chapter 8

Respiratory Acid–Base Disturbances

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_{HCO3}. 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 CO_2 in muscle is high, as these states are accompanied by a higher capillary and thereby higher cellular P_{CO_2}. 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 P_{CO_2} in the extracellular fluid (ECF) and/or in the intracellular fluid (ICF) compartment is higher or lower than expected.
- To illustrate that the *arterial* P_{CO_2} reflects alveolar ventilation; nevertheless, it also sets the lower limit for the P_{CO_2} in capillary blood of all organs.
- To illustrate that the *capillary* P_{CO_2} directly determines whether the bicarbonate buffer system is able to remove H^+ in all organs. Although the capillary P_{CO_2} cannot be measured directly, one can predict its value for an individual organ by measuring the P_{CO_2} 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.

		ARTERIAL BLOOD	BRACHIAL VENOUS BLOOD
H^+	nmol/L	50	80
pH		7.30	7.10
P_{CO_2}	mm Hg	30	60
P_{HCO_3}	mmol/L	15	18
L-Lactate	mmol/L	10	12

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, $H{\bullet}PTN^+$; Fig. 8-1). To achieve this "good buffering" of H^+, there must be a low P_{CO_2} in the location where the vast majority of HCO_3^- are present (i.e., in the ICF and ECF of skeletal muscle).

Which P_{CO_2} should be used to assess buffering of H^+ by bicarbonate buffer in skeletal muscle?

Arterial P_{CO_2}

- The arterial P_{CO_2} is the lowest possible value for the P_{CO_2} in capillaries, but it does not reflect the actual value of the capillary P_{CO_2}.
- Therefore, the arterial P_{CO_2} does not provide the needed data to assess buffering of H^+ by the bicarbonate buffer systems in skeletal muscle.

The P_{CO_2} in arterial blood has the same value as the P_{CO_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 P_{CO_2} in *capillaries* is the one that reflects the P_{CO_2} in *both* the interstitial fluid in the ECF compartment and in cells surrounding these capillaries. Nevertheless, the arterial P_{CO_2} is indirectly related to the P_{CO_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

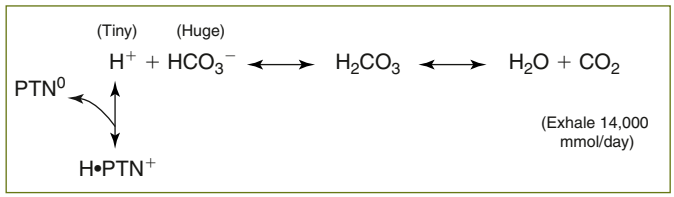


FIGURE 8-1 Bicarbonate buffer system and respiratory acid-base disorders. Binding of H^+ to ICF proteins increases their net positive charge ($H{\bullet}PTN^+$) and possibly compromises their function. Thus, the key principle is that new H^+ must be removed by binding to HCO_3^- so that very few H^+ can bind to proteins (PTN^o) in cells. To force H^+ to bind to HCO_3^-, the P_{CO_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 P_{CO_2} rises in brain capillaries, which makes the bicarbonate buffer system ineffective and hence more of the H^+ load binds to proteins in brain cells.

Venous P_{CO_2}

- The P_{CO_2} in the venous drainage of an organ is determined by the arterial P_{CO_2} *and* the amount of 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 O_2 is extracted from and more 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 P_{CO_2} is close to 6 mm Hg higher than the arterial P_{CO_2}.

MIXED VENOUS P_{CO_2}
The mixed venous P_{CO_2} provides an overview of buffering by the bicarbonate buffer system, but it does not indicate how this buffering was apportioned to skeletal muscles versus cells of vital organs such as the brain. Hence, it is not as valuable as the brachial or femoral P_{CO_2} to assess the likelihood of H^+ binding to proteins in the brain.

The venous P_{CO_2} reflects the P_{CO_2} in capillaries and hence the P_{CO_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 P_{CO_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 P_{CO_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 H^+ adequately, the concentration of H^+ rises in blood and its P_{HCO3} falls. As a result, more H^+ are delivered to vital organs (e.g., brain cells) and a larger proportion ultimately binds to their intracellular proteins.

OVERVIEW OF CO_2 HOMEOSTASIS

Production of CO_2

- CO_2 is the major carbon end product of oxidative metabolism.
- More CO_2 is produced when there is increased work.

