Introduction

In the traditional approach to the diagnosis and management of respiratory acid-base disorders, the emphasis is on values for the arterial $P_{CO_2}$ and $P_{HCO_3^-}$. In this chapter, we emphasize the importance of the $P_{CO_2}$ in capillaries of individual organs because this determines whether the bicarbonate ($HCO_3^-$) buffer system can remove $H^+$ during metabolic acidosis. Since most of the bicarbonate buffer system exists in the interstitial compartment and in cells of skeletal muscle, buffering of a $H^+$ load by the bicarbonate
buffer system is impaired if blood flow to skeletal muscle is low and/or the production of CO₂ in muscle is high, as these states are accompanied by a higher capillary and thereby higher cellular P₇CO₂. Therefore, the degree of acidemia will be more severe and more H⁺ will be delivered to and thus bind to intracellular proteins in vital organs (e.g., heart and brain). We refer to this state as a tissue form of respiratory acidosis.

**OBJECTIVES**

- To emphasize that a respiratory acid-base disorder is present when the P₇CO₂ in the extracellular fluid (ECF) and/or in the intracellular fluid (ICF) compartment is higher or lower than expected.
- To illustrate that the arterial P₇CO₂ reflects alveolar ventilation; nevertheless, it also sets the lower limit for the P₇CO₂ in capillary blood of all organs.
- To illustrate that the capillary P₇CO₂ directly determines whether the bicarbonate buffer system is able to remove H⁺ in all organs. Although the capillary P₇CO₂ cannot be measured directly, one can predict its value for an individual organ by measuring the P₇CO₂ in the vein that drains this organ.
- Because the bulk of the bicarbonate buffer system is in skeletal muscle, impaired function of this buffer system results in a larger circulating H⁺ load and thereby, more H⁺ bind to proteins in brain cells.

**CASE 8-1: DOES THIS PATIENT HAVE RESPIRATORY ACIDOSIS?**

*(Case discussed on page 239)*

A 58-year-old man had a myocardial infarction and was brought to hospital with great haste. On arrival in the emergency department, he had a cardiac arrest. He was intubated, ventilated, and successfully resuscitated. Nevertheless, he continued to have a very low cardiac output. At this point, both an arterial and a venous blood were examined.

<table>
<thead>
<tr>
<th></th>
<th>ARTERIAL BLOOD</th>
<th>BRACHIAL VENOUS BLOOD</th>
</tr>
</thead>
<tbody>
<tr>
<td>H⁺ (nmol/L)</td>
<td>50</td>
<td>80</td>
</tr>
<tr>
<td>pH</td>
<td>7.30</td>
<td>7.10</td>
</tr>
<tr>
<td>P₇CO₂ (mm Hg)</td>
<td>30</td>
<td>60</td>
</tr>
<tr>
<td>P₇HCO₃ (mmol/L)</td>
<td>15</td>
<td>18</td>
</tr>
<tr>
<td>L-Lactate (mmol/L)</td>
<td>10</td>
<td>12</td>
</tr>
</tbody>
</table>

**Questions**

Does the patient have respiratory acidosis of the ventilatory type?
Does the patient have respiratory acidosis of the tissue type?
Is the patient able to buffer H⁺ appropriately using his bicarbonate buffer system in skeletal muscle?
PART A
REVIEW OF THE PERTINENT PHYSIOLOGY

THE BICARBONATE BUFFER SYSTEM

This topic was discussed in detail in Chapter 1, page 11; hence, we provide only a brief synopsis in this chapter. The major function of the bicarbonate buffer system is to prevent an unwanted large rise in the concentration of $H^+$ and thereby excessive binding of $H^+$ to proteins in cells, which causes their charge to become more positive (or less negative, $H\cdot PTN^+$; Fig. 8-1). To achieve this “good buffering” of $H^+$, there must be a low $PCO_2$ in the location where the vast majority of $HCO_3^-$ are present (i.e., in the ICF and ECF of skeletal muscle).

Which $PCO_2$ should be used to assess buffering of $H^+$ by bicarbonate buffer in skeletal muscle?

Arterial $PCO_2$

- The arterial $PCO_2$ is the lowest possible value for the $PCO_2$ in capillaries, but it does not reflect the actual value of the capillary $PCO_2$.
- Therefore, the arterial $PCO_2$ does not provide the needed data to assess buffering of $H^+$ by the bicarbonate buffer systems in skeletal muscle.

The $PCO_2$ in arterial blood has the same value as the $PCO_2$ in alveolar air because there are no important diffusion barriers for $CO_2$ in alveoli; hence, it is valuable to assess alveolar ventilation. In acid-base terms, however, it directly influences the function of the bicarbonate buffer system only in the arterial component of the vascular volume. The $PCO_2$ in capillaries is the one that reflects the $PCO_2$ in both the interstitial fluid in the ECF compartment and in cells surrounding these capillaries. Nevertheless, the arterial $PCO_2$ is indirectly related to the $PCO_2$ in capillaries in the brain because the brain has a near-constant rate of consumption of oxygen (and thus $CO_2$ production) and blood flow, because the latter is autoregulated. If autoregulation...

**Figure 8-1** Bicarbonate buffer system and respiratory acid-base disorders. Binding of $H^+$ to ICF proteins increases their net positive charge ($H\cdot PTN^+$) and possibly compromises their function. Thus, the key principle is that new $H^+$ must be removed by binding to $HCO_3^-$ so that very few $H^+$ can bind to proteins ($PTN^0$) in cells. To force $H^+$ to bind to $HCO_3^-$, the $PCO_2$ must fall in cells despite the fact that cells produce an enormous quantity of $CO_2$. 
of blood flow to the brain fails because of a very low effective arterial blood volume in a patient with metabolic acidosis, the $\text{PCO}_2$ rises in brain capillaries, which makes the bicarbonate buffer system ineffective and hence more of the $\text{H}^+$ load binds to proteins in brain cells.

Venous $\text{PCO}_2$

- The $\text{PCO}_2$ in the venous drainage of an organ is determined by the arterial $\text{PCO}_2$ and the amount of $\text{O}_2$ extracted from each liter of blood that is supplied to that organ; the latter is influenced by the rate of blood flow to that organ; more $\text{O}_2$ is extracted from and more $\text{CO}_2$ is added to each liter of blood if blood flow to that organ declines, but its metabolic rate remains largely unchanged.
- At rest, the brachial venous $\text{PCO}_2$ is close to 6 mm Hg higher than the arterial $\text{PCO}_2$.

