufficient to replenish the deficit that developed during the renal compensation to the chronic respiratory acidosis, which induces a negative chloride balance. If chloride is deficient, the serum bicarbonate will remain persistently elevated, a phenomenon termed posthypercapnic metabolic alkalosis.

**Clinical Presentation.** Acute respiratory acidosis can produce headaches, confusion, irritability, anxiety, and insomnia, although the symptoms are difficult to separate from concomitant hypoxemia. Symptoms may progress to asterixis, delirium, and somnolence. The severity of the clinical presentation correlates more closely with the rapidity of the development of the disturbance rather than the absolute PCO$_2$ level.

**Treatment.** The treatment of respiratory acidosis is focused on alleviating the underlying disorder. In patients with acute respiratory acidosis and hypoxemia, supplemental oxygen is appropriate. However, to treat the hypercapnia, an increase in effective alveolar ventilation is necessary through either reversal of the underlying cause or, if necessary, mechanical ventilation. The administration of bicarbonate in respiratory acidosis when a coexisting metabolic acidosis is not present is potentially harmful. Bicarbonate in the setting of acute respiratory acidosis may precipitate acute pulmonary edema, metabolic

---

**Table 42.8**

<table>
<thead>
<tr>
<th>CAUSES OF RESPIRATORY ACIDOSIS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Airway obstruction</td>
</tr>
<tr>
<td>Neuro muscular disorders of respiration</td>
</tr>
<tr>
<td>Chronic:</td>
</tr>
<tr>
<td>Central respiratory depression</td>
</tr>
<tr>
<td>Respirator disorders</td>
</tr>
</tbody>
</table>
alkalosis, and augmented carbon dioxide production, leading to increased PCO₂ in patients with inadequate respiratory reserve (46-49).

During chronic respiratory acidosis, renal compensation leads to a near-normalization of the arterial pH. In treating chronic respiratory acidosis, the objective is to ensure adequate oxygenation and, if possible, to increase alveolar ventilation. The administration of excessive oxygen and use of sedatives should be avoided because these treatments can depress the respiratory drive. Mechanical ventilation may be indicated when there is an acute exacerbation of chronic hypercapnia. If mechanical ventilation is used, the PCO₂ should be decreased gradually, avoiding precipitous drops, as rapid correction may cause severe alkalosis. Also, this may increase the cerebrospinal fluid pH, because carbon dioxide rapidly equilibrates across the blood-cerebrospinal fluid barrier. This complication can lead to serious neurologic problems, including seizures and death.

Special Scenario: Permissive Hypercapnia. It has been shown that ventilator strategies to reduce ventilator-associated lung injury (VALI) improve intensive care unit outcomes (46-49). This strategy is referred to as permissive hypercapnia and may reduce VALI through several mechanisms: by reducing stretch trauma and associated release of cytokines, and by preventing translocation of endotoxin and bacteria across the alveolar capillary barrier (50–54). It is not known for certain if respiratory acidosis per se has a beneficial effect, though there are recent data to suggest such an effect (55). Primary elevation of PCO₂ is also suggested to be deleterious on cardiac function (27,28), though this may be outweighed by protective effects of hypercapnia on lung injury (56). Further studies will be needed to delineate the specific roles of low tidal volume and respiratory acidosis with or without buffering in the management of acute lung injury.

Case Scenario #7: Respiratory Alkalosis

A 56-year-old morbidly obese patient is admitted to the hospital with severe cellulitis of the right lower extremity that fails to respond to intravenous antibiotics. On hospital day 3, he undergoes a right below-knee amputation and, although recovering well, complains of severe pain postoperatively. His blood cultures drawn at admission are negative. His past medical history is significant for diabetes mellitus and chronic lower extremity ulceration that is evidenced by the increased serum bicarbonate with a decreased pH. This is consistent with a history of obesity, which can lead to a restrictive pattern of lung disease characterized by chronic respiratory insufficiency. An acute respiratory alkalosis is present because the expected degree of renal compensation is not present as it would be if the patient had a chronic elevation of the PCO₂ to levels of 110 mm Hg. The acute respiratory failure is most likely secondary to narcotic overdose, and thus fentanyl is the most likely causative agent.

**Respiratory Alkalosis**

Pathophysiology. Respiratory alkalosis is due to a primary increase in ventilation, which leads to a decrease in the PCO₂ and occurs commonly in the intensive care unit either as a treatment (e.g., for elevated intracranial pressure), as an iatrogenic complication of mechanical ventilation, or as part of a disease presentation (Table 42.9) (57). The lowered PCO₂ in turn reduces carbonic acid levels, which decreases systemic pH. The buffering system and, ultimately, renal compensation are the counterregulatory measures that are directed at maintaining plasma pH in this setting. In the setting of acute respiratory alkalosis, proteins, phosphates, and hemoglobin liberate H⁺. These liberated protons subsequently react with bicarbonate to form carbonic acid. At the level of the erythrocyte, a shift of chloride to the extracellular compartment ensues, as bicarbonate and cations enter in exchange for protons. The net effect of this buffering system reduces plasma pH and accounts for a 2 mEq/L decrease in the serum bicarbonate for every 10 mm Hg decrease in the PCO₂ that occurs in the acute setting (Table 42.2). Persistent respiratory alkalemia elicits the renal response, which leads to a net decrease in the secretion of H⁺. This renal compensation causes a decrease in the proximal reabsorption of bicarbonate and a decrease in the excretion of titratable acids and of ammonium. Recall that the excretion of one H⁺ in the kidney leads to the regeneration of a HCO₃⁻ molecule; therefore, these renal changes decrease renal acid excretion.

<table>
<thead>
<tr>
<th>Case Scenario #7: Respiratory Alkalosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>A 56-year-old morbidly obese patient</td>
</tr>
<tr>
<td>admitted to the hospital with severe</td>
</tr>
<tr>
<td>that fails to respond to intravenous</td>
</tr>
<tr>
<td>antibiotics. On hospital day 3, he</td>
</tr>
<tr>
<td>undergoes a right below-knee amputation</td>
</tr>
<tr>
<td>and, although recovering well,</td>
</tr>
<tr>
<td>complains of severe pain postoperati-</td>
</tr>
<tr>
<td>vely. His blood cultures drawn at</td>
</tr>
<tr>
<td>admission are negative. His past</td>
</tr>
<tr>
<td>medical history is significant for</td>
</tr>
<tr>
<td>diabetes mellitus and chronic</td>
</tr>
<tr>
<td>lower extremity ulceration that is</td>
</tr>
<tr>
<td>evidenced by the increased serum</td>
</tr>
<tr>
<td>bicarbonate with a decreased pH. This</td>
</tr>
<tr>
<td>is consistent with a history of obesity,</td>
</tr>
<tr>
<td>which can lead to a restrictive pattern</td>
</tr>
<tr>
<td>of lung disease characterized by chronic</td>
</tr>
<tr>
<td>respiratory insufficiency. An acute</td>
</tr>
<tr>
<td>respiratory alkalosis is present</td>
</tr>
<tr>
<td>because the expected degree of renal</td>
</tr>
<tr>
<td>compensation is not present as it would</td>
</tr>
<tr>
<td>of the PCO₂ to levels of 110 mm Hg.</td>
</tr>
<tr>
<td>The acute respiratory failure is most</td>
</tr>
<tr>
<td>likely secondary to narcotic overdose,</td>
</tr>
<tr>
<td>and thus fentanyl is the most likely</td>
</tr>
<tr>
<td>causative agent.</td>
</tr>
</tbody>
</table>

**Table 42.9: Causes of Respiratory Alkalosis**

<table>
<thead>
<tr>
<th>Cause of Respiratory Alkalosis</th>
<th>Example</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypoxia</td>
<td>High altitude</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>Severe V/Q mismatch</td>
</tr>
<tr>
<td>Lung diseases</td>
<td>Pulmonary fibrosis</td>
</tr>
<tr>
<td>Pulmonary edema</td>
<td>Pulmonary embolism</td>
</tr>
<tr>
<td>Drugs</td>
<td>Salicylates</td>
</tr>
<tr>
<td>Progestosterone</td>
<td>Nicotine</td>
</tr>
<tr>
<td>Direct stimulation of respiratory drive</td>
<td>Psychogenic hyperventilation</td>
</tr>
<tr>
<td>Carboxis</td>
<td>Gram-negative sepsis</td>
</tr>
<tr>
<td>Pregnancy (progestosterone)</td>
<td>Excessive mechanical ventilation</td>
</tr>
<tr>
<td>Neurologic disorders (e.g., pontine tumors)</td>
<td></td>
</tr>
</tbody>
</table>

**Note:** Table 42.9 lists the most likely causes of respiratory alkalosis with their examples. The laboratory values are consistent with acute respiratory acidosis, secondary to fentanyl, likely in the setting of a chronic respiratory acidosis, and probably secondary to restrictive lung disease from obesity. The chronic respiratory acidosis is evidenced by the increased serum bicarbonate with a decreased pH. This is consistent with a history of obesity, which can lead to a restrictive pattern of lung disease characterized by chronic respiratory insufficiency. An acute respiratory alkalosis is present because the expected degree of renal compensation is not present as it would be if the patient had a chronic elevation of the PCO₂ to levels of 110 mm Hg. The acute respiratory failure is most likely secondary to narcotic overdose, and thus fentanyl is the most likely causative agent.
production of HCO$_3^-$). This compensatory response is maximal 3 to 4 days following the onset of alkalemia and leads to further decrease in serum HCO$_3^-$. Clinical Presentation. Respiratory alkalosis may lead to a wide range of clinical manifestations ranging from alteration in consciousness, perioral paresthesias, and muscle spasms to cardiac arrhythmias. In addition, alkalemia also can affect metabolism of divergent ions. By stimulating glycolysis, alkalemia causes phosphate to shift from the extracellular space into the intracellular compartment as glucose-6-phosphate is formed. Additionally, the level of ionized calcium in the blood may also decrease due to increased binding of calcium to albumin.

Treatment. The underlying cause for respiratory alkalosis should be sought (Table 42.9). Curhosis can lead to respiratory alkalosis through impaired clearance from the circulation of progesterones and estrogens, similar to pregnancy (58). This is a commonly seen acid-base disorder in the intensive care unit. In psychogenic hyperventilation, rebreathing air using a bag increases the systemic PCO$_2$ and can treat alkalemia. Specific therapy, other than treatment of the underlying cause, is typically not necessary.