RESPIRATORY QUOTIENT (RQ)
- **The RQ is the quantity of CO_2 produced divided by the quantity of O_2 consumed.**
- **The RQ helps one deduce which type of fuel is being oxidized.**

When carbohydrates are oxidized, 1 mmol of CO_2 is produced for every mmol of O_2 that is consumed (the respiratory quotient [RQ] is 1.0; *see margin note*). In contrast, less CO_2 is formed per unit of 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 CO_2 at rest

- Overall, cells consume close to 12 mmol of O_2 and produce close to 10 mmol of CO_2 per minute.

When more work is being performed, the rate of consumption of O_2 rises and more CO_2 is produced. For example, during vigorous aerobic exercise, the rate of consumption of O_2 increases close to 20-fold and more CO_2 is produced. In addition, CO_2 is also produced in this setting as a result of buffering of H^+ from L-lactic acid by HCO_3^-

TABLE 8-1 **CLINICAL SETTINGS WITH ALTERED RATES OF PRODUCTION OF CO_2**

The rate of production of CO_2 is shown as mmol/min in a 70-kg adult. These values are estimates and are for illustrative purposes only.

STATE	ORGAN	USUAL CO_2 PRODUCTION RATE	ALTERED CO_2 PRODUCTION
Coma/anesthesia	Brain	3	1.5
Low glomerular filtration rate	Kidney	2	<1
Cachexia/paralysis	Muscle	2.4	<1
Vigorous exercise	Muscle	2.4	180
Ketogenesis	Liver	2.4	0

during a sprint. This "acid-base" CO_2 influences only the P_{CO_2} in the venous drainage bed of the organ that performs this anaerobic work; this extra CO_2 is eliminated when blood is delivered to the lungs. A list of clinical settings with altered CO_2 production in individual organs is provided in Table 8-1.

CO_2 PRODUCTIONS DURING METABOLISM

- **There are circumstances when O_2 is consumed but no CO_2 is produced (e.g., when ethanol or fatty acids are converted to keto-acids in the liver; see Table 8-2 for more discussion).**
- **There are also settings where CO_2 is produced, but no O_2 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.**

Because arterial blood contains 8 to 9 mmol/L of O_2, close to 8 mmol of CO_2 can be added to 1 L of blood when most of its O_2 is extracted—hence, the venous P_{CO_2} is considerably higher than the arterial P_{CO_2}. There are two extremes where most of the O_2 that is delivered in a liter of blood may be consumed—a rise in the rate of metabolism without a change in the rate of O_2 delivery, and the delivery of fewer liters of blood per minute, with no change in the rate of metabolism. *Of clinical relevance, when the effective arterial blood volume is contracted and the blood flow rate falls, more oxygen is extracted from each liter of blood delivered, and hence each liter of capillary blood must carry more CO_2 to the lungs; to do this, there must be a higher P_{CO_2} in capillaries and in cells.*

The type of fuel that is being oxidized also influences the rate of production of CO_2; this can be evaluated by considering the amount of CO_2 formed per ATP regenerated from the oxidation of the different fuels (Table 8-2; *see margin note*).

Removal of CO_2

- CO_2 excretion = alveolar ventilation × P_{CO_2} in alveolar air.

All of the CO_2 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 CO_2 (10 mmol/min ÷ 5 L/min) compared with arterial

TABLE 8-2 **IMPORTANCE OF THE METABOLIC FUEL UTILIZED IN DETERMINING THE RATE OF CO_2 PRODUCTION**

The oxidation of carbohydrates produces more CO_2 than does the oxidation of fat-derived fuels when viewed in terms of the yield of ATP. No CO_2 is produced when O_2 is consumed in the liver if fatty acids or ethanol are converted to ketoacids.

FUEL	PRODUCTS	mmol CO_2/100 mmol ATP
Carbohydrate	$CO_2 + H_2O$	17
Fatty acids	$CO_2 + H_2O$	12
Fatty acids	Ketoacids	0
Ethanol	$CO_2 + H_2O$	11
Ethanol	Ketoacids	0

TABLE 8-3 **QUANTITATIVE ANALYSIS OF ALVEOLAR VENTILATION**

When the concentration of CO_2 in alveolar air is 2 mmol/L, its P_{CO_2} is 40 mm Hg. Similarly, when the concentration of CO_2 in alveolar air is 2.5 mmol/L, its P_{CO_2} is 50 mm Hg, and if this were a steady-state condition, the patient would have chronic respiratory acidosis of the ventilatory type.