The venous $\text{PCO}_2$ reflects the $\text{PCO}_2$ in capillaries and hence the $\text{PCO}_2$ in both cells and in the interstitial fluid in their venous drainage bed. CO$_2$ must diffuse from the cell to the capillary; therefore, the $\text{PCO}_2$ in the cell must be at least slightly higher than that in its capillary bed. Because most of the bicarbonate buffer system exists in skeletal muscles, the $\text{PCO}_2$ of brachial or femoral venous blood provides insights into how well the majority of the bicarbonate buffer system in the body is functioning (see margin note). If this buffer system cannot remove $\text{H}^+$ adequately, the concentration of $\text{H}^+$ rises in blood and its $\text{P}_{\text{HCO}_3}$ falls. As a result, more $\text{H}^+$ are delivered to vital organs (e.g., brain cells) and a larger proportion ultimately binds to their intracellular proteins.

OVERVIEW OF $\text{CO}_2$ HOMEOSTASIS

Production of $\text{CO}_2$

- $\text{CO}_2$ is the major carbon end product of oxidative metabolism.
- More $\text{CO}_2$ is produced when there is increased work.

When carbohydrates are oxidized, 1 mmol of $\text{CO}_2$ is produced for every mmol of $\text{O}_2$ that is consumed (the respiratory quotient [RQ] is 1.0; see margin note). In contrast, less $\text{CO}_2$ is formed per unit of $\text{O}_2$ consumed when fatty acids are oxidized (RQ ~ 0.7). On a typical Western diet, the usual RQ is close to 0.8, which reflects the oxidation of the mixture of fat and carbohydrate in the diet.

Factors that influence rate of production of $\text{CO}_2$ at rest

- Overall, cells consume close to 12 mmol of $\text{O}_2$ and produce close to 10 mmol of $\text{CO}_2$ per minute.

When more work is being performed, the rate of consumption of $\text{O}_2$ rises and more $\text{CO}_2$ is produced. For example, during vigorous aerobic exercise, the rate of consumption of $\text{O}_2$ increases close to 20-fold and more $\text{CO}_2$ is produced. In addition, $\text{CO}_2$ is also produced in this setting as a result of buffering of $\text{H}^+$ from 1-lactic acid by $\text{HCO}_3^-$.
CO2 PRODUCTIONS DURING METABOLISM
- There are circumstances when O2 is consumed but no CO2 is produced (e.g., when ethanol or fatty acids are converted to ketoacids in the liver; see Table 8-2 for more discussion).
- There are also settings where CO2 is produced, but no O2 is consumed—examples include fatty acid synthesis with increased flux in the hexose monophosphate shunt or the pentose-phosphate pathway, or during the buffering of H+ by the bicarbonate buffer system.

TABLE 8-1 CLINICAL SETTINGS WITH ALTERED RATES OF PRODUCTION OF CO2

The rate of production of CO2 is shown as mmol/min in a 70-kg adult. These values are estimates and are for illustrative purposes only.

<table>
<thead>
<tr>
<th>STATE</th>
<th>ORGAN</th>
<th>USUAL CO2 PRODUCTION RATE</th>
<th>ALTERED CO2 PRODUCTION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coma/anesthesia</td>
<td>Brain</td>
<td>3</td>
<td>1.5</td>
</tr>
<tr>
<td>Low glomerular filtration rate</td>
<td>Kidney</td>
<td>2</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Cachexia/paralysis</td>
<td>Muscle</td>
<td>2.4</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Vigorous exercise</td>
<td>Muscle</td>
<td>2.4</td>
<td>180</td>
</tr>
<tr>
<td>Ketogenesis</td>
<td>Liver</td>
<td>2.4</td>
<td>0</td>
</tr>
</tbody>
</table>

Removal of CO2

- CO2 excretion = alveolar ventilation x Pco2 in alveolar air.

All of the CO2 produced (~10 mmol/min) enters the venous blood so that it can be transported to the lungs for elimination. Because the cardiac output is 5 L/min at rest, venous blood must carry an extra 2 mmol/L of CO2 (10 mmol/min ÷ 5 L/min) compared with arterial

TABLE 8-2 IMPORTANCE OF THE METABOLIC FUEL UTILIZED IN DETERMINING THE RATE OF CO2 PRODUCTION

The oxidation of carbohydrates produces more CO2 than does the oxidation of fat-derived fuels when viewed in terms of the yield of ATP. No CO2 is produced when O2 is consumed in the liver if fatty acids or ethanol are converted to ketoacids.

<table>
<thead>
<tr>
<th>FUEL</th>
<th>PRODUCTS</th>
<th>mmol CO2/100 mmol ATP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carbohydrate</td>
<td>CO2 + H2O</td>
<td>17</td>
</tr>
<tr>
<td>Fatty acids</td>
<td>CO2 + H2O</td>
<td>12</td>
</tr>
<tr>
<td>Fatty acids</td>
<td>Ketoacids</td>
<td>0</td>
</tr>
<tr>
<td>Ethanol</td>
<td>CO2 + H2O</td>
<td>11</td>
</tr>
<tr>
<td>Ethanol</td>
<td>Ketoacids</td>
<td>0</td>
</tr>
</tbody>
</table>
blood. This 10 mmol of CO₂ is exhaled in 5 L of alveolar ventilation per minute (same numeric value as the cardiac output per minute). If the alveolar ventilation is doubled to 10 L/min (e.g., during metabolic acidosis or salicylate overdose) and if there is no change in the rate of production of CO₂, the P₉CO₂ of alveolar air and arterial blood falls by 50%. Conversely, as alveolar ventilation falls, the concentration of CO₂ in alveolar air must rise in steady state (as does the arterial P₉CO₂) to remove all the CO₂ that is produced (this is akin to the concentration of creatinine in plasma and the glomerular filtration rate (GFR). When the GFR falls to half its usual value, the concentration of creatinine in plasma is double its usual value (Table 8-3).

**Control of ventilation**

As an overview, the concentration of O₂ (6 mmol/L) is much higher than the concentration of CO₂ (2 mmol/L) in alveolar air, and the consumption of O₂ and the production of CO₂ occur in close to a 1:1 ratio. Therefore, the supply of O₂ to the alveolus markedly exceeds demand. Accordingly, it is not surprising that the control of the rate of ventilation is to adjust the P₉CO₂ rather than the P₉O₂ in blood unless the arterial P₉O₂ is quite low (see the discussion of Question 8-2 on page 240 for more discussion).

**PHYSIOLOGY OF CO₂ TRANSPORT**

About 10 mmol of CO₂ are produced per minute, and they diffuse into red blood cells in capillary blood. The carbonic anhydrase in these cells converts CO₂ into H⁺ and HCO₃⁻ (Fig. 8-2). This maintains a low P₉CO₂ in the red blood cells, which aids further diffusion of CO₂. The HCO₃⁻ formed is transported into the plasma in exchange

![Figure 8-2 Carriage of CO₂ in blood](image-url)

**FIGURE 8-2 Carriage of CO₂ in blood.** When CO₂ diffuses into red blood cells, it is converted very rapidly to H⁺ plus HCO₃⁻ because of the high activity of carbonic anhydrase (CAII). As shown in the green shaded area, the resulting H⁺ bind to hemoglobin, which promotes the dissociation of O₂. Most of the CO₂ is carried as HCO₃⁻ in venous blood and delivered to the lungs. Another property of hemoglobin is that it binds CO₂ to form a carbamino compound, and this helps lower the P₉CO₂ in capillary blood (see margin note).
for Cl\(^-\) (“chloride-shift”), and the H\(^+\) bind to deoxyhemoglobin (H\(^+\)•Hgb).