Case Scenario #8: Severe Acute Respiratory Alkalosis: A Potential Complication of Mechanical Ventilation

A 42-year-old patient with morbid obesity is admitted to the hospital with shortness of breath and fever. In the emergency room, he is started on intravenous antibiotics. Over the next 3 hours, he becomes severely short of breath and develops a diminished level of consciousness. He is intubated and placed on mechanical ventilation. His past medical history is significant for diabetes mellitus and hypertension. The social history is significant for smoking for 20 years. Current medications include amlodipine 5 mg PO daily, enalapril 5 mg PO bid, and hydrochlorothiazide 12.5 mg PO QD. Physical exam shows blood pressure of 156/80 mm Hg, pulse of 70 beats/minute, and temperature of 100.8°F. The patient is morbidly obese. The cardiovascular exam is normal. Lung exam reveals bilateral breath sounds with diffuse crackles on the right and egophony. Thirty minutes after mechanical ventilation laboratory studies are sent, with the following results:

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum</td>
<td></td>
</tr>
<tr>
<td>Sodium (mEq/L)</td>
<td>140</td>
</tr>
<tr>
<td>Cholesterol (mg/dL)</td>
<td>187</td>
</tr>
<tr>
<td>Bicarbonate (mg/dL)</td>
<td>97</td>
</tr>
<tr>
<td>BUN (mg/dL)</td>
<td>13</td>
</tr>
<tr>
<td>Creatinine (mg/dL)</td>
<td>0.9</td>
</tr>
<tr>
<td>Phosphorus (mg/dL)</td>
<td>4.0</td>
</tr>
<tr>
<td>Albumin (g/dL)</td>
<td>3.9</td>
</tr>
<tr>
<td>Glucose (mg/dL)</td>
<td>146</td>
</tr>
</tbody>
</table>

Arterial blood gas
- pH: 7.56
- PO$_2$: 80 mm Hg
- PCO$_2$: 340 mm Hg

What PCO$_2$ goal should be targeted in order to correct the acid-base disorder and attain a normal pH?

The respiratory rate should be decreased to maintain the pH at a level of about 55 mm Hg, as this will lead to a pH of approximately 7.4. When a patient with chronic respiratory acidosis and appropriate renal compensation is placed on mechanical ventilation, he or she is at risk of developing a posthypopcapnic metabolic alkalosis, as occurred in this case. Quickly lowering the PCO$_2$ in a patient with an elevated bicarbonate can lead to a dangerous degree of alkalosis. This occurs because mechanical ventilation can remove PCO$_2$ from the blood quickly, thus increasing the pH precipitously. However, it takes time for the kidney to adapt to the change in blood pH. In time, the kidney can adapt by decreasing bicarbonate reabsorption, leading to loss of bicarbonate in the urine; but this does not happen quickly, usually requiring a minimum of 24 to 36 hours. The appropriate measure is to decrease the minute ventilation to reduce the PCO$_2$ level to a level that would lead to a normal or slightly acidic pH. The target PCO$_2$ can be calculated by using the Henderson-Hasselbalch equation; however, this degree of precision is not always necessary. The minute ventilation can simply be decreased and titrated to achieve the desired pH.

**MIXED ACID-BASE DISORDERS**

Mixed acid-base disorders are more difficult to diagnose than simple acid-base disorders. A good general rule is to keep in mind that in patients with a known primary acid-base disorder, a mixed disorder needs to be suspected if the pH is normal or if the apparent “compensation” has led to a pH that is beyond the normal. For example, if a patient with metabolic acidosis has a pH of 7.47, this indicates an accompanying respiratory alkalosis since a compensation would not lead to an alkaline pH if the primary disorder is an acidosis.

**Metabolic and Respiratory Acidosis**

In this mixed disorder, respiratory compensation is insufficient for the degree of decrease in bicarbonate. The most extreme example of this mixed-condition disorder occurs following cardiopulmonary arrest. In this setting, there is a decrease in bicarbonate levels—a metabolic acidosis secondary to lactic acidosis—and retention of carbon dioxide secondary to respiratory arrest. The pH in this setting is very low. Mixed metabolic and respiratory acidosis is also commonly seen in patients with a primary metabolic acidosis and concomitant lung disease. The lung disease impairs the ability of the patient to increase the ventilatory rate to appropriately decrease the PCO$_2$. Furthermore, this combination of disorders can manifest as a patient with a chronically elevated PCO$_2$ and an inability to increase the serum bicarbonate. This would indicate a chronic respiratory acidosis and possibly a metabolic acidosis due to a “normalized” serum bicarbonate in a setting in which the bicarbonate would be expected to be elevated. Finally, the presence of an anion gap, despite a normal serum bicarbonate level, should raise the index of suspicion for this combination of conditions.

**Metabolic and Respiratory Alkalosis**

Acidemia is better tolerated than is alkalemia. For example, a pH of 7.2 is well tolerated, whereas a pH of greater than 7.6 is associated with significant mortality. Mixed metabolic and respiratory alkalosis can lead to a significant elevation in the pH and is therefore very serious. This condition typically occurs in patients on mechanical ventilation. Often, mechanical ventilation, by mandating a minimum minute ventilation, will not allow the patient to elevate the PCO$_2$ significantly in response to alkalemia. Frequently, the metabolic alkalosis in this setting...
Section IV: Essential Physiologic Concerns

is due to diuretic use, administration of bicarbonate solutions, or massive transfusions with a citrate load.

Respiratory Alkalosis and Metabolic Acidosis

Most commonly, this combination is seen in Gram-negative sepsis, which can stimulate the respiratory drive—resulting in respiratory alkalosis—and also cause circulatory collapse with subsequent lactic acidosis. In the medical intensive care unit, salicylate intoxication classically leads to a mixed metabolic acidosis and respiratory alkalosis (23). Salicylates directly lead to an anion gap metabolic acidosis, and they also directly stimulate respiration.

Approach to Mixed Acid-base Disorders

There is no simple algorithm to use in the approach to a mixed acid-base disorder. The approach outlined in Figure 42.5 assumes that only a single disorder is present. Complex acid-base problems should be suspected when the values cannot be explained by a single disorder and its compensation. An example of this might be a patient with lactic acidosis and an alkaline pH.

Key Points

1. In patients with a known primary acid-base disturbance, a mixed acid-base disorder should always be suspected if the pH is normal or the “compensation” has surpassed the normal pH.
2. Mixed metabolic and respiratory acidosis occurs when the respiratory compensation is insufficient for the degree of decrease in bicarbonate.
3. The presence of an increased anion gap despite normal serum bicarbonate levels should raise suspicion for mixed metabolic acidosis and metabolic alkalosis.
4. Non-anion gap metabolic acidosis and anion gap metabolic acidosis can coexist.
5. Gram-negative sepsis is a common cause of respiratory alkalosis and metabolic acidosis.

Case Scenario #9: Mixed Acid-base Disorder: Metabolic Acidosis and Respiratory Acidosis

A 64-year-old is admitted to the intensive care unit with pneumonia and septic shock. The patient states that he has had increasing shortness of breath and fever over the past 4 days. His past medical history is significant for hypertension. Surgical history is significant for a previous cholecystectomy. Medications include amiodipine and hydrochlorothiazide. Physical exam shows a blood pressure of 85/50 mm Hg, pulse of 110 beats/minute, and temperature of 101.8°F. The cardiovascular examination is significant for a 2/6 systolic murmur and there are crackles over his entire right lung field. There is trace pedal edema. Chemistry values on admission are given below:

<table>
<thead>
<tr>
<th>Test</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sodium (mEq/L)</td>
<td>135</td>
</tr>
<tr>
<td>Potassium (mEq/L)</td>
<td>4.8</td>
</tr>
<tr>
<td>Chloride (mEq/L)</td>
<td>101</td>
</tr>
<tr>
<td>Bicarbonate (mEq/L)</td>
<td>10</td>
</tr>
<tr>
<td>BUN (mg/dL)</td>
<td>22</td>
</tr>
<tr>
<td>Creatinine (mg/dL)</td>
<td>1.4</td>
</tr>
<tr>
<td>Phosphorus (mg/dL)</td>
<td>2.8</td>
</tr>
<tr>
<td>Albumin (g/dL)</td>
<td>3.8</td>
</tr>
<tr>
<td>Glucose (mg/dL)</td>
<td>115</td>
</tr>
<tr>
<td>Arterial blood pH</td>
<td>6.85</td>
</tr>
<tr>
<td>PO2 (mm Hg)</td>
<td>51</td>
</tr>
<tr>
<td>PCO2 (mm Hg)</td>
<td>45</td>
</tr>
</tbody>
</table>

What acid-base disorder(s) is (are) present in this patient?

The acid-base disorder is a mixed anion gap metabolic acidosis with a respiratory acidosis. The decrease in bicarbonate accompanied by an elevated anion gap is consistent with a primary metabolic acidosis. The expected PCO2 using the Winter formula \(\text{PCO}_2 = (\text{HCO}_3^- - 1) \times 4 + 18\). The PCO2 is significantly elevated above this level, and thus a respiratory acidosis is present. The PCO2 is much higher than would be expected based on the degree of acidemia, and thus a respiratory acidosis, secondary to inadequate ventilation from pneumonia, is present.

References

The last few decades have yielded significant insights into the mechanisms of acute cerebral injury. The most important finding has been that a significant proportion of neurologic damage after injury occurs secondarily and, thus, is potentially preventable or treatable. This discovery has altered the approach to acute neurologic injury and, coupled with improved diagnos-
tic techniques, has reversed the therapeutic nihilism that had previously marked the field. In this chapter, we will attempt to provide a foundation in the basics of cerebrovascular physiology. Based on these foundations, we will attempt to outline a rational approach to the treatment of both general and specific neurologic emergencies.
**CEREBRAL METABOLISM AND HYPOXIC ISCHEMIC BRAIN INJURY**

Approximately 20% of the cardiac output and oxygen consumption is utilized by the human brain, which accounts for only 2% of the total body mass (1). The majority of cerebral oxygen consumption occurs at the highly metabolically active gray matter structures of the brain. The relatively high metabolic activity of these cells is needed to sustain the electrical activity, synthesis of transmitters, and maintain the infrastructure of the cell (2).

The central nervous system utilizes intracellular stores of phosphocreatine and adenosine triphosphate (ATP) as its energy source. These stores are constantly replenished through the aerobic oxidative phosphorylation of glucose at the inner membrane of the neuronal mitochondria. Glucose is the main substrate for brain metabolism, with specific glucose transporters in the capillary endothelium providing entry into the neuronal cytoplasm. Brain energy reserves are limited. Electrical activity is inhibited within seconds, and cellular breakdown occurs within minutes of lack of oxygen delivery to the neurons. Anaerobic metabolism provides only a small amount of the energy needed to maintain neuronal cellular activity (2).