	CO_2 EXCRETION	ALVEOLAR VENTILATION	$[CO_2]$ IN ALVEOLAR AIR
Normal	10 mmol/min	5 L/min	2 mmol/L
Chronic respiratory acidosis	10 mmol/min	4 L/min	2.5 mmol/L

blood. This 10 mmol of CO_2 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 CO_2, the P_{CO_2} of alveolar air and arterial blood falls by 50%. Conversely, as alveolar ventilation falls, the concentration of CO_2 in alveolar air must rise in steady state (as does the arterial P_{CO_2}) to remove all the CO_2 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 O_2 (6 mmol/L) is much higher than the concentration of CO_2 (2 mmol/L) in alveolar air, and the consumption of O_2 and the production of CO_2 occur in close to a 1:1 ratio. Therefore, the supply of O_2 to the alveolus markedly exceeds demand. Accordingly, it is not surprising that the control of the rate of ventilation is to adjust the P_{CO_2} rather than the P_{O_2} in blood unless the arterial P_{O_2} is quite low (see the discussion of Question 8-2 on page 240 for more discussion).

PHYSIOLOGY OF CO_2 TRANSPORT

About 10 mmol of CO_2 are produced per minute, and they diffuse into red blood cells in capillary blood. The carbonic anhydrase in these cells converts CO_2 into H^+ and HCO_3^- (Fig. 8-2). This maintains a low P_{CO_2} in the red blood cells, which aids further diffusion of CO_2. The HCO_3^- formed is transported into the plasma in exchange

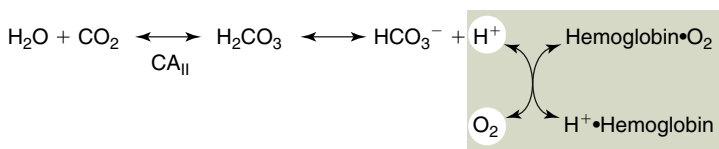


FIGURE 8-2 Carriage of CO_2 in blood. When CO_2 diffuses into red blood cells, it is converted very rapidly to H^+ plus HCO_3^- because of the high activity of carbonic anhydrase (CA_{II}). As shown in the *green shaded area,* the resulting H^+ bind to hemoglobin, which promotes the dissociation of O_2. Most of the CO_2 is carried as HCO_3^- in venous blood and delivered to the lungs. Another property of hemoglobin is that it binds CO_2 to form a carbamino compound, and this helps lower the P_{CO_2} in capillary blood (*see margin note*).

FOCUS: SUPPLY O_2 WITH A HIGH P_{O_2} TO CELLS
(Examine the *shaded portion* of the figure.)
- **When CO_2 and/or L-lactic acid is produced in cells, the concentration of H^+ rises in plasma and in red blood cells (in the *top white circle*).**
- **This higher concentration of H^+ increases the binding of H^+ to *oxyhemoglobin* and, as a result, O_2 is released (*lower white circle*).**

FOCUS: EXTRACT O_2 AND EXCRETE CO_2 IN ALVEOLAR AIR
(Begin at the *bottom far right corner* of the figure.)
- **When the P_{O_2} is high in the alveoli and thus in red blood cells, this higher concentration of O_2 binds to *deoxyhemoglobin* and, as a result, H^+ are released.**
- **These H^+ react with HCO_3^-, forming CO_2, which is exhaled, completing the cycle.**

TABLE 8-4 **EXPECTED RESPONSES IN PATIENTS WITH RESPIRATORY ACID-BASE DISORDERS**

DISORDER	EXPECTED RESPONSE
Respiratory acidosis	
Acute	For every 1-mm Hg rise in the arterial P_{CO_2} from 40 mm Hg, the plasma [H^+] rises by close to 0.8 nmol/L from 40 nmol/L.
Chronic	For every 1-mm Hg rise in arterial P_{CO_2} from 40 mm Hg, the P_{HCO_3} should rise by close to 0.3 mmol/L from 25 mmol/L.
Respiratory alkalosis	
Acute	For every 1-mm Hg fall in arterial P_{CO_2} from 40 mm Hg, the plasma [H^+] falls by close to 0.8 nmol/L from 40 nmol/L.
Chronic	For every 1-mm Hg fall in arterial P_{CO_2} from 40 mm Hg, the P_{HCO_3} should fall by close to 0.5 mmol/L from 25 mmol/L.

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_{O_2} of alveolar air drives the diffusion of O_2 into blood, which raises the P_{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_{CO_2}

- The P_{HCO3} 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_{HCO3}. Therefore, patients with chronic respiratory acidosis have a P_{HCO3} 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_{HCO3}, 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_{O_2} in capillary blood?*

PART B
RESPIRATORY ACID–BASE DISORDERS

- The traditional definition of respiratory acid-base disorders is based on changes in the arterial Pbn_2.
- The definition of respiratory acidosis should also include the "tissue" type of respiratory acidosis.