In the lung, the process is reversed. This begins when the high P\(\text{O}_2\) of alveolar air drives the diffusion of O\(_2\) into blood, which raises the P\(\text{O}_2\) in red blood cells and thereby promotes the binding of O\(_2\) to hemoglobin. As a result, the H\(^+\) that are bound to deoxyhemoglobin combine with the HCO\(_3^-\) in red blood cells to form CO\(_2\); this new CO\(_2\) diffuses into the alveoli. The lower concentration of HCO\(_3^-\) in red blood cells leads to the entry of HCO\(_3^-\) on the Cl\(^-\)/HCO\(_3^-\) anion exchanger in their cell membranes with the exit of Cl\(^-\). The net result is the addition of O\(_2\) and removal of CO\(_2\) from capillary blood in the lungs.

### RENAL RESPONSE TO A CHRONIC CHANGE IN P\(\text{CO}_2\)

- The P\(\text{HCO}_3^-\) is higher than normal in chronic respiratory acidosis.

In chronic respiratory acidosis, the intracellular acidosis in proximal convoluted tubule cells leads to an increase in both HCO\(_3^-\) reabsorption and NH\(_4^+\) production and excretion, but for only a transient period; this increase leads to a higher P\(\text{HCO}_3^-\). Therefore, patients with chronic respiratory acidosis have a P\(\text{HCO}_3^-\) that is persistently higher than normal. The opposite occurs in chronic respiratory alkalosis. Thus, individuals with chronic respiratory acid-base disturbances have a different steady-state P\(\text{HCO}_3^-\) and hence H\(^+\) concentration, than those with acute respiratory acid-base disorders (Table 8-4). It is therefore important for the clinician to clarify, on clinical grounds, whether the acid-base disturbance is acute or chronic.

### QUESTIONS

(Discussions on pages 239 and 240)

8-1 Can respiratory alkalosis and respiratory acidosis occur in the same patient at the same time?

8-2 What allows oxygen to diffuse quickly to skeletal muscle cells during the performance of vigorous exercise despite a low P\(\text{O}_2\) in capillary blood?

<table>
<thead>
<tr>
<th>DISORDER</th>
<th>EXPECTED RESPONSE</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Respiratory acidosis</strong></td>
<td></td>
</tr>
<tr>
<td>Acute</td>
<td>For every 1-mm Hg rise in the arterial P(\text{CO}_2) from 40 mm Hg, the plasma [H(^+)] rises by close to 0.8 nmol/L from 40 nmol/L.</td>
</tr>
<tr>
<td>Chronic</td>
<td>For every 1-mm Hg rise in arterial P(\text{CO}_2) from 40 mm Hg, the P(\text{HCO}_3^-) should rise by close to 0.3 mmol/L from 25 mmol/L.</td>
</tr>
<tr>
<td><strong>Respiratory alkalosis</strong></td>
<td></td>
</tr>
<tr>
<td>Acute</td>
<td>For every 1-mm Hg fall in arterial P(\text{CO}_2) from 40 mm Hg, the plasma [H(^+)] falls by close to 0.8 nmol/L from 40 nmol/L.</td>
</tr>
<tr>
<td>Chronic</td>
<td>For every 1-mm Hg fall in arterial P(\text{CO}_2) from 40 mm Hg, the P(\text{HCO}_3^-) should fall by close to 0.5 mmol/L from 25 mmol/L.</td>
</tr>
</tbody>
</table>
PART B
RESPIRATORY ACID-BASE DISORDERS

• The traditional definition of respiratory acid-base disorders is based on changes in the arterial Pbn₂.
• The definition of respiratory acidosis should also include the “tissue” type of respiratory acidosis.

Because there is a very large flux of CO₂ relative to the Pco₂, if a transient discrepancy between production and removal of CO₂ develops, the resultant change in arterial Pco₂ is large enough to cause a significant displacement of the bicarbonate buffer system equilibrium (see Fig. 8-1). A rise in the arterial Pco₂ results in an increased concentration of H⁺ (respiratory acidosis), and a fall in arterial Pco₂ causes a fall in the concentration of H⁺ (respiratory alkalosis). Notwithstanding, it is the capillary Pco₂ (reflected by the venous Pco₂) that determines whether H⁺ are buffered by the bicarbonate buffer system or bind to intracellular proteins.

RESPIRATORY ACIDOSIS

• The hallmark of respiratory acidosis is a high Pbn₂ in arterial and/or venous blood.

Respiratory acidosis can be divided into two types: respiratory acidosis of the ventilatory type and respiratory acidosis of the tissue type.

Ventilatory type

This form of respiratory acidosis occurs when ventilation transiently fails to remove all the CO₂ produced by normal metabolism. As a result, the alveolar Pco₂ rises, and this increases the arterial Pco₂. At this new level of arterial and alveolar Pco₂, all the CO₂ that is produced can now be removed despite the reduced ventilation (see margin note).

The clinician should establish the basis of the hypoventilation. Patients who hypoventilate can be divided into two groups—those who will not breathe (e.g., defective stimuli because of drugs that suppress the respiratory center), and those who cannot breathe (e.g., respiratory muscle weakness, pulmonary parenchymal disease, or obstructive airway disease).

Tissue type

Although this form of respiratory acidosis is less well appreciated by clinicians, it is important to recognize because of its implications for normal function of cells. The arterial Pco₂ might be suitably low, but the venous Pco₂ may still be high because either CO₂ production is increased in cells and/or the rate of blood flow to an organ is not as high as is needed to maintain a low venous Pco₂ (see margin note for a quantitative example). The venous Pco₂ reflects the Pco₂ in capillaries and...
hence the $\text{PCO}_2$ in cells and in the interstitial fluid in this drainage area. As mentioned previously, the $\text{PCO}_2$ of brachial or femoral venous blood provides insights into how well the majority of the bicarbonate buffer system could function. If the bicarbonate buffer system in skeletal muscles (in the cells and interstitial space) does not function adequately, the pH in blood falls and more $\text{H}^+$ bind to intracellular proteins in vital organs, which changes their charge and may affect their shape and function.