Under normal conditions, cerebral blood flow (CBF) and regional distribution of oxygen are tightly coupled. Increases in cerebral metabolism lead to an increase in the delivery of oxygen and glucose to metabolically active tissue. Cerebral blood flow is, by convention, measured in milliliters of flow per 100 g of tissue per minute. Normal CBF ranges between 30 and 70 mL/100 g/min. The cerebral metabolic rate of oxygen consumption (CMRO₂) is the rate of oxygen utilized by cerebral tissues. It is calculated by the Fick method of measuring the product of CBF and the cerebral oxygen arterial–venous difference of an inert nondiffusible substance. Direct and indirect methods exist to estimate both CBF and CMRO₂. Cerebral oxygen delivery (CMDO₂) is the product of CBF and the oxygen-carrying capacity of hemoglobin. The normal mean capillary partial pressure of oxygen (PO₂) is approximately 65 mm Hg, representing a difference between normal arterial PO₂ (90–95 mm Hg) and venous PO₂ (35–40 mm Hg). Normal values for standard measures of CBF, CMRO₂, and CMDO₂ are detailed in Table 43.1.

Cerebral ischemia develops if cerebral oxygen utilization cannot meet metabolic demands. This can result from problems with cerebral oxygen delivery, increased metabolic demands, or impaired oxygen utilization. Decreases in CMDO₂ can occur with decreases in cerebral blood flow due to stroke, increased intracranial pressure (ICP), decreased cardiac output, or hypotension. The cerebral metabolic rate increases with increased cerebral activity; seizures, or hyperthermia. Blood loss or carbon monoxide poisoning can decrease the oxygen-carrying capacity (3).

Inadequate oxygen delivery due to decreased CBF is the most common cause of cerebral ischemia. Synaptic transmission, and hence electrical activity, discontinues at CBF below 15 to 20 mL/100 g/min. Further decreases in CBF lead to ischemic cell damage and decreased brain metabolism (3). Cerebral oxygen delivery can also be affected by changes in the concentration of oxygen bound to hemoglobin. Hemoglobin has a high affinity for binding oxygen, with greater than 90% of the hemoglobin binding sites for oxygen saturated at arterial partial pressures of oxygen (PaO₂) greater than 70 mm Hg. Increasing PaO₂ with increases in inspired oxygen above this level, therefore, has little effect on oxygen delivery. However, a large oxygen gradient is needed at the cellular level to provide an adequate pressure gradient for the oxygen molecule to diffuse to the mitochondrial inner membrane. The critical required PO₂ at the level of the mitochondria is estimated at 3 mm Hg, hence, at low oxygen gradients (venous PO₂ levels below 30 mm Hg), cerebral insufficiency will develop (2).

Several mechanisms exist to maintain oxygen delivery to the brain. Cerebral hyperperfusion will lead to the depolarization of medullary neurons mediating sympathetic output, which consequently results in a compensatory increase in blood pressure and heart rate. Decreased cerebral perfusion leading to decreased arterial oxygen delivery to the cerebral capillary bed will lead to venodilation lowering of the postcapillary pressure and increasing flow across the capillary bed. Oxygen extraction bound to hemoglobin is increased across the capillary bed as CBF continues to decrease. This increase in oxygen extraction can be detected by measuring jugular venous blood and comparing its arterial oxygen content. Finally, increases in local hydrogen ion concentration will occur as ischemia develops, presumably due to lactate production from anaerobic metabolism. The resultant shift in the oxygen delivery curve of hemoglobin to the right will result in increased oxygen release from hemoglobin to the local cerebral tissue. Cerebral ischemia can be categorized into focal and global causes. *Focal ischemia* occurs when there is severe or complete reduction of blood flow to one of the major arteries of the brain. Neurologic impairment develops in functional patterns attributable to the particular arterial distribution that is involved. This most commonly is seen secondary to embolic or atheroembolic large vessel occlusion. *Global ischemia* refers to severe reductions or cessation of blood flow to the entire brain. This most commonly occurs after cardiac arrest but can be seen in any condition that leads to global cerebral hyperperfusion or hypoxia (2,3).

Cerebral tissues exhibit selective vulnerability to ischemia. Neurons are the least resistant to cerebral ischemia, followed by oligodendroglia, astrocytes, and endothelial cells in order of

<table>
<thead>
<tr>
<th>TABLE 43.1</th>
<th>NORMAL VALUES FOR CEREBRAL BLOOD FLOW AND METABOLISM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cerebral blood flow (CBF)</td>
<td>50 mL/100 g/min</td>
</tr>
<tr>
<td>Systemic arterial oxygen content (CaO₂)</td>
<td>14–20 mL/100 mL</td>
</tr>
<tr>
<td>Jugular venous oxygen content (CvO₂)</td>
<td>8–13 mL/100 mL</td>
</tr>
<tr>
<td>Jugular venous oxygen saturation (SjvO₂)</td>
<td>65%</td>
</tr>
<tr>
<td>Cerebral arterial–venous oxygen content difference</td>
<td>6.3 mL/100 mL</td>
</tr>
<tr>
<td>Cerebral oxygen delivery (CMDO₂ = CBF × CaO₂)</td>
<td>10 mL/100 g/min</td>
</tr>
<tr>
<td>Cerebral metabolic rate of oxygen consumption</td>
<td>3.5 mL/100 g/min</td>
</tr>
</tbody>
</table>
susceptibility. Specific neuronal populations also exhibit selective vulnerability to ischemia and hypoxia. The most susceptible neurons to anoxia are the CA1 and CA3 cell populations located in the medial hippocampus. These cells are the most widely connected and have the highest resting metabolic rate of all neurons. Similarly, highly metabolically active cells with high susceptibility to ischemia include the cerebellar Purkinje cells, cortical cell levels 3 and 5, and the medium-size neurons of the stratum (2,4).

Vascular patterns of neuronal injury encountered with cerebral anoxia can be attributed to the selective ischemic vulnerability of varying cerebral cell types, coupled with the different mechanisms by which ischemia or hypoxia can occur. watershed or border zone infarctions occur at the boundary between the perfusion territories of the large cerebral arteries. Hypoxia after cardiac, septic, or hemorrhagic shock is the most common etiology for this phenomenon. Selective loss of neurons in the hippocampus, basal ganglia, cortex, and cerebellum can lead to laminar necrosis of these tissues, and may occur after ischemia leads to cell death in these cells, but circulation is restored prior to involvement of other neuronal cell populations. Dysmyelination of the central white matter can develop in the setting of hypotension where hypoxia does not occur. Cerebral white matter is believed to be selectively vulnerable to this condition due to its decreased resting regional CBF compared to the more metabolically active gray matter (2).

Neuronal cell death is a product of both the severity and time of ischemia; thus, incomplete degrees of ischemia can be tolerated for longer periods of time. However, there is a critical threshold of ischemia that will ultimately lead to necrosis. The duration and severity of ischemia needed to reach a critical threshold can be modified by metabolic factors such as hyperglycemia, temperature, and metabolic activity. Critical reductions of oxygen, therefore, produce significant but nonfatal degrees of ischemia and neuronal function. Lethal reductions of oxygen imply that some threshold has been crossed that will lead to a series of events, and ultimately to cell death (2).

Oxygen deprivation leading to neuronal cell death proceeds through several distinctive steps. The high metabolic activity of neurons rapidly depletes oxygen-derived ATP and phosphocreatine stores, resulting in failure of synaptic transmission. The electroencephalogram (EEG) at this point becomes flat, and consciousness is lost. Electrical failure occurs as CBF falls below 16 to 20 mL/100 g tissue/minute and cerebral oxygen consumption falls below one-third of its normal resting metabolism, but restoration of CBF after electrical failure will allow functional recovery of the cell. Further decreases in CBF to less than 10 mL/100 g tissue/minute will lead to failure of the energy needed to maintain the activity of the membrane sodium potassium pump. As flow continues to decrease, membrane depolarizations occur, and ionic gradients are lost as potassium effluxes from the cell and sodium and water enter the cells, leading to the development of cytotoxic edema (Fig. 43.1). Release of excessive amounts of glutamate is believed to mediate the process of excitatory cell death after ischemia. Normally, glutamate, an excitatory neurotransmitter, is released into the synaptic cleft and rapidly cleared by energy-dependent cellular uptake mechanisms. In the setting of energy failure, extracellular glutamate levels increase. Most glutamate neurotoxicity is mediated through N-methyl-D-aspartate (NMDA) receptors. Stimulation of these receptors activates calcium channels-mediated entry into the cell. Intracellular calcium subsequently activates a number of destructive enzymatic processes, including protease destruction of structural proteins and phospholipase destruction of plasma membranes, with release of arachidonic acid and endonucleases capable of fragmenting DNA repair mechanisms. Mitochondrial uptake of calcium leads to the interruption of electron transport and the development of oxygen-free radicals (1,3,5,6).

The above process leads to necrosis of brain tissue with distinctive neuropathologic features. Necrosis is characterized by cellular swelling, membrane wall lysis, and a resultant inflammatory reaction to clear the necrotic tissue. Cells die in groups, leaving large areas of necrotic tissue (7). Apoptosis, or programmed cell death, also occurs in cerebral ischemia. Apoptosis is an organized and regulated form of cell death where intra- and extracellular signals lead to a programmed process of cell death with preservation of the mitochondria. Pathologically, apoptosis leads to cell shrinkage, chromatin condensation, and dissolution of the cell membrane. Inflammation is not commonly seen. These two distinctive forms of cell death probably represent a spectrum of the biochemical and morphologic changes that can occur in cerebral ischemia (1). In focal ischemia and infarction, a central region of necrosis can be surrounded by a potentially viable area of tissue described as the ischemic penumbra. The ischemic penumbra can be defined through CBF measurements and electrophysiology, or biochemical and genetic methods. The penumbra, by definition, is tissue that is potentially salvageable if circulation is restored. Neurocritical care focuses on methods to restore flow to the ischemic penumbra and potentially limit the extent of neuronal cell death.
REGULATION OF CEREBRAL CIRCULATION

Methods of Cerebral Blood Flow Measurements

The study of modern cerebrovascular physiology began in the 1940s when Kety and Schmidt described a direct method for quantifying CBF based on the Fick principle (8). The original Fick equation stated that oxygen uptake in the lung was equal to the product of cardiac output and the arteriovenous difference of oxygen (9). Kety substituted nitrous oxide, an inert, nonmetabolizable, diffusible tracer in place of oxygen (10), and thus, the accumulation of nitrous oxide in the brain was substituted for the absorption of oxygen in the lungs (11). This technique is still considered the gold standard for quantifying CBF, but is invasive and limits measurements only to global CBF (12).