Because there is a very large flux of CO_2 relative to the P_{CO_2}, if a transient discrepancy between production and removal of CO_2 develops, the resultant change in arterial P_{CO_2} is large enough to cause a significant displacement of the bicarbonate buffer system equilibrium (see Fig. 8-1). A rise in the arterial P_{CO_2} results in an increased concentration of H^+ (respiratory acidosis), and a fall in arterial P_{CO_2} causes a fall in the concentration of H^+ (respiratory alkalosis). Notwithstanding, it is the capillary P_{CO_2} (reflected by the venous P_{CO_2}) 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 Pbn_2 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 CO_2 produced by normal metabolism. As a result, the alveolar P_{CO_2} rises, and this increases the arterial P_{CO_2}. At this new level of arterial and alveolar P_{CO_2}, all the CO_2 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 P_{CO_2} might be suitably low, but the venous P_{CO_2} may still be high because either CO_2 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 P_{CO_2} (*see margin note* for a quantitative example). The venous P_{CO_2} reflects the P_{CO_2} in *capillaries* and

EXPECTED VALUE FOR THE ARTERIAL P_{CO_2}
Although the normal arterial P_{CO_2} is 40 mm Hg, its value must be evaluated in conjunction with other clinical information (e.g., in a patient with metabolic acidosis and a P_{HCO_3} of 10 mmol/L, the expected arterial P_{CO_2} should be close to 25 mm Hg).

EFFECT OF RATE OF BLOOD FLOW ON THE VENOUS P_{CO_2}
Consider an organ that extracts 6 mmol of O_2 per minute to perform its biologic work.

- If the rate of blood flow to this organ is 2 L/min, each liter of blood would lose 3 mmol of its total of 8 mmol of O_2 if the hemoglobin is fully saturated with oxygen. Now if the RQ is 1 for simple arithmetic, each liter of venous blood would have to carry an extra 3 mmol of CO_2 (largely as HCO_3^-) to the lungs, and it would have a P_{CO_2} in the mid-40 mm Hg range.
- If the blood flow rate to that organ is reduced to 1 L/min and its biologic work is unchanged, this liter of blood would lose 6 mmol of its O_2 and be forced to carry an extra 6 mmol of CO_2 to the lungs. Hence, the venous P_{CO_2} will be close to 60 mm Hg.

hence the P_{CO_2} in cells and in the interstitial fluid in this drainage area. As mentioned previously, the P_{CO_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 H^+ bind to intracellular proteins in vital organs, which changes their charge and may affect their shape and function.

Clinical approach

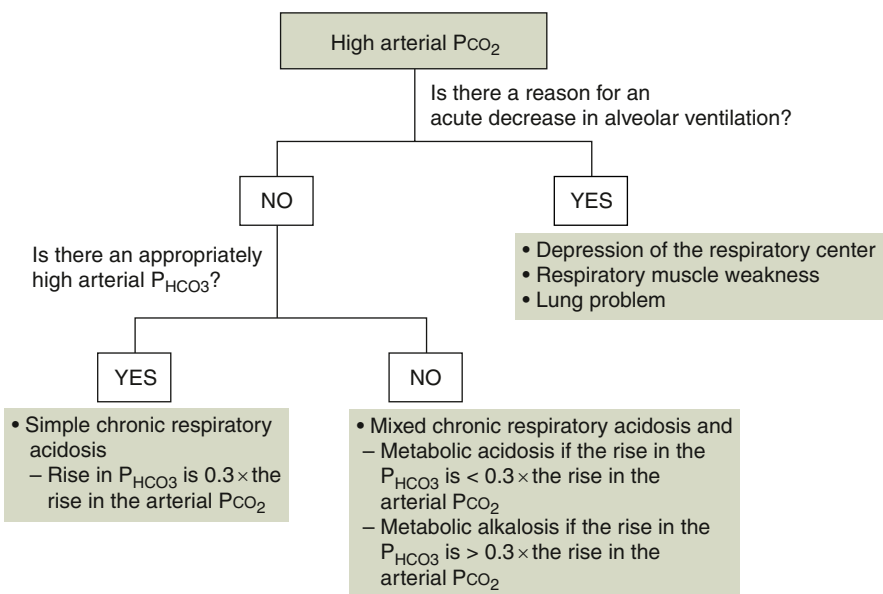
The diagnostic approach to the ventilatory type of respiratory acidosis is outlined in Flow Chart 8-1. First, decide whether the patient has chronic lung disease by the history, physical examination, and available past records. Then, compare the acid-base status with that expected for this acid-base 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 CO_2 and/or a slow blood flow rate.