**Clinical approach**

The diagnostic approach to the ventilatory type of respiratory acidosis is outlined in Flow Chart 8-1. First, decide whether the patient has chronic lung disease by the history, physical examination, and available past records. Then, compare the acid-base status with that expected for this acid-base disorder. If the expected responses are not present, the patient has a mixed acid-base disorder.

The diagnostic approach to the tissue type of respiratory acidosis is shown in Flow Chart 8-2. The key elements to analyze are reasons for a high production of $\text{CO}_2$ and/or a slow blood flow rate.

**Permissive hypercapnia**

- This name is incorrect, because the primary aim is to minimize the risk of ventilator-induced lung injury—the consequence, however, is a higher arterial $\text{PCO}_2$.

This form of hypercapnia is not “permissive” but rather “permitted” to minimize lung trauma resulting from high pressure/volume ventilation. With the traditional way of mechanical ventilation, although one could achieve better arterial blood gases, the price to pay, especially

---

**FLOW CHART 8-1 Diagnostic approach to respiratory acidosis.** In a patient with an elevated arterial $\text{PCO}_2$, determine whether the patient has acute respiratory acidosis on clinical grounds, because emergency therapy is usually needed. Conversely, if there is no evidence of an acute disorder, the patient may have chronic lung disease or a chronic central reason for hypoventilation. The causes of the acid-base disorder and the laboratory features are shown in the green boxes.
in patients with high airway pressures, is the danger of causing barotrauma and/or a pneumothorax. Hence, the strategy is to deliberately ventilate these patients with a lower tidal volume and pressure. The lungs may be “saved”; however, the ability to exhale CO₂ at a low alveolar Pₐₗₗ₅ is compromised, and the result is a higher concentration of CO₂ in the alveolus and in arterial blood. In other words, hypercapnia is not the goal but rather the consequence of this therapy.

Because a high Pₐₗ₅ causes dilatation of cerebral arterioles, permissive hypercapnia is potentially dangerous in the patient with traumatic brain injury or cerebrovascular disease. Another concern with this mode of ventilation is in the patient with metabolic acidosis, as the high venous Pₐₗ₅ compromises the effectiveness of the bicarbonate buffer system in removing a H⁺ load. Therefore, H⁺ bind to intracellular proteins. This results in a change in their charge and perhaps shape and function, leading to possible detrimental effects on cell function, especially in vital organs (e.g., brain and heart). To date, no prospective, randomized controlled studies have unequivocally demonstrated appreciable improvements in clinical outcome when permissive hypercapnic ventilation was compared with conventional mechanical ventilation.

**RESPIRATORY ALKALOSIS**

Respiratory alkalosis is a common abnormality that is often ignored. In fact, the mortality rate in hospitalized patients with respiratory alkalosis is greater than that in patients with respiratory acidosis, which likely reflects the importance of the underlying disease process. Respiratory alkalosis may result from stimulation of the peripheral chemoreceptors (hypoxemia), the afferent pulmonary reflexes (intrinsic pulmonary disease), or the respiratory center in the brain (Table 8-5). An increase in ventilation may be difficult to recognize clinically, and the diagnosis of respiratory alkalosis is often made only by determination of the blood gases.

Respiratory alkalosis occurs when the removal of CO₂ via ventilation transiently exceeds its rate of production; thus, the alveolar and arterial Pₐₗ₅ fall. If this persists, a new steady state is achieved where the daily production of CO₂ is removed, but at a lower arterial Pₐₗ₅.
A fall in the P\textsubscript{CO\textsubscript{2}} in cells lower their concentration of H\textsuperscript{+} and thereby result in the removal of H\textsuperscript{+} from intracellular proteins. This leads to a change in their charge, shape, and possibly function.

Clinical approach

- Chronic respiratory alkalosis is the only acid-base disorder in which the concentration of H\textsuperscript{+} in plasma may be in the normal range (see Table 8-4 for the expected P\textsubscript{HCO\textsubscript{3}} in a patient with chronic respiratory alkalosis).

The diagnostic approach to respiratory alkalosis begins by deciding on clinical grounds whether there is a disease process present that is associated with acute respiratory alkalosis; if not, the patient is presumed to have chronic respiratory alkalosis. Salicylate intoxication is the most important cause of respiratory alkalosis, and it is discussed in more detail subsequently.

Salicylate intoxication

- Respiratory alkalosis is the usual acid-base disorder that accompanies salicylate intoxication.
- The major issue is not the respiratory alkalosis but rather the toxicity of salicylate anions in cells.
- The treatment is to accelerate the removal of salicylate. If alkali is used, avoid creating a severe degree of alkalemia. If acetazolamide is used, give a small dose because it competes with salicylate for binding to albumin.

Toxicity of salicylate

The major issue with an overdose of aspirin is the toxicity related to the effect of salicylate anions in cells. This may result from direct toxic effects of salicylate on cell functions. It is also possible that this organic acid could uncouple oxidative phosphorylation, akin to dinitrophenol or metformin (see Chapter 6, page 174 for more discussion). This may lead to some of the central nervous system manifestations of salicylate intoxication. For example, if an increased consumption of O\textsubscript{2} and production of CO\textsubscript{2} occurs near the respiratory center, this could stimulate alveolar ventilation and perhaps explain the respiratory alkalosis that is commonly seen in these patients. In severe intoxications, the degree of uncoupling of oxidative phosphorylation may be excessive. If this compromises the rate of conversion of ADP to ATP, anaerobic glycolysis is stimulated and a severe degree of l-lactic acidosis develops (see margin note).

---

**TABLE 8-5 CAUSES OF RESPIRATORY ALKALOSIS**

<table>
<thead>
<tr>
<th>CONDITION</th>
<th>CAUSES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypoxia</td>
<td>Intrinsic pulmonary disease, high altitude, congestive heart failure, congenital heart disease (cyanotic)</td>
</tr>
<tr>
<td>Pulmonary receptor</td>
<td>Pneumonia, pulmonary embolism, asthma, pulmonary fibrosis, pulmonary edema</td>
</tr>
<tr>
<td>stimulation</td>
<td>Drugs Salicylates, alkaloids, catecholamines, theophylline, progesterone</td>
</tr>
<tr>
<td>Central nervous system</td>
<td>Subarachnoid hemorrhage, primary hyperventilation syndrome</td>
</tr>
<tr>
<td>disorders</td>
<td>Miscellaneous Psychogenic hyperventilation, liver cirrhosis, fever, gram-negative sepsis, pregnancy</td>
</tr>
</tbody>
</table>

**ABBREVIATIONS**

ASA, acetylsalicylic acid
SA, salicylate anions
H+SA, nonionized salicylic acid

**UNCOUPLING OF OXIDATIVE PHOSPHORYLATION BY SALICYLATE**

The degree of uncoupling must be low enough to prevent an appreciable rise in the already tiny concentration of ADP, which leads very quickly to very rapid rates of glycolysis. Because the velocity of glycolysis is much greater than that of pyruvate oxidation, the net result is an acute accumulation of l-lactic acid. If the degree were to become more severe, ATP levels will fall, and this can be catastrophic.
Reye’s syndrome is a specific example of central nervous system toxicity of salicylate related to uncoupling of oxidative phosphorylation (see margin note).