The development of external detection systems allowed for the use of radioactive tracers to measure regional areas of CBF. Focal perfusion and washout of substances could be used to determine flow into local brain regions. Xenon\(^{133}\), a diffusible \(\gamma\)-emitting substance, was used initially as an injection and later through inhalation. Perfusion and washout were calculated using a rotating \(\gamma\)-counter. Later, the application of computed tomographic techniques (Xenon CT) allowed for improved resolution of regional areas of cerebral blood flow (rCBF) (13). Single photon emission computed tomography (SPECT) uses technetium\(^{99}\) as a ligand to measure rCBF, and is the most commonly used technique to measure CBF. Technetium\(^{99}\) crosses the blood–brain barrier and is trapped within cells. The tracer accumulates in varying brain regions according to the rate of delivery, and thus is a marker for rCBF. Multidetector systems are used to quantify the accumulation of tracer (14). Positron emission tomography (PET) is similar to SPECT in that an external detector is used to measure an accumulated radioactive substance. The generation and use of positrons, however, significantly improve resolution. A positron is an electron with a positive charge formed by the decay of radioisotopes. It requires a cyclotron or linear accelerator for its production. The collision of a positron with an electron produces two photons that are sent off at 180 degrees. The simultaneous detection of these photons allows for improved resolution and three-dimensional reconstruction of CBF. In addition to measuring CBF, different radiolabeled ligands can be used to measure cerebral blood volume (CBV), glucose metabolism, or cerebral oxygen extraction. PET provides the highest quan
tifiable measure of rCBF and can be used for a variety of physiologic experiments (15). However, it is expensive, requires a cyclotron, and is limited to a few academic centers (Fig. 43.2).

New techniques of bolus tracking with magnetic resonance imaging (MRI) and computed tomography (CT) have allowed for acute assessments of cerebral perfusion. In these techniques, a bolus of a contrast agent is detected either through changes in the T\(_2\) signal or Hounsfield units. Estimations of CBF can be made by measuring the transit time required for these boluses to pass through cerebral tissue. These techniques are being used widely for the acute assessments of cerebral infarctions (16,17).

Factors that Regulate Cerebral Blood Flow

Cerebral autoregulation refers to the capacity of CBF to remain constant despite changes in cerebral perfusion pressure. It is a pressure phenomenon that needs to be differentiated from the effect of carbon dioxide and arterial oxygen tension on CBF. This control, and thus the shape of the autoregulatory curve, can be modified by a number of extrinsic factors. Hypertension, hypocapnia, and increased sympathetic nervous activity will increase both the upper and lower ranges of autoregulation. Chronic hypotension, hypercapnia, and parasympathetic activity will lower the set points of autoregulation. The autoregulatory curve will shift upward with advancing age. In the healthy, normotensive individual, CBF is a pressure-passive phenomenon below perfusion pressures of 50 to 60 mm Hg and above perfusion pressures of 150 to 160 mm Hg. Between these broad parameters, CBF increases only slightly (18,19) (Fig. 43.3).

In most vascular beds, autoregulation occurs at the level of the arterioles. A significant proportion of vascular resistance in the cerebral circulation, however, is modulated at the level of the cerebral arteries. In cats, dogs, and monkeys, approximately 40% of the cerebral vascular resistance is mediated by changes in the baseline puls arterial diameter of vessels greater than 400 \(\mu\)m in diameter (20). In response to hypotension, both cerebral arteries and arterioles will dilate to maintain constant CBF. Vessel dilation progresses from the largest vessels to the smallest with decreases in cerebral perfusion pressure (21). Cerebral arterioles will also continue to dilate below the lower limit of autoregulation (19). Further drops in pressure flow slowly across the capillary bed and lead to an increase in the oxygen extraction coefficient.
The myogenic theory postulates that the local changes in cerebral blood flow that are not significant. Alternately, myogenic factors may work synergistically with metabolic factors, providing changes in vascular tone that may optimize the metabolic response (26).

Metabolic Theory. The metabolic theory of pressure autoregulation postulates that the local changes in cerebral blood flow found with changes in cerebral metabolic activity are mediated through the release of local neurochemical substances from the nonvascular cells of the central nervous system (18). The tight coupling of flow to metabolism and the timing of autoregulation support this postulated mechanism. Several substances have been suggested including hydrogen ion concentrations, carbon dioxide, nitric oxide, adenosine, potassium, and calcium (27). Experimental evidence exists in favor of and against all of the postulated mediators (18,28–30). Varying combinations have also been suggested. Most recently, changes in potassium levels mediated through alterations in calcitonin gene-related peptides have been suggested as a mechanism of arteriolar dilation (31). Changes in cerebral perfusion pressure have been observed that alter the degree of endothelial oxygen tension, and have been suggested as an important mechanism for autoregulation (32).

Neurogenic Influences. The role of direct neurogenic influences on cerebral autoregulation is limited. As mentioned, the sympathetic and parasympathetic nervous system plays a role in modulating the cerebral autoregulatory curve. However, direct neural control over small arteries or arterioles that regulate focal changes in CBF does not occur, and other intrinsic nerve fibers may be in a position to regulate vascular tone (33). The localization or central control of these nerves has so far proved elusive (18,34).

Regulation of Cerebral Blood Flow by Carbon Dioxide and Oxygen

Changes in the partial pressure of carbon dioxide (PaCO₂) have significant effects on CBF. A 1-mm Hg change in PaCO₂ results in an approximately 2.5% to 4% change in CBF. This effect is more pronounced in the gray matter than white matter. The response curve of PaCO₂ is sigmoidal, with the CBF response flattening below 15 to 20 mm Hg and above 100 mm Hg. The vasodilation occurs in all vessel sizes but is most pronounced on the smaller arterioles (11) (Fig. 43.4).

Changes in vessel diameter are mediated through alterations in cerebrospinal hydrogen ion concentrations (CSF pH). The direct application of CO₂ or bicarbonate to pial arterioles does not affect vessel diameters. Since CO₂ is freely diffusible across the blood–brain barrier, changes in PaCO₂ will affect both cerebrospinal fluid hydrogen ion and bicarbonate concentrations (35). The response of changes in hydrogen ion concentration is relatively short-lived, lasting only a few hours, as the choroid plexus of the brain will compensate for changes in hydrogen ion concentration by adjusting the production of cerebrospinal fluid bicarbonate (36).

At partial pressures of oxygen below 50 mm Hg, there is a rapid increase in CBF. Again, this is more significant in gray, as opposed to white, matter. There is a linear relationship between

Mechanisms of Cerebral Autoregulation

There are several theories that have been proposed to explain the mechanisms of cerebral autoregulation. These can be broadly categorized into the myogenic, metabolic, and neurogenic hypotheses of autoregulatory control (18).

Myogenic Theory. The myogenic theory postulates that the smooth muscle cells of the cerebral arteries and arterioles contract or dilate in response to the transmural pressure generated across the vessel wall (22). This may be mediated by alterations in the position of the actin myosin filament in the vessel wall (23). Another theory is that changes in vessel wall shear stress induced by alterations in blood flow induce the release of vasoactive substances from the vascular endothelium that subsequently leads to vessel wall constriction or dilation (24). The myogenic theory is supported by the rapidity with which cerebral autoregulation occurs, although the myogenic theory by itself cannot account for all of the regulation that occurs. In jugular venous hypertension, cerebral arterial pressure is increased. While this condition should lead to arterial vasoconstriction, vasodilation is most commonly found under these circumstances (25). It is thus postulated that myogenic factors may play a significant role only when metabolic factors are not significant. Alternately, myogenic factors may work synergistically with metabolic factors, providing changes in vascular tone that may optimize the metabolic response (26).

From hemoglobin (18). Continued hypotension progresses to cerebral hypoperfusion and ischemia as previously discussed. In a similar fashion, cerebral pial arteries and arterioles will constrict as perfusion pressure increases. Maximal vasoconstriction occurs at cerebral perfusion pressures of 160 to 170 mm Hg. Above these pressures, there is a forced vasodilation of the cerebral vessels with a large increase in CBF. The ensuing hypertensive encephalopathy is due to blood-brain barrier disruption and the development of cerebral edema (21). The initial distribution of this edema commonly is located in the occipital lobes. This is speculated to occur due to the limited sympathetic innervation of the posterior circulation.

Cerebral blood flow remains constant between cerebral perfusion pressures (CPP) of 50 and 150 mm Hg (solid line). Superimposed curve of cerebral blood volume (CBV) at variable CPP (dotted line). The top portion of the figure illustrates the cerebral arteriolar caliber. Note that at CPP below the level of cerebral autoregulation, arteries and arterioles begin to collapse (passive collapse). CBV decreases from a point of maximal dilation seen near the lower end of CA (vasodilatory cascade zone) to a constant blood volume (zone of normal autoregulation). Higher CPP leads to autoregulatory breakthrough and parallel increases in both CBF and CBV (autoregulatory breakthrough zone). ICP, intracranial pressure. (From Rose JC, Mayer SA. Optimizing blood pressure in neurological emergencies. Neurocrit Care. 2004;1:287–299.)

FIGURE 43.3. Cerebral autoregulatory curve with cerebral blood flow remaining constant between cerebral perfusion pressures (CPP) of 50 and 150 mm Hg (solid line). Superimposed curve of cerebral blood volume (CBV) at variable CPP (dotted line). The top portion of the figure illustrates the cerebral arteriolar caliber. Note that at CPP below the level of cerebral autoregulation, arteries and arterioles begin to collapse (passive collapse). CBV decreases from a point of maximal dilation seen near the lower end of CA (vasodilatory cascade zone) to a constant blood volume (zone of normal autoregulation). Higher CPP leads to autoregulatory breakthrough and parallel increases in both CBF and CBV (autoregulatory breakthrough zone). ICP, intracranial pressure. (From Rose JC, Mayer SA. Optimizing blood pressure in neurological emergencies. Neurocrit Care. 2004;1:287–299.)

Neurogenic Influences. The role of direct neurogenic influences on cerebral autoregulation is limited. As mentioned, the sympathetic and parasympathetic nervous system plays a role in modulating the cerebral autoregulatory curve. However, direct neural control over small arteries or arterioles that regulate focal changes in CBF does not occur, and other intrinsic nerve fibers may be in a position to regulate vascular tone (33). The localization or central control of these nerves has so far proved elusive (18,34).

Regulation of Cerebral Blood Flow by Carbon Dioxide and Oxygen

Changes in the partial pressure of carbon dioxide (PaCO₂) have significant effects on CBF. A 1-mm Hg change in PaCO₂ results in an approximately 2.5% to 4% change in CBF. This effect is more pronounced in the gray matter than white matter. The response curve of PaCO₂ is sigmoidal, with the CBF response flattening below 15 to 20 mm Hg and above 100 mm Hg. The vasodilation occurs in all vessel sizes but is most pronounced on the smaller arterioles (11) (Fig. 43.4).

Changes in vessel diameter are mediated through alterations in cerebrospinal hydrogen ion concentrations (CSF pH). The direct application of CO₂ or bicarbonate to pial arterioles does not affect vessel diameters. Since CO₂ is freely diffusible across the blood–brain barrier, changes in PaCO₂ will affect both cerebrospinal fluid hydrogen ion and bicarbonate concentrations (35). The response of changes in hydrogen ion concentration is relatively short-lived, lasting only a few hours, as the choroid plexus of the brain will compensate for changes in hydrogen ion concentration by adjusting the production of cerebrospinal fluid bicarbonate (36).

At partial pressures of oxygen below 50 mm Hg, there is a rapid increase in CBF. Again, this is more significant in gray, as opposed to white, matter. There is a linear relationship between
Section IV: Essential Physiologic Concerns

**FIGURE 43.4.** Alterations in cerebral blood flow with changes in the partial pressure of carbon dioxide. Note the S-shaped curve, with flat portions at the extremes of the curve. Data obtained from normotensive dogs. (From Harper AM, Glass HI. Effect of alterations in the arterial carbon dioxide tension on the blood flow through the cerebral cortex at normal and low arterial pressures. J Neurol Neurosurg Psychiatry. 1965;28:449–452.)

The arterial oxygen content and CBF in hypoxia (Fig. 43.5) (21,37). Vasoactive effects may be mediated directly through oxygen or adenosine A$_2$ receptors (11).

**FIGURE 43.5.** Alterations of regional cerebral blood flow to changes in arterial oxygen tension. Note oxygen tensions below approximately 50 lead to a sharp increase in regional cerebral blood flow (rCBF). Regional areas of cerebral blood flow. In: Welch KMA, Caplan LR, Reis DJ, et al., eds. Primer on Cerebrovascular Disease. San Diego: Academic Press; 1997:58-60.)

Normal ICP measures between 5 and 8 mm Hg, with statistical variations ranging as high as 15 mm Hg. Beyond this level, some degree of intracranial pathology should be suspected (38). Normal ICP fluctuates rhythmically, approximately 3 to 5 mm Hg. The sinusoidal pattern of this fluctuation can be seen on ICP pressure traces and was originally described by Traube and Hering (39). The origin of the ICP waves is unknown, but may have to do with phasic constriction and dilation of the cerebral arterioles (40). Cerebral perfusion pressure (CPP) is the perfusion pressure of blood through the brain. This is defined as the pressure difference between mean arterial pressure (MAP) and mean jugular venous pressure. However, when ICP is greater than jugular venous pressure, ICP is substituted for jugular venous pressure, and hence, CPP is typically reported as MAP – ICP (36).

The intracranial pressure volume curve demonstrates a relatively flat portion where increases in volume are accommodated with little change in pressure. At some inflection point, these processes are exhausted, and small changes in volume lead to larger increases in ICP. (Fig. 43.6). This pressure volume curve may, thus, represent the displacement of various fluids from the intracranial space.

The approximate contents of the intracranial cavity consist of the brain parenchyma (75%), blood (20%), and CSF (5%). Most of the intracranial blood resides on the venous side of the circulation (38). According to the Monroe doctrine, the overall volume of the contents of the intracranial cavity must remain constant. Accordingly, any increase in the intracranial contents from venous engorgement, intracerebral hemorrhage, tumors, edema, etc., must be compensated by an equal displacement of fluids or tissue. Monroe postulates that the flat portion of the ICP volume curve represents displacement of CSF into the more compliant spinal subarachnoid space. Progressive increases in volume lead to further displacement of venous and arterial blood. Finally, brain tissue is displaced and herniation will occur (Fig. 43.6) (41).

Intracranial compliance can be determined by measuring the change in ICP to a given volume. A volume pressure response (VPR) is estimated by measuring the ICP response to an infusion of 1 mL of sterile saline into an intraventricular catheter (42). Small changes in response to this increased volume suggest that the patient was on the flat portion of the volume pressure curve. Increases in ICP greater than 4 mm Hg in response to 1 mL of fluid would suggest that intracranial reserve was limited. A more widely used index to measure intracranial compliance has been the pressure volume index (PVI). This index estimates the volume needed to increase ICP by a factor of 10 (43).

Spontaneous and sustained elevations in ICP were noted by Lunberg early in the study of cerebral hemodynamics (44). The origin of these “plateau waves” had been speculative until the 1970s when Rosner et al. provided a potential rationale as to how these could develop. Rosner accounted for these waves through the observation of subtle changes in MAP and ICP, and their effect on CBV and ICP. Rosner observed that plateau waves were always preceded by subtle drops in CPP. As previously noted, decreases in CPP will lead to cerebral vasodilation of the cerebral arterioles and arteries, which consequently...
FIGURE 43.6. Three forms of the intracranial pressure volume curves. The curve on the left represents the traditional teaching that compensatory mechanisms allow for small changes in pressure as intracranial volume increases. The middle section suggests that pressure may be better defined as the force per unit area needed to displace a certain volume of the intracranial contents. The last section suggests that the traditional pressure volume curve actually represents superimposed displacement curves of varying substances in the cranial cavity. At low pressures (flat portion), cerebral spinal fluid is displaced downward into the compliant spinal subarachnoid space. As pressure increases, venous and arterial blood are displaced before brain parenchyma is displaced at very high pressures (cerebral herniation). CSF, cerebrospinal fluid. (From Rosner MJ. Pathophysiology and management of increased intracranial pressure. In: Andrews BT, ed. Neurosurgical Intensive Care. New York: McGraw-Hill; 1993:57–112.)

result in an increase in total CBV through an increase of blood in the cerebral venous system. At some point, however, continued decreases in CBF will lead to a decrease in CBV (Fig. 43.3) (45). The cerebral engorgement of blood that occurs with the initial decrease in MAP increases ICP and decreases CPP, thus initiating a cycle of decreasing CPP, increasing CBV, and increasing ICP. The process is spontaneously reversed by an acute elevation of blood pressure from a Cushing response. This sympathetic response occurs in the setting of decreased CPP as the brainstem center’s modulating sympathetic activity becomes oligemic (46). Rosner has used these observations as the basis for management of cerebral perfusion pressure due to head trauma (41).

Cerebral Edema

Intracranial hypertension can be caused by expanding masses, cerebral engorgement, or the development of cerebral edema. Cerebral edema may compress brain structures, leading to herniation, or reduce cerebral perfusion with subsequent infarction (47). Cerebral edema is roughly defined as an increase in the brain tissue water and sodium content of the extravascular space (48). Cerebral edema is, therefore, different from brain engorgement, which represents an increase in the blood volume of the intravascular space (49).

Cerebral edema can be defined according to its location or mechanism of production. According to location, edema can occur either inside the brain cells (intracellular) or outside the cells and the intravascular space in the interstitium (interstitial). While certain forms of cerebral edema may predominate, pure forms of either type of edema rarely exist. Cytotoxic edema is the term employed to describe the intracellular edema that develops after the loss of cell wall integrity (50). The terminology implies a toxic etiology, but it is most often seen in cellular energy failure due to ischemia or hypoxia. Vasogenic edema represents an expansion of the interstitium due to disruption of the capillary blood-brain barrier, which allows the extravasation of fluid from the intravascular space. Interstitial edema develops secondary to increases in the hydrostatic pressures of the ventricular system draining the CSF. Osmotic edema refers to the intracellular swelling that occurs due to rapid changes in brain sodium concentrations or the osmotic disequilibrium syndromes (48).

MECHANISMS OF BRAIN INJURY AND THERAPEUTIC CONCERNS

Immediate Concerns

The most important features in managing acute neurologic injury are rapid transport to a trauma center or stroke center; management of airway, oxygenation, and circulation issues; careful and repeated monitoring; and prompt head imaging, with immediate medical or surgical management of expanding mass lesions (51). The mechanisms of neurologic injury will, of course, vary depending upon the nature of the injury, but all will include—to some degree—secondary injury caused by cerebral ischemia. In head trauma, shearing injury develops due to different deceleration rates of gray and white matter. The resultant disruption of neurologic tracts is followed by a period of ischemia and secondary injury. Prolonged seizure activity in status epilepticus leads to hippocampal ischemia, cell death, and atrophy (52). A zone of ischemia surrounds all areas of cerebral infarction and cerebral hemorrhage (53).

The primary goal of acute neurologic management is to prevent secondary injury. This is attained by initiating measures
Chapter 37.5: Essential Physiologic Concerns

Section IV: Essential Physiologic Concerns

to support cerebral oxygen delivery and limit cerebral metabolism. Hypoxemia, hypotension, expanding mass lesions, persisting edema, and intracranial hypertension all potentially worsen secondary injury by limiting cerebral oxygen delivery and increasing cerebral metabolism. Immediate attention and correction of the above problems can have a significant impact on both immediate and long-term outcome (51–53). A sense of urgency of the treating team is critical to providing early and aggressive resuscitative efforts (53).

The specific management of acute neurologic emergencies will vary according to the nature of the illness or injury, but some general concepts can be applied to all neurologic emergencies. The basics of all life support protocols focus on the initiation of adequate airway control, restoration of adequate respiration, and circulation. Loss of pharyngeal tone leading to airway obstruction can occur in patients with a depressed level of consciousness. Impairment of respiratory drive can occur after seizures, head trauma, anoxic injury, stroke, or metabolic disturbances. Decreases in cerebral perfusion are common after head or multisystem injury, shock, sepsis, and hemorrhage.

The acute management of neurologic injury must focus on the maintenance of cerebral oxygen delivery. To accomplish this goal, adequate oxygenation, respiration, and blood pressure must be ensured. Airway control via endotracheal intubation for the neurologic patient should be performed immediately in all patients with a Glasgow coma score (GCS) of 8 or less. Supplemental oxygenation and red blood cell transfusions should be given to provide adequate oxygenation. Once the basics of life support have been secured, a rapid history should be obtained from supporting personnel or family members, in many circumstances, the patient will be unable to provide an adequate history. The immediate details surrounding the incident are crucial to understanding the nature or type of injury. A general physical exam prior to the neurologic assessment should focus on possible trauma or other medical conditions. Raccoon eyes or a Battle sign (bruising of the orbits and mastoid region respectively) is evidence for a basilar skull fracture. In head trauma with loss of consciousness, neck injury should be assumed and cervical stabilization provided. A fundoscopic exam may reveal papilledema or subhyaloid hemorrhages. Underlying body or breath odors may suggest intoxication. New onset atrial fibrillation may be the only clue to subclinical seizure activity. A rapid neurologic assessment focusing on the level of consciousness, the cranial nerve exam, and any localizing features can be obtained within minutes. The GCS is commonly used as a quantitative assessment of neurologic function (54).

More recently, a new coma score has been developed that has been validated in the neurointensive care unit (55) (Fig. 43.7). Further validations of this scale are under way in nonneurologic populations both worsened outcome and increased length of stay (70).

In addition to the above measures designed to maintain adequate cerebral oxygen delivery, there has been a growing interest in the role of temperature, glucose, and blood pressure modulation in the management of neurologic injury. There is a large body of evidence in standardized laboratory animal models of cerebral ischemia that elevations in brain temperature both increase the amount of neuroapathologic damage to injured tissue and induce damage to brain areas not usually involved (61). Excitotoxicity is believed to be the most likely mechanism for induction of these changes.