The effect of acidemia on the concentration of salicylates in blood and in cells is illustrated in Table 8-6. The key point in this table is that there is a much larger change in the pH outside as compared to inside these cells. Therefore, the concentration of salicylate rises appreciably in cells during acidemia and this should increase its toxicity. Thus, one should take measures to keep the arterial pH in the high-normal to modestly alkalemic range.

### Signs and symptoms

The central nervous system manifestations of aspirin overdose include tinnitus, fever, vertigo, and nausea. The gastrointestinal manifestations include upper abdominal pain, vomiting, and diarrhea. Lung toxicity is manifested by noncardiogenic pulmonary edema. With more severe intoxication, the degree of altered mental status is more profound (e.g., coma), and this may lead, ultimately, to death.

### Acid-base considerations

The most common acid-base disturbance associated with salicylate intoxication is respiratory alkalosis from central stimulation of respiration. Metabolic acidosis may be present in acute salicylate intoxication, but it is not usually an important issue (see margin note).

### Diagnosis

The diagnosis of salicylate intoxication should be suspected on the basis of a history of ingestion or symptoms of tinnitus and light-headedness and a severe degree of respiratory alkalosis. An unexplained ketosis, hypouricemia (high-dose salicylate has a uricosuric effect), noncardiogenic pulmonary edema, or an increased urine net charge (Na⁺ and K⁺ greatly exceed Cl⁻ when the urine does not contain HCO₃⁻, as a result of the excretion of salicylate anions) should

### Table 8-6 Effect of Acidemia on the Concentration of Salicylates in Cells

<table>
<thead>
<tr>
<th></th>
<th>Normal</th>
<th></th>
<th>Acidemia</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ECF</td>
<td>ICF</td>
<td>ECF</td>
</tr>
<tr>
<td>pH</td>
<td>7.4</td>
<td>7.1</td>
<td>7.1</td>
</tr>
<tr>
<td>H•SA (μmol/L)</td>
<td>0.3</td>
<td>0.3</td>
<td>0.6</td>
</tr>
<tr>
<td>Salicylate (mmol/L)</td>
<td>7.0</td>
<td>3.5</td>
<td>7.0</td>
</tr>
</tbody>
</table>

**Reye’s Syndrome**

In these patients, the activity of pyruvate dehydrogenase in the brain may be barely sufficient to regenerate the usual amount of ATP needed by that organ. In the absence of ketoacids, glucose oxidation is the only pathway of importance for ATP regeneration in the brain; hence, a small increment in the degree of uncoupling of oxidative phosphorylation may compromise brain function because of a lower rate of regeneration of ATP and also binding of H⁺ to proteins in brain cells as a result of the production of l-lactic acid.

**Thiamin Deficiency**

Patients with thiamin deficiency also have a decreased activity of pyruvate dehydrogenase in their brain. Therefore, the intake of salicylates can lead to similar sequences in the brain as described earlier.

**Metabolic Acidosis During Salicylate Intoxicaton**

- Toxicity caused by the monovalent salicylate anion occurs when its concentration is 3 to 5 mmol/L. Thus, if the Pₐ⁻gap is elevated by a much greater amount, look for reasons why other anions are present (e.g., l-lactate or ketoacid anions).
- A modest degree of uncoupling of oxidative phosphorylation can increase the production of ketoacids in the liver (see Chapter 5, page 147).
- A more severe degree of uncoupling can lead to l-lactic acidosis.
raise suspicion of salicylate intoxication. The diagnosis is confirmed by measuring the concentration of salicylate in blood.

**Treatment**

- The focus of treatment is to avoid salicylate toxicity in cells.

Dialysis should be instituted if salicylate levels exceed 90 mg/dL (6 mmol/L). If levels of salicylate exceed 60 mg/dL (4 mmol/L), dialysis should be considered, particularly if further absorption is anticipated. In patients with an unexplained decreased level of consciousness, dialysis should be started at even lower levels of salicylate in blood because of the poor prognosis. Hemodialysis is more efficient for the removal of salicylate, but peritoneal dialysis may be considered if there will be a long delay before hemodialysis can be initiated.

In the absence of severe toxicity, the therapeutic efforts in salicylate intoxication are to decrease the concentration of salicylic acid in blood and to promote the urinary excretion of salicylate via the following two maneuvers.

**Alkali therapy.** This should be instituted in a patient with salicylate intoxication who has metabolic acidosis to decrease the concentration of H⁺SA in the blood and thus diminish its diffusion into brain cells (see Table 8-6; Fig. 8-3). Some authorities advise creating an alkaline urine pH to promote salicylate excretion. Notwithstanding, aggressive therapy with NaHCO₃ should be avoided because the patient may become very alkalemic due to the coexistent respiratory alkalosis.

**Use of acetazolamide**

- Acetazolamide, a carbonic anhydrase inhibitor, may be useful in the therapy for salicylate intoxication. Its mechanism of action is controversial.
- Avoid using large doses of acetazolamide because this drug can diminish binding of salicylate to albumin.

The traditional view is that acetazolamide increases the excretion of the salicylate by raising the pH in the lumen of the proximal convoluted tubule, thereby decreasing the concentration of the

**FIGURE 8-3** Nonionic diffusion of salicylic acid versus salicylate anions. The circle represents the cell membrane or the luminal membrane of the proximal convoluted tubule. The assumption made is that the organic acid form of salicylate (H⁺SA) can cross cell membranes by diffusion because it is uncharged, whereas salicylate anions cannot do so (see double vertical lines) unless there is a transporter that can permit transport of salicylate anion.
undissociated acid form of salicylic acid (H-SA), which can cross cell membranes by diffusion (see margin note). Caution is needed, however, since acetazolamide may increase the toxicity of salicylate because it competes with salicylate anions for binding to P_Albumin, which may increase the free salicylate concentration in blood. In addition, acetazolamide may induce acidemia by increasing the excretion of HCO₃⁻ in the urine, which may make more uncharged salicylic acid available to enter cells, and hence increase the toxicity.

There is some experimental evidence in humans, which suggests that 250 mg of acetazolamide has a tubular effect that lasts for about 16 hours. Therefore, very little drug is needed to achieve beneficial effects, and one could use a low dose instead of alkali therapy in the patient with a high blood pH (i.e., >7.5) and a modestly elevated level of salicylate.