Hyperthermia

Hyperthermia increases both glutamate release and extracellular concentration. Free radical production is accelerated, and the sensitivity of neurons to excitotoxic injury is increased (62, 63). The role for excitotoxicity is corroborated by a noted increase in cellular acidosis and depolarization in the ischemic penumbra. Other postulated mechanisms for neurologic damage with hyperthermia include inhibition of protein kinases responsible for synaptic transmission and cellular repair, and the release of neuronal proteases. The latter is believed to be the mechanism for worsening cerebral edema at higher brain temperatures (64–67). Hyperthermia worsens outcomes in ischemic stroke patients (68), with a 2.2-fold increase in morbidity and mortality for every 1° increase in temperature above 37.5°C (69). Similarly, these results have been extended to the neurologic intensive care unit population. Hyperthermia in this population both worsened outcome and increased length of stay (70).

Hypothermia

Hypothermia may have a neuroprotective role in preventing many of the neuroapathologic changes described with hyperthermia. Early applications of hypothermia protocols were problematic, with significant cardiac complications occurring below temperatures of 30°C. Most protocols were used during
Chapter 43: Central Nervous System


**Eye response**

4 Eyelids open or opened, tracking, or blinking to command
3 Eyelids open but not tracking
2 Eyelids closed but open to loud voice
1 Eyelids closed but open to pain
0 Eyelids remain closed with pain

**Eye response (E)**

Grade the best possible response after at least 3 trials in an attempt to elicit the best level of alertness. A score of E4 indicates at least 3 voluntary excursions. If eyes are closed, the examiner should open them and examine tracking of an object or object, tracking with the opening of 1 eyelid will suffice in cases of eyelid edema or facial trauma. If tracking is absent horizontally, examine vertical tracking. Alternatively, 2 blinks on command should be documented. This will recognize a locked-in syndrome (patient is fully aware). A score of E2 indicates the absence of voluntary tracking with open eyes. A score of E2 indicates eyelids opening to loud voice. A score of E1 indicates eyelids open to pain stimulus. A score of E0 indicates no eyelids opening to pain.

**Motor response**

4 Thumbs-up, fist, or peace sign to command
3 Locating to pain
2 Flexion response to pain
1 Extensor posturing
0 No response to pain or generalized myoclonic status epilepticus

**Motor response (M)**

Grade the best possible response of the arms. A score of M4 indicates that the patient demonstrated at least 1 of 3 hand positions (thumbs-up, fist, or peace sign) with either hand. A score of M3 indicates that the patient touched the examiner’s hand after a painful stimulus compressing the temporomandibular joint or supraorbital nerve (localization). A score of M2 indicates any flexion movement of the upper limbs. A score of M1 indicates extensor posturing. A score of M0 indicates no motor response or myoclonic status epilepticus.

**Brainstem reflexes**

4 Pupil and corneal reflexes present
3 One pupil wide and fixed
2 Pupil or corneal reflexes absent
1 Pupil and corneal reflexes absent
0 Absent pupillary, corneal, and cough reflex

**Brainstem reflexes (B)**

Grade the best possible response. Examine pupillary and corneal reflexes. Preferably, corneal reflexes are tested by instilling 2-3 drops of sterile saline on the cornea from a distance of 4-6 inches (this minimizes corneal trauma from repeated examinations). Cotton swabs can also be used. The cough reflex to tracheal suctioning is tested only when both of these reflexes are absent. A score of B4 indicates pupil and cornea reflexes are present. A score of B3 indicates one pupil wide and fixed. A score of B2 indicates other pupillary or corneal reflexes are absent. B1 indicates both pupil and cornea reflexes are absent. A score of B0 indicates pupillary, corneal, and cough reflex (using tracheal suctioning) are absent.

**Respiration**

4 Not intubated, regular breathing pattern
3 Not intubated, Cheyne-Stokes breathing pattern
2 Not intubated, irregular breathing pattern
1 Breaths above ventilator rate
0 Breaths at ventilator rate or apnea

**Respiration (R)**

Determine spontaneous breathing pattern in a nonintubated patient and grade simply as regular R4, irregular R2, or Cheyne-Stokes R3 breathing. In mechanically ventilated patients, assess the pressure waveform of spontaneous respiratory pattern or the patient triggering of the ventilator R1. The ventilator monitor displaying respiratory patterns is used to identify the patient-generated breaths on the ventilator. No adjustments are made to the ventilator while the patient is graded, but grading is done preferentially with Psco within normal limits. A standard apnea (oxygen-diffusion) test may be needed when patient breathes at ventilator rate R0.
cardiac arrest with cardiac and neurosurgical procedures with varying results (71). Moderate hyperthermia (33-34°C) has been employed successfully, with significant improvements in neurologic outcome in two randomized trials for global cerebral ischemia after cardiac arrest (72,73). In both of these protocols, hyperthermia was induced early—within 2 to 8 hours—and maintained for 12 to 24 hours before passive rewarming. Sedation and pharmacologic paralysis were instituted to prevent the hypermetabolism and hyperthermia that occurs with shivering. Hyperthermia, however, failed to improve outcome in a randomized trial of patients with severe head trauma (74). Subgroup analysis revealed worse outcomes in patients older than 45 years and in spontaneous hypothermic patients who were actively rewarmed. It is speculated that the lack of efficacy was due to the delay in the initiation of treatment (71). Hyperthermia has been applied to patients with ischemic stroke in a small case series with promising results (75). A multicenter trial using a randomized application of hyperthermia for large hemispheric infarcts is currently under way.

Hyperglycemia

Glucose control in patients with neurologic injury has recently received a considerable amount of attention. Hyperglycemia has been well documented to increase infarct size and worsen outcome in ischemic stroke (76,77). More recent studies in patients treated with thrombolitics have supported these observations (78-81). The negative effects of hyperglycemia may be limited to large-vessel ischemia or occlusions (82). Hyperglycemia has also been associated with a worsened outcome in subarachnoid hemorrhage (83), and results in head trauma have been inconclusive (84,85).

Hyperglycemia in acute neurologic injury may be attributed to several different mechanisms. The most common proposed mechanism for the development of hyperglycemia is a hormonally induced stress response that occurs with neurologic injury, thus leading to an increase in catecholamine and cortisol release. Other proposed means by which hyperglycemia can occur in neurologic injury include pituitary ischemia, direct irritation of glucose regulatory centers, and the discovery of latent hyperglycemia. The release of local nitric oxide could potentially lead to increased vasodilation and perfusion of the ischemic penumbra surrounding the core of infarct tissue (96). A multicenter glucose and insulin trial in ischemic stroke is currently under way.

Blood Pressure

Blood pressure management in neurologic injury is controversial. Hypertension is common after neurologic injury. The etiology is often multifactorial, and may include underlying hypertension, catecholamine release to pain and stress, direct hypothermic damage, or a physiologic response to volume depletion. The center of the controversy, thus, is determining whether the hypertension encountered during neurologic injury is pathologic or a normal compensatory and protective physiologic response. In addition, cerebral autoregulation is disturbed to varying degrees after brain injury; after the completion of autoregulation, CBF directly correlates with MAP. Disturbances in cerebral autoregulation can be global or focal, involving only areas adjacent to the damaged brain.

The controversy surrounding the optimal blood pressure after neurologic injury is based on competing processes. In areas surrounding neurologic injury, the blood-brain barrier is often damaged. In these areas, hypertension can lead to the development of cerebral edema by increasing the intravascular Starling forces, driving fluid into the interstitium of the brain. Brain area surrounding tumors, arteriovascular malformations, or local areas of trauma or infarction are particularly susceptible. Blood pressure management is often titrated to maintain systolic pressures below 140 mm Hg after neurosurgery to avoid the complications of postoperative edema and breakthrough hemorrhage. In severe carotid stenosis, the CPP to the affected cerebral hemisphere may be compromised, leading to a shift of the cerebral autoregulatory curve to lower blood pressures. Hypertension after carotid endarterectomy may need to be treated to avoid the similar complications of breakthrough hyperemia and hemorrhage. Large cerebral infarcts similarly have a tendency for hemorrhagic conversion with sustained hypertension.

AlTERNATIVELY, overly aggressive management of hypertension after neurologic injury can be potentially deleterious. Brain areas with disturbed autoregulation may require a specific pressure to maintain adequate perfusion. An example of this is the development of plateau waves after head trauma that represents cerebral vasodilatation in response to inadequate cerebral perfusion. Cerebral vasospasm after subarachnoid hemorrhage (SAH) is treated with induced hypertension. In selected small case series, induced hypertension has been used in the treatment of stroke (97). Optimal blood pressure may need to be titrated to the individual patient and disease process.

Endotracheal Intubation

Medical complications are common after neurologic injury and worsen outcome (98,99). The risk of aspiration pneumonia is increased in patients with a depressed level of consciousness. Early recognition and treatment of this complication are needed. Endotracheal intubation is required for neurologic patients who are unable to maintain airway patency or protect their airway from secretions. Endotracheal intubation provides
a poor outcome for patients with ischemic and hemorrhagic stroke (100). The timing of extubation in the neurologic pa-
tient is controversial, since many patients remain intubated solely for airway protection. Dogma mandates that patients remain intubated until their GCS improves to greater than 8. However, a more recent prospective study has suggested that prolonged intubation in neurologic patients increases the rate of ventilator-acquired pneumonias, increases length of stay, and worsens outcomes. The authors recommended early extubation based on the patient's ability to control secretions (101). Alter-
natively, early tracheostomy may be considered.

Cardiac Stunning and Neurogenic Pulmonary Edema
Cardiac stunning and neurogenic pulmonary edema can oc-
cur after acute neurologic catastrophes. This is most com-
monly seen after severe head trauma, subarachnoid hemor-
rhage, status epilepticus, or intracerebral hemorrhage. The mechanism of cardiopulmonary damage is believed to occur through massive catecholamine release mediated through the sympathetic nervous system (102). In neurogenic pulmonary edema, sympathetic-mediated pulmonary vasoconstriction is believed to create the Starling forces necessary to develop pul-
monary edema (103). The sympathetic nervous system also in-
nervates the contractile elements of the pulmonary endothelial cells. Catecholamine-mediated constriction of these cells can lead to opening of the tight junctions of the capillaries, allow-
ing protein to flux into the pulmonary parenchyma (104). The process is self-limited, and aggressive diuresis and high levels of positive end-expiratory pressure (PEEP) are usually adequate to improve oxygenation.

Sympathetically-induced cardiac changes may be more se-
vere. The sympathetic innervation of the heart parallels the cardiac conductive system, which probably accounts for the noted electrocardiogram (ECG) changes that can occur with severe neurologic injury. Deep T-wave inversions are usually reported as “cerebral T waves”; however, the spectrum of sympa-
thetically induced ECG changes is broad, and includes ST elevations and depressions (102). Pathologically, cardiac con-
traction bands are seen surrounding the entry zone of the sym-
pathetic endplates into the myocardium. These bands represent reperfusion injury from ischemic cardiac muscle. The muscle dies in a hypercontracted state and ultimately becomes cal-
cified (105). Cardiac enzymes are elevated, but this finding does not necessarily implicate coronary artery disease. Clini-
cally, myocardial contraction is impaired, and cardiac output and ejection fraction are decreased. Pulmonary edema is com-
mon, complicating an oftentimes concurrent process of neuro-
genic pulmonary edema. More recently, apical ballooning has been described with catecholamine excess, the so-called “Tako-
Tsubo” cardiomyopathy (106). Serial echocardiography sug-
gests that cardiac function usually improves over the course of a week, although it is important to note that the diagnosis of catecholamine-induced cardiac stunning implies a more severe neurologic injury, complicates medical management, and may portend a worse outcome (99).

Sodium Metabolism and Homeostasis
Disturbances in sodium metabolism and homeostasis are found in a variety of neurologic diseases. The syndrome of inap-
propriate antidiuretic hormone (SIADH) may be seen early in head trauma. Circulating levels of antidiuretic hormone (ADH)

are elevated in a number of acute neurologic emergencies sec-
ondary to a catecholamine-induced stress response. This raises the question of whether the hyponatremia encountered is itself due to inappropriate ADH release or simply represents an ap-
propriate but significant release of the hormone. In either case, the release of ADH has significant implication for the manage-
ment of the neurologic patient. Acute hyponatremia leads to the development of intracellular edema, with expansion of the size of the neuronal cell body. Unlike other cells in the body, the neuron needs to maintain its cell size and integrity in order to transmit electrical signals. The cellular response of the neu-
ron to intracellular edema is to extrude intracellular osmoles to reduce the intracellular osmolality and return the cell size to normal (107). Thus, chronic hyponatremia can be tolerated well. However, cellular swelling in response to acute hypona-
tramia will lead to mental obtundation and seizures. Due to these considerations, normal saline is the preferred intravenous solution in the neurologic intensive care unit.

Salt-wasting Nephropathy
A self-limited, salt-wasting nephropathy can develop after SMT. This process will lead to hyponatremia and volume de-
plication if not recognized and treated (108). The etiology re-
 mains somewhat difficult to identify. In dogs and guinea pigs, the process is mediated through the renal sympathetic nerve. Transection of this nerve will prevent salt wasting. This re-
 sponse is species specific, and is not true for rats; the human response is unknown (109). A variety of circulating hormones or substances have been proposed to initiate this response. The leading candidate is the B isoform of atrial natriuretic peptide (ANP), which has been found in some series to be elevated prior to the development of hyponatremia and cerebral vasospasm (110).

Diabetes insipidus (DI) leading to hyponatremia is expected after pituitary surgery, and is seen in any process that affects the hypothalamus or pituitary stalk. Head trauma leading to shearing injury of the pituitary stalk is a common cause for delayed DI. The diagnosis is made by the development of hyponatremia in the setting of hypertonic diuresis that is not induced by diuret-
ics. This process must be differentiated from a postoperative diuresis. Normal postoperative diuresis will not spontaneously develop hyponatremia. Correction of the hyponatremia must be achieved slowly if hyponatremia has been present for more than a few hours (107).
their ICP maintained at less than 20 mm Hg compared with more than 90% mortality for patients who had uncontrollable sustained intracranial hypertension (53,111). Therefore, treat-
ment was focused on measures to decrease ICP, which might include diuresis, aggressive treatment of hypertension, keeping the patient relatively hypovolemic, and elevation of the head of bed.

The work by the Richmond group in the 1970s and 1980s largely changed the focus on head trauma treatment from using measures designed to lower ICP to those designed to maintain adequate CPP. As previously described, in some circumstances, elevations in ICP may be related to inadequate perfusion (41). Treatment thus shifted to include maintaining adequate blood volume and cerebral perfusion, as well as treating sustained elevations in ICP. What constitutes an adequate CPP has been debated and may vary under different conditions; however, the most recent Brain Trauma Foundation guidelines have recom-

mended a minimum CPP of 60 mm Hg (112).

In addition to maintaining adequate cerebral perfusion, a treatment strategy has been proposed that tailors hyperventila-
tion based on the results of jugular venous O2 (SvO2) mon-
itoring (113). In some circumstances, elevated ICP can be at-
tributed to cerebral hyperemia. In this condition, a narrow ar-
terial venous gradient can be normalized by inducing cerebral vasoconstriction through hyperventilation. Similarly, widened arterial venous gradients would suggest a high risk of cere-ral ischemia and prompt efforts to increase cerebral perfu-
sion. Both methods have their proponents, but most agree that attention to details and standardization of care in the severely injured neurologic patient are crucial (114,115).

More recently, brain tissue oxygen monitoring has been used in head trauma to guide therapy. Brain tissue oxygen tension is measured by placement of a small flexible probe, usually through a cranial bolt directly into the brain parenchyma. CBF and PET studies have reported that low oxygen tensions corre-
late with low CBF measures and high oxygen extraction ratios (116,117). Two small observational studies have suggested an improved neurologic outcome with therapies designed to main-
tain brain tissue oxygen tensions greater than 10 mm Hg (118); however, to date, no randomized trials have been completed (119).

Intracranial hypertension is treated through the removal of space-occupying lesions, decreasing cerebral edema or venous engorgement, or expanding the cranial vault. Expanding brain masses—tumors, subdural or epidural hematomas—need to be evacuated as soon as possible to avoid cerebral herniation and damage to important brain structures. Removal of CSF through an external ventricular drain is a means to reduce the volume of the intracranial contents. Placement of an external ventricular drain also allows for the direct measurement of ICP.

Hyperventilation is useful for the acute management of in-
tracranial hypertension. Intracranial hypertension is treated through decreases in CBV that are mediated through arte-
riosclerotic vasoconstriction. Chronic hyperventilation is generally avoided due to concerns that prolonged vasoconstriction may worsen cerebral ischemia (120). The effect of hyperventilation on ICP is also self-limited, generally lasting only 3 to 6 hours; thus, hyperventilation is usually used for ICP control in the acute setting until a longer-acting strategy can be employed. Osmotic agents are typically employed to lower ICP. Mannitol, given in boluses of 0.25 to 1.0 g/kg, is the most commonly used agent in the United States. Mannitol lowers ICP through a number of mechanisms. The intravascular osmotic gradient created by mannitol can lead to extracellular fluid being drawn into the intravascular space and removed through osmotic di-
uresis. Paczynski et al. were able to demonstrate a decrease in hemispheric brain water in a rat stroke model with large bol-
uses of mannitol, although the effect was small and delayed for several hours (121). More likely, mannitol exerts its effect on ICP by decreasing CBV. According to this theory, the os-
mosis gradient initiated by an infusion of mannitol causes an influx of extravascular water into the intravascular space. This leads to a decrease in blood viscosity due to a hemodilution of red blood cell mass and fibrinogen. The decrease in ICP can be explained through the use of the Hagen-Pouisselle equation.

In this equation, flow is indirectly related to the fourth power of the radius of the cerebral vessel and inversely related to serum viscosity. If flow remains constant and viscosity is reduced, then vessel diameter must decrease. CPP, cerebral perfusion pressure. (From Rosner M. Pathophysiology and manage-
ment of increased intracranial pressure. In: Andrews BT, ed. Neurosur-

Hypertonic saline in place of mannitol has been recently advocated. Hypertonic saline may have an advantage of less nephrotoxicity, although this has not been studied. Theoret-
ically, its mechanism of action should be the same as mannitol. Widely used of hypertonic saline, however, has been limited by a lack of a standardized dosing regimen (122,123).

An overall strategy for treating intracranial hypertension is to attempt to maintain the most optimal CPP at the lowest pos-
able ICP. To attain this goal, other maneuvers may be necessary. Sedation and paralysis can be helpful to decrease ICP if chest wall compliance is high or if the patient is exhibiting respira-
tory dyssynchrony with the ventilator. Since the spinal venous plexus lacks valves, there is a theoretical concern that eleva-
tions in PEEP could be transmitted directly to the brain, thus increasing ICP. This is rarely problematic in noncompliant pul-
monary states, but can occur if PEEP is elevated—some would say at a value of greater than 20 cm H₂O—under conditions of increased pulmonary and decreased intracranial compliance (125).

Corticosteroids are useful in treating the vasogenic edema from tumors and meningitis. The use of glucocorticoids in head trauma, though, is not recommended as several randomized trials have found no therapeutic benefit (124–127).

Barbiturates are effective in lowering ICP by decreasing cere-
bral metabolism. Their use is generally reserved for cases of

$$F = \frac{8dPr^4}{\pi n l}$$

where $F$ = flow

$dp$ = pressure gradient (CPP)

$r$ = vessel diameter

$n$ = viscosity

$l$ = vessel length

FIGURE 43.8. Rearrangement of the Pouisselle equation. Flow is di-
rectly related to the fourth power of the radius of the cerebral vessel and inversely related to serum viscosity. If flow remains constant and viscosity is reduced, then vessel diameter must decrease. CPP, cerebral perfusion pressure. (From Rosner M. Pathophysiology and manage-
ment of increased intracranial pressure. In: Andrews BT, ed. Neurosur-
Refractory intracranial hypertension, and dosing is often titrated to a burst suppression pattern monitored on the EEG. One randomized trail reported improved mortality (128) with barbiturate use, although in head trauma, this remains debatable due to the limited quality of life of survivors (129).

Early hemicraniectomy—defined as occurring within 48 hours—with duraplasty is gaining recognition as a possible alternative for treatment of recalcitrant traumatic cerebral edema (130). Future randomized trials will need to be performed for further research.

**Seizure Control and Status Epilepticus**

Seizures are common after neurologic injury and can worsen outcome by increasing metabolic demands beyond oxygen delivery capabilities. Anticonvulsant prophylaxis may be employed for patients with subarachnoid hemorrhage, or intracerebral hemorrhages that abut the cortical surface of the brain. Anticonvulsants are recommended during the first week after severe head trauma to prevent posttraumatic epilepsy (131). Immediate treatment of seizures should utilize generous dosing of benzodiazepines.

Status epilepticus (SE) is a neurologic emergency that is associated with significant morbidity and mortality. Traditional definitions of SE that require 30 minutes of sustained seizure activity or nonarousal between sequential seizures have proved impractical in initiating timely treatment. A new operational definition suggests the immediate treatment of all seizures that last more than 5 minutes (52). Protocols have been developed for the sequential application of anticonvulsants (52). Aggressive early initiation of treatment is important, as SE becomes more difficult to control as seizures continue. It is important to note that SE is often underrecognized. Generalized tonic-clonic movements during electrical seizure activity evolve through a progression of clinical stages where a form of electrical mechan-ical disassociation can occur. Over time, physical movements become progressively more subtle and are manifested only by slight movements of the lips, fingers, or eyelids. A common misconception is to assume that seizures have discontinued after loading with anticonvulsants and initiating pharmacologic paralysis. This underscores the importance of EEG monitoring to ensure that seizures have been adequately treated. Attention to airway management and hemodynamics is important, as many of the anticonvulsants will have respiratory and cardiovascular depressant effects.