---

PART C
INTEGRATIVE PHYSIOLOGY

PHYSIOLOGY OF O₂

The vast majority of O₂ in blood is bound to hemoglobin (4 mmol of O₂ per mmol of hemoglobin). Because blood contains 2 mmol/L of hemoglobin, the content of O₂ in blood is 8 mmol/L (see margin note). The affinity of hemoglobin for O₂ is high, but it can be reduced by elevated concentrations of H⁺, CO₂, and 2,3-bis-phosphoglycerate or 2,3-dis-phosphoglycerate. All of these factors cause the S-shaped oxygen-hemoglobin dissociation curve to be shifted to the right (Fig. 8-4). Therefore, when O₂ is extracted, there is a higher Pₒ₂, which aids in diffusion of oxygen to cells (Fig. 8-5).

---

CONCENTRATIONS OF SALICYLATES
- Under normal conditions, the concentrations of the free acid form are very low and equal inside and outside the cell.
- The concentration of salicylate anions is much lower in cells, as the concentration of H⁺ is higher in the ICF compartment and cell membranes are impermeable to these anions.

---

O₂ CONTENT AND CONCENTRATION OF HEMOGLOBIN
- The concentration of hemoglobin in blood is close to 140 g/L and the molecular weight of hemoglobin is close to 70,000; hence, each liter of blood contains 2 mmol of hemoglobin. Each mmol of hemoglobin carries 4 mmol of O₂.
- The rate of consumption of O₂ is 12 mmol/min.
- With a cardiac output of 5 L/min, 40 mmol/min of O₂ are delivered to body tissues. Therefore, even if the hemoglobin concentration in blood is decreased appreciably, organs can still extract sufficient O₂ to perform their work because each liter of blood has a threefold surplus of O₂. Hence, anemia is virtually never the sole cause of hypoxia-induced lactic acidosis at rest.

---

**FIGURE 8-4** Relationship between the content and concentration of O₂ in 1 liter of blood. The content of O₂ in each liter of blood (shown on the y-axis) has a sigmoid relationship to the arterial Pₒ₂ (shown on x-axis). When the concentration of H⁺ and/or the pCO₂ rises in capillaries, the S-shaped curve is shifted to the right, so the affinity of hemoglobin for O₂ is diminished and the Pₒ₂ rises. Therefore, there is a higher Pₒ₂, which aids the diffusion of O₂.
**THE ALVEOLAR-ARTERIAL $\text{P}_2$ DIFFERENCE**

- Calculation of the alveolar-arterial (A-a) $\text{P}_2$ difference is used clinically to assess the cause of hypoxemia (see margin note).

The arterial $\text{P}_2$ is determined by both the $\text{P}_2$ of alveolar air and the ability of $\text{O}_2$ to diffuse across the alveolar capillary membrane. The A-a $\text{P}_2$ difference is useful to estimate how much of the fall in the arterial $\text{P}_2$ is the result of a change in alveolar $\text{P}_2$ (ventilation) and how much is the result of reduced transfer of $\text{O}_2$ from alveolus to blood (intrinsic lung disease). One must, however, be able to estimate the $\text{P}_2$ of the inspired air to calculate the A-a difference (see margin note). In the alveoli, $\text{CO}_2$ is part of the “non-nitrogen” gases. Therefore, as the $\text{P}_{\text{CO}_2}$ of alveolar air rises, the $\text{P}_2$ falls. One can calculate the alveolar $\text{P}_2$ using the abbreviated alveolar gas equation (see equations).

\[
\text{Alveolar air } \text{P}_2 = \text{inspired air } \text{P}_2 - (\text{arterial } \text{P}_{\text{CO}_2})/\text{RQ}
\]

\[
= \text{inspired air } \text{P}_2 - (\text{arterial } \text{P}_{\text{CO}_2})/0.8
\]

Two major types of pulmonary lesions cause the arterial $\text{P}_2$ to be substantially lower than that of alveolar air. First, blood can pass from the pulmonary artery to the pulmonary vein without perfusing alveoli that have a high $\text{P}_2$ (i.e., a shunt). Second, there may be a barrier to diffusion of $\text{O}_2$ from alveolar air to the capillaries in lungs (e.g., inflammation, pulmonary edema).

The usual value for the A-a $\text{P}_2$ difference is up to 10 mm Hg, and higher values are observed with increasing age. The usual value for the A-a $\text{P}_2$ difference results from mixing of a small shunt of blood with a lower oxygen content with the fully oxygenated blood leaving the lungs.

**Pitfalls in the use of the alveolar-arterial difference**

- The A-a difference uses the $\text{P}_2$ instead of the $\text{O}_2$ saturation, which reflects the content of $\text{O}_2$. 

---

**ALVEOLAR-ARTERIAL $\text{P}_2$ DIFFERENCE**

The difference in $\text{P}_2$ between the alveolar air and arterial blood is referred to as the A-a gradient. In truth, this calculation is a “difference” rather than a “gradient” because diffusion of a nonelectrolyte is involved.

**ESTIMATE THE $\text{P}_2$ OF INSPIRED AIR**

Room air is 21% $\text{O}_2$, barometric pressure is 760 mm Hg, and water vapor pressure is 47 mm Hg. Therefore, the $\text{P}_2$ of inspired air is $0.21 \times (760 - 47)$, or close to 150 mm Hg.

---

**FIGURE 8-5 Delivery of $\text{O}_2$ to mitochondria by diffusion.** The structure on the left is a capillary and the structure on the right is a mitochondrion. A large quantity of $\text{O}_2$ must be delivered to mitochondria in exercise to have a high rate of regeneration of ATP. Both a high $\text{P}_2$ in capillaries and “stirring of the interstitial compartment” are needed for rapid rates of diffusion of $\text{O}_2$ to muscle cells. Nevertheless, the $\text{P}_2$ in mitochondria needs to be only a few mm Hg to regenerate ATP at maximal rates. Hgb, hemoglobin.
O2 is extracted from blood that has a lower content of O2 because of a disease process that causes a reduction in content of O2 in blood from 8 mmol/L to 6 mmol/L results in a large A-a difference because it lies on the flat portion of the oxygen-hemoglobin dissociation curve. Therefore, there is a relatively large fall in its O2, despite a very small change in O2 saturation or the content of oxygen. A similar decrease in its content of O2 of blood, but from 6 mmol/L to 4 mmol/L, results in a much smaller increase in the A-a difference. As a result, a worsening pulmonary condition may not be readily detected by the A-a difference.

2. With a fixed volume of a shunt from pulmonary artery to pulmonary vein, the arterial PO2 is strongly influenced by the content of O2 in the blood in the pulmonary artery (see margin note). Therefore, nonpulmonary factors (e.g., sepsis or liver disease) can influence the magnitude of the A-a difference.