Refactory SE is defined as SE that has not responded to the usual first-line medications. Propofol, midazolam, and thiopental—or pentobarbital infusions under EEG monitoring—are required for treatment. However, propofol use has fallen into relative disfavor due to several case reports of deaths during infusions (132,133). It is not used in children with SE due to concerns over the development of a propofol infusion syndrome (114).

**Subarachnoid Hemorrhage**

Mortality from aneurysmal SAH remains high, with 15% of patients dying before getting medical attention (135). The care of patients with SAH can be divided into management before and after a cerebral aneurysm is secured. Management prior to aneurysmal treatment is designed to prevent rebleed-
ing. Rebleeding occurs in approximately one third of all patients with aneurysmal SAH, and is highest within a few days after SAH. Neurosurgeons repair or embolize cerebral vasospasm of the aneurysm is therefore instituted as soon as possible.

Most patients will have acute elevations in blood pressure due to the stress of significant pain and the catecholamine surge that occurs after SAH. Management of blood pressure after SAH is controversial, although most neurosurgeons and neurointensivists will treat acute hypertension in patients with unsecured aneurysms. The rationale for treatment is based on the International Cooperative Aneurysmal trial (136) and, more recently, on a large Japanese observational study that noted a higher incidence of rebleeding in patients with sustained systolic elevations in blood pressure of more than 160 mm Hg (137). Blood pressure is preferentially treated with /3-blockers, which do not significantly affect CBF and can narrow the pulse pressure. Hydralazine and angiotensin-converting enzyme (ACE) inhibitors have minimal effects on CBF. In general, nitroprusside is avoided due to concerns that it may induce cerebral vasoconstriction and increase ICP. Intravenous nicardipine is the drug of choice if intravenous infusion is needed to control blood pressure (135).

The use of antifibrinolytic agents to prevent rebleeding is controversial. Previously a mainstay of treatment, the use of antifibrinolytic agents was largely abandoned after studies revealed increased mortality from the development of cerebral vasospasm. More recently, however, a randomized nonblinded study suggested that rebleeding rates could be decreased without increasing the rate of cerebral vasospasm (138). This study awaits further confirmatory research before antifibrinolytic agents are used after SAH and requires the placement of an external ventricular drain.

Once the aneurysm is secured, care focuses on the evaluation and treatment of cerebral vasospasm. Cerebral vasospasm is a pathologic narrowing of the basal cerebral arteries that occurs after SAH. Pathologically, the cerebral vessels display intimal hyperplasia, collagen remodeling, and a diffuse cellular infiltrate (139). The process takes approximately 4 days to develop and resolves after approximately 2 weeks. This process is initiated by a breakdown product of hemoglobin found in the subarachnoid space. The likelihood of developing cerebral vasospasm is predicted by the amount of subarachnoid blood visualized on a 24-hour CT scan (140). Larger amounts of blood predict a higher likelihood of vasospasm, and the location of the clot usually correlates with the site of most severe vasospasm (141).

Cerebral vessel narrowing can be monitored by the use of transcranial Doppler ultrasonography (TCD). Rising flow velocities may precede the development of neurologic deficits but, oftentimes, will ideally need to be verified by CBF measures to verify the significance of TCD findings (139). The onset of vasospasm is treated with intravascular fluid expansion and hemodynamic augmentation. Cerebral salt wasting can occur, and is best treated with hypertonic solutions and fluidresorpsion. Cerebral autoregulation is impaired in cases of cerebrovascular disease, and may induce cerebral vasoconstriction and increase ICP. Intravenous nicardipine is the drug of choice if intravenous infusion is needed to control blood pressure (135).

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of nearly 75% of ischemic lesions from cerebral vasospasm with the above measures (144). Recalcitrant deficits may require interventional angioplasty to open the narrowed vessels. Nimodipine, a calcium channel blocker, is used as a neuropro- tectant in patients with SAH.

Intracerebral Hemorrhage

Intracerebral hemorrhage (ICH) is bleeding that occurs directly into the brain parenchyma. ICH is classified as primary, sec- ondary to underlying lesions, or spontaneous. The most com- mon etiology of ICH is hypertension, which weakens and rup- tures the small perforating vessels of the basal cerebral arteries. A growing source of ICH is secondary to long-term anticoag- ulant use (145).

Clinically, ICH presents with severe headaches and focal neurologic deficits, usually prompting an immediate transfer to an emergency room. Serial head CT studies have revealed that hematoma expansion occurs in approximately 40% of patients with ICH within the first 6 hours (146). A double- blinded randomized trial suggested that recombinant factor VIIa used within the first 4 hours of ictus decreased the hematoma expansion and improved outcome (147), but questions still re- main, since an increase in thrombotic complications was noted in the treatment group. Acute hypertension is, again, common after ICH, and blood pressure control is controversial since ag- gressive management may extend the ischemic penumbra sur- rounding the hematoma. Conversely, PET studies suggest that modest control of hypertension is safe (148). A large random- ized study evaluating the surgical evacuation of supratentorial ICH did not report a benefit over medical management. How- ever, subgroup analysis did suggest a benefit to evacuation of primarily cortical hemorrhages (149). A subsequent study is currently ongoing. Corticosteroids have not shown any benefit in the treatment of ICH (150).

Ischemic Stroke

The use of thrombolytics has dramatically changed the manage- ment of acute ischemic stroke. The National Institute of Neuro- logical Disorders and Stroke (NIHSD) trial demonstrated im- proved 3-month outcomes in patients treated within 3 hours of onset with intravenous tissue plasminogen activator (tPA) (59). Intrar-terial lysis of clots has been successfully used in small trials and has extended the treatment windows up to 6 hours for the anterior circulation and 12 hours for the pos- terior circulation (58). Most recently, devices used for direct mechanical disruption and removal of intra-arterial clots have been approved (151).

Hypertension is common in the setting of an acute stroke, but usually resolves within a few hours of ictus, and treatment is controversial. Hemorrhagic conversion of ischemic infarc- tions is increased with sustained systolic pressures greater than 180 mm Hg; blood pressure must be below this limit prior to tPA administration (59). However, overly aggressive treatment of blood pressure is commonplace and may actually result in extension of the primary ischemic insult.

Large hemispheric infarctions—defined as strokes involving more than 50% of the middle cerebral artery (MCA) territory—are at risk for the subsequent development of cerebral edema and herniation (152). Close neurologic monitoring is required to identify any signs of deterioration. Treatments designed to lower ICP can be effective but act only as temporizing mea- sures, since cerebral tissue shifts and not increased ICP are most likely to be the source of neurologic deterioration (153). Hemiconractomy has been successfully used in a small case se- ries and one pilot trial (154–156). The application and timing of this procedure, however, remain debatable.

SUMMARY

This chapter has attempted to provide an overview of cerebral vascular physiology and cerebral ischemia. A grasp of these principles is vital to understanding the nature of treatments de- signed to maintain adequate CBF and prevent secondary neu- rologic injury. Future treatments that focus on the details of critical care and maintaining tissue oxygenation show promise in improving outcome after neurologic injury.

PEARLS

Physiology

- Cerebral ischemia develops if oxygen utilization cannot meet the metabolic requirements of the tissue. This most com- monly occurs due to a decrease in oxygen delivery to the cell.
- Ischemia is categorized into focal and global etiologies, with varying brain cell subtypes and neurons displaying selective vulnerability to ischemia.
- Neuronal cell death is a product of the degree and time of ischemia modulated by several metabolic factors.
- Cell death proceeds through several distinctive steps, leading to either necrosis or apoptosis.
- In focal ischemia, a core of central necrotic tissue is sur- rounded by ischemic but potentially viable tissue.

Cerebral Circulation

- Various methods to measure CBF and CMRO2 have been developed and utilized to study cerebrovascular physiology. Newer perfusion techniques involving magnetic resonance and computed tomography perfusion may expand clinical applications.
- Cerebral autoregulation refers to the ability of the cerebral vasculature to maintain constant CBF over a range of CPP.
- Cerebral autoregulation is maintained through a variety of proposed mechanisms that lead to vasospasticity and di- lation of both the cerebral arteries and arterioles.
- Cerebral autoregulation is disturbed in most neuropatho- logic processes and increases the risk of secondary ischemic insult.
- Carbon dioxide and oxygen tensions have distinctive effects on CBF. The effects of carbon dioxide are mediated through changes in CSF hydrogen ion concentration.
- Intracranial pressure volume curves may reflect the pressure needed to displace various cerebral contents from the in- tracranial cavity.
Acute elevations in ICP, known as plateau waves, can be explained by cerebral vasodilation induced by decreases in CPP. Cerebral edema is described by its location and mechanism of production.

**Treatment Issues**

Secondary injury accounts for a significant proportion of the neurologic injury that occurs after stroke, trauma, or seizures.

Secondary injury can be reduced by:
- Prompt transport to a trauma or stroke center
- Initiation of brain resuscitative measures designed to improve cerebral oxygen delivery
- Emergent brain imaging with available neurosurgical procedures as needed
- Serial neurologic assessment and monitoring
- Specific protocols exist for treatment of specific neurologic emergencies.

**General Therapeutic Considerations**

Hyperthermia and hyperglycemia extend neurologic damage in animal models of ischemia and are associated with worse neurologic outcomes.

Moderate hyperthermia improved neurologic outcomes in patients with cerebral anoxia after cardiac arrest and may be helpful for other types of neurologic injury.

Control of hyperglycemia may lead to improved outcomes in neurologic injury.

Blood pressure management after acute neurologic injury needs to be titrated to maintain adequate cerebral perfusion, but not worsen the development of cerebral edema.

Medical complications are frequent after acute neurologic injury and need to be treated aggressively.

**Specific Treatment Options**

Management of head trauma has expanded from the primary focus on lowering ICP to maintaining adequate CPP. Attention to oxygen extraction ratios and brain tissue oxygenation may also improve outcomes.

Status epilepticus is an emergency that can be successfully treated if recognized and treated early.

Treatment of aneurysmal SAH focuses on methods for preventing rebleeding prior to aneurysmal repair and methods to increase CBF during cerebral vasospasm after aneurysm repair.

Early strategies to lyse clots in ischemic stroke and hydrogen ions at critical levels of brain ischemia. Stroke 1975;8:11.


1994;266:H11.


1982;243:H442.


1978;58:656.


Cerebral edema is described by its location and mechanism of production.
664

Section IV: Essential Physiologic Concerns