3. In the calculation of the alveolar PO2, one must estimate the amount of O2 removed and replaced by CO2. To do so, one uses the arterial PCO2 and assumes an RQ of 0.8. Notwithstanding, the RQ could be 1.0 if carbohydrate is the only type of fuel being metabolized. This will increase the A-a difference (see margin note for an example).

The pitfalls are the following:
1. The same reduction in O2 content has a different impact on the PO2 at different sites on the oxygen-hemoglobin dissociation curve because of its sigmoid shape (see Fig. 8-4). Therefore, a disease process that causes a reduction in content of O2 of blood from 8 mmol/L to 6 mmol/L results in a large A-a difference because it lies on the flat portion of the oxygen-hemoglobin dissociation curve. Therefore, there is a relatively large fall in its PO2, despite a very small change in O2 saturation or the content of oxygen. A similar decrease in its content of O2 of blood, but from 6 mmol/L to 4 mmol/L, results in a much smaller increase in the A-a difference. As a result, a worsening pulmonary condition may not be readily detected by the A-a difference.

CONTROL OF THE RELEASE OF ERYTHROPOIETIN

• The central issue is that the PO2 at the site of release of erythropoietin should be influenced solely by the concentration of hemoglobin in blood.

The following features make the renal cortex the ideal site for the O2 sensor that regulates the release of erythropoietin because they allow the concentration of hemoglobin to be the only variable that influences the PO2 at the site of the O2 sensor (see margin note).

Fall in PO2 induced by small reduction in the concentration of hemoglobin must be easily recognized

• The key to understanding this sensitivity is revealed by examining the oxygen-hemoglobin dissociation curve (compare the right and the left graphs of Fig. 8-6).

Because the kidney has a large blood flow, only a small amount of O2 is extracted from each liter of blood. When the same amount of O2 is extracted from blood that has a lower content of O2 because of a lower hemoglobin concentration, the drop in PO2 would be larger because one is still operating near the flat part of the sigmoid-shaped oxygen-hemoglobin dissociation curve (see Fig. 8-6).

Ratio of consumption of O2 to delivery of O2 in renal cortex must be constant to ensure that sensor for O2 is exposed to near-constant PO2 unless blood has lower hemoglobin concentration

• O2 is consumed when work is performed.
The vast majority of renal work is to reabsorb close to 99.5% of filtered Na⁺ (see margin note).

The amount of filtered Na⁺ is the product of the GFR and the PNa. Because there is little variation in the PNa in healthy subjects, renal work (or O₂ consumption) is directly related to the GFR. Moreover, the ratio between the GFR (O₂ consumption) and renal plasma flow rate (O₂ delivery)—that is, filtration fraction—does not vary appreciably from day to day in humans (see equation in margin note). This is achieved because the glomerulus lies between two arterial systems, each with different modulators of vessel tone.

A high renal cortical blood flow rate speeds up the diffusion of O₂ from its capillaries to the receptor for O₂ deep in the renal cortex

The high cortical blood flow eliminates another variable, the slow speed of diffusion of O₂. This makes the signal to release erythropoietin related to only an abnormal concentration of hemoglobin in blood (see the discussion of Question 8-2).

A shift in the oxygen-hemoglobin dissociation curve must not interfere with the sensitivity of this system to release erythropoietin

If the oxygen-hemoglobin dissociation curve in capillaries of the renal cortex is always shifted to the right, the PO₂ signal is not influenced by other factors that may influence this shift. In fact, this is achieved by having a high PCO₂ in blood vessels in the renal cortex (~65 mm Hg).
**QUESTIONS**

(Discussions on pages 240 and 242)

8-3 Why might sports anemia (see margin note) be tolerated without an apparent erythropoietin-induced drive to synthesize red blood cells to correct the anemia?

8-4 Why does a young patient with diabetes mellitus who has a high GFR not develop polycythemia?

**DISCUSSION OF CASE 8-1**

**CASE 8-1: DOES THIS PATIENT HAVE RESPIRATORY ACIDOSIS?**

(Case presented on page 223)

Does the patient have respiratory acidosis of the ventilatory type?

The low blood pH (7.30) and low $P_{HCO_3}$ (15 mmol/L) indicate that he has metabolic acidosis. Because the $P_{HCO_3}$ has fallen 10 mmol/L, the expected arterial $P_{CO_2}$ should be close to 30 mm Hg, and it is. Hence, he does not have respiratory acidosis of the ventilatory type.

Does the patient have respiratory acidosis of the tissue type?

Because his brachial venous $P_{CO_2}$ is higher than expected (60 vs. close to 46 mm Hg), he does have respiratory acidosis of the tissue type. To decide why it is present (see Flow Chart 8-2), we see that he has a low cardiac output as a result of his myocardial infarction. It is also possible that he had a high production of CO$_2$ if $L$-lactate + H$^+$ were being released from his muscles and some of the H$^+$ were being titrated by his bicarbonate buffer system.

Is the patient able to buffer H$^+$ appropriately using his bicarbonate buffer system in skeletal muscle?

This patient’s brachial venous $P_{CO_2}$ is higher than expected; therefore, his bicarbonate buffer system is compromised in the interstitial fluid as well as in the ICF compartment of skeletal muscle. Because these sites contain the vast majority of bicarbonate buffer system, a much larger fraction of the H$^+$ load is presented to vital organs because of the more severe acidemia, which results from removing fewer H$^+$ in skeletal muscle. As a result, a much greater number of H$^+$ are bound to proteins in brain cells. This may have untoward effects; therefore, efforts should be made to increase the blood flow rate to skeletal muscles.

**DISCUSSION OF QUESTIONS**

8-1 Can respiratory alkalosis and respiratory acidosis occur in the same patient at the same time?

On the surface, the obvious answer is “no,” because one cannot have a high and a low $P_{CO_2}$ at the same time. Nevertheless, when considered in more depth, and defining events at the cellular level, the answer becomes “yes.”

**SPORTS ANEMIA**

Trained athletes often have a lower hematocrit level that results from a normal red blood cell pool size and an increased plasma volume. Nevertheless, they do not have the expected response to anemia as a result of blood loss where there is evidence of accelerated synthesis of new red blood cells.
Think of ventilation controlling the arterial \( \text{PCO}_2 \) in a patient with diabetic ketoacidosis who is hyperventilating excessively because of aspiration pneumonitis (respiratory alkalosis is present). Because of the low ECF volume, the cardiac output is very low. Now the venous \( \text{PCO}_2 \) is high and therefore the tissue \( \text{PCO}_2 \) is high, so the patient has respiratory acidosis at the cellular level (tissue form of respiratory acidosis is present). This is not just a play on words, because the emergency therapy is to allow buffering of \( \text{H}^+ \) by the bicarbonate buffer system in skeletal muscles (increase their blood flow rate). As a result of reexpansion of the effective arterial blood volume, the \( \text{PCO}_2 \) in brachial and femoral venous blood will fall. This permits more \( \text{H}^+ \) removal by the bicarbonate buffer system in skeletal muscles, which in turn diminishes the binding of \( \text{H}^+ \) to intracellular proteins in vital organs (e.g., in brain cells).

8-2 What allows oxygen to diffuse quickly to skeletal muscle cells during the performance of vigorous exercise despite a low \( \text{PO}_2 \) in capillary blood?

Because \( \text{O}_2 \) is poorly soluble in water, virtually 100% of \( \text{O}_2 \) is transported in blood bound to hemoglobin in red blood cells. It is important to ensure that the \( \text{PO}_2 \) is high in capillary blood so that the diffusion of \( \text{O}_2 \) into mitochondria can proceed at a sufficiently rapid rate (see Fig. 8-5). There are three issues to consider.

1. *Raise the \( \text{PO}_2 \) in capillaries during vigorous exercise*: To have \( \text{O}_2 \) delivery at a high \( \text{PO}_2 \) (\( \text{O}_2 \) concentration), the kinetics of \( \text{O}_2 \) binding to hemoglobin must have special properties. Hence, the shape of the curve relating the content of \( \text{O}_2 \) in 1 liter of blood to its \( \text{PO}_2 \) is S-shaped (see Fig. 8-4). When the objective is to have a large off-loading of \( \text{O}_2 \) from hemoglobin at the highest \( \text{PO}_2 \), this curve must be shifted to the right. The most likely set of signals for this rightward shift can be deduced from the setting where the demand for \( \text{O}_2 \) is maximal—vigorous exercise. Therefore, the signals that cause this rightward shift are the products associated with high rates of ATP turnover (\( \text{CO}_2 \), \( \text{H}^+ \), heat).

2. *“Stirring” of the interstitial compartment*: When the blood flow rate is very high, many more capillaries are open, which shortens the distance for diffusion of \( \text{O}_2 \) and accelerates the speed of the diffusion step. “Stirring” has the same result. The importance of this effect becomes evident when one notes that while the cardiac output rises four to five times during vigorous exercise, the consumption of \( \text{O}_2 \) increases by more than 20 times; virtually all of this rise in cardiac output goes to muscles and the skin for heat dissipation.

3. *Faster diffusion of oxygen through the cytoplasm of muscle*: Because the concentration of \( \text{O}_2 \) is tiny, having \( \text{O}_2 \) bind to another compound with a much higher concentration in muscle cells accelerates this diffusion step. The concentration of myoglobin is high in muscle cells, and its affinity for \( \text{O}_2 \) (a few mm Hg) is in an appropriate range to achieve this function.

8-3 Why might sports anemia be tolerated without an apparent erythropoietin-induced drive to synthesize red blood cells to correct the anemia?

During training, athletes retain extra \( \text{NaCl} \) and water. Thus, they have a larger ECF volume than prior to training. This is retained as long as training persists, even though exercise is performed over
perhaps less than 10% of the day. Part of this extra ECF volume is retained in the vascular bed, which lowers the hematocrit without lowering the red blood cell volume. Perhaps most of this volume is stored in the large venous capacitance vessels; if there were a lower venous tone, this would not provide a signal to excrete the extra Na+ in the urine. In physiologic terms, there may be an advantage when exercise is performed. In this context, the adrenergic surge would cause venoconstriction to cause this “extra” blood to enter the effective vascular volume and lead to an improved cardiac output (see margin note). Thus, physicians may recognize this condition as sports anemia, whereas a thin runner may recognize it by weight gain during training or weight loss that occurs along with a diuresis several days after training stops.

There must also be a diminished stimulus to produce erythropoietin even though anemia is present. We speculate that there may be a lower filtration fraction resulting from less efferent arterial constriction and/or a higher renal blood flow rate, which could cause the PO_2 to be higher deep in the renal cortex. In addition, with higher renal blood flow, there is more vigorous stirring to aid diffusion of O_2 or shorten the distance for diffusion if more capillaries are open (see the discussion of Question 8-2). A new steady state could exist with a low hematocrit, a higher plasma volume, and an altered hemodynamic pattern in the kidney. Direct data are needed to test this hypothesis.

Sports anemia is an example of a change in erythrocytosis, which may occur if the ratio of O_2 consumption (GFR) to O_2 delivery (renal blood flow) is altered because the hemoglobin concentration would not be the only variable that determines the PO_2 near the sensor for the release of erythropoietin. We stress that it is not the GFR per se that alters the signal to cause the release of erythropoietin. Rather it is the ratio of renal O_2 consumption (GFR) to O_2 delivery plus the

**FIGURE 8-7** Possible independent role of the renal blood flow rate on the PO_2 near the receptor for O_2 deep in the renal cortex. The graph depicts the PO_2 that is likely to be present in capillary blood deep in the renal cortex (points to the left of the line depict diffusion) and its fall during diffusion to the site of the receptor for O_2 near the corticomedullary junction (points to the right of the line). The o symbols represent the normal control subjects and the X symbols represent patients with type 1 diabetes mellitus who have hyperfiltration and a higher filtration fraction. Although the capillary PO_2 is likely lower in the group with diabetes, the higher renal blood flow rate may accelerate the slow diffusion step and thereby diminish the fall in PO_2 during diffusion. As a result, the PO_2 near the receptor may not be appreciably different in these two populations.
THERAPY FOR ERYTHROCYTOSIS AFTER RENAL TRANSPLANTATION

Angiotensin-converting enzyme inhibitors are used to diminish the red blood cell mass in this setting. One possible explanation of why these drugs are effective is that they reduce efferent arteriolar tone; hence, they lead to a lower GFR and thereby renal work (O₂ consumption) without influencing the renal blood flow to a major extent. Thus, there is a higher Po₂ in capillary blood in the renal cortex, which diminishes the stimulus for the release of erythropoietin.

EARLY RENAL LESION IN DIABETES MELLITUS

The patients with very early changes of diabetes mellitus are not necessarily symptomatic. Therefore, what is called “early” is likely to represent a somewhat later stage of the disease.

8-4 Why does a young patient with diabetes mellitus who has a high GFR not develop polycythemia?

The hyperfiltration early on in patients with diabetes mellitus does not lead to erythrocytosis despite the fact that they may have higher filtration fractions and thereby, a lower Po₂ in renal cortical capillaries. To explain this finding, it is noteworthy that this population, with diabetes, has higher renal plasma flow rates (see margin note). If a higher blood flow rate could minimize the fall in Po₂ in the slow diffusion step between capillaries and the receptor for O₂ deep in the renal cortex, there may not be a lower Po₂ near its receptor to signal the release of more erythropoietin (Fig. 8-7). Hence, one must examine both the filtration fraction and the renal blood flow rate to deduce what the Po₂ may be deep in the renal cortex.