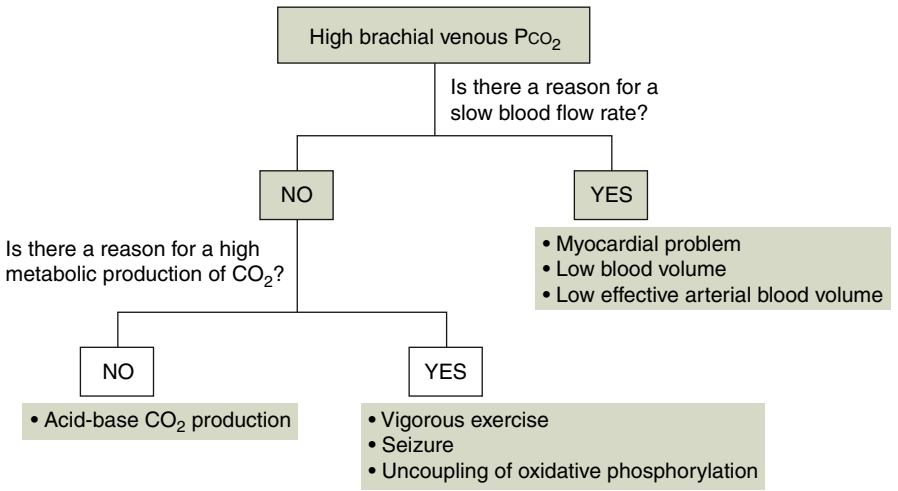
Permissive hypercapnia

- 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 P_{CO_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 P_{CO_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*.



FLOW CHART 8-2 Respiratory acidosis of the tissue type. For details, see legend to Flow Chart 8-1. If the brachial venous P_{CO_2} is greater than 10 mm Hg above the arterial P_{CO_2}, determine whether the problem is a low blood flow rate and/or a high rate of production of CO_2.

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 CO_2 at a low alveolar P_{CO_2} is compromised, and the result is a higher concentration of CO_2 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 P_{CO_2} 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 P_{CO_2} 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 CO_2 via ventilation transiently exceeds its rate of production; thus, the alveolar and arterial P_{CO_2} fall. If this persists, a new steady state is achieved where the daily production of CO_2 is removed, but at a lower arterial P_{CO_2}.

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

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

A fall in the P_{CO_2} in cells lower their concentration of H^+ and thereby result in the removal of H^+ 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^+ in plasma may be in the normal range (see Table 8-4 for the expected P_{HCO3} 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.

ABBREVIATIONS
ASA, acetylsalicylic acid
SA, salicylate anions
H•SA, nonionized salicylic acid

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_2 and production of CO_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*).

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.

TABLE 8-6 **EFFECT OF ACIDEMIA ON THE CONCENTRATION OF SALICYLATES IN CELLS**

In the example shown, the total salicylate concentration in the extracellular fluid (ECF) is 7 mmol/L. Because of its low pK (~3.5), only a very tiny fraction is in the undissociated form at normal blood pH values (i.e., salicylic acid [H•SA = 0.3 μmol/L]). H•SA diffuses across cell membranes and at equilibrium, its concentration is equal inside and outside cells. In the cell, the concentration of salicylate depends on the intracellular fluid (ICF) pH. Because the ICF pH is normally close to 0.3 pH units lower than the ECF pH, the intracellular salicylate will be half that in the ECF at equilibrium (3.5 mmol/L vs. 7.0 mmol/L). If the pH in ECF drops to 7.1, the concentration of H•SA will rise from 0.3 μmol/L to 0.6 μmol/L. Because H•SA diffuses across cell membranes to achieve equilibrium, the difference between the ECF and ICF pH now is small, so the intracellular salicylate concentration rises from 3.5 mmol/L to 6.0 mmol/L.

	NORMAL		ACIDEMIA	
	ECF	*ICF*	*ECF*	*ICF*
pH	7.4	7.1	7.1	7.0
H•SA (μmol/L)	0.3	0.3	0.6	0.6
Salicylate (mmol/L)	7.0	3.5	7.0	6.0

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.

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.

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.

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.

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*).

METABOLIC ACIDOSIS DURING SALICYLATE INTOXICATION
- Toxicity caused by the monovalent salicylate anion occurs when its concentration is 3 to 5 mmol/L. Thus, if the $P_{Anion\ gap}$ 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.

Diagnosis

The diagnosis of salicylate intoxication should be suspected on the basis of a history of ingestion or symptoms of tinnitus and lightheadedness 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 HCO_3^-, as a result of the excretion of salicylate anions) should

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 $NaHCO_3$ should be avoided because the patient may become very alkalemic due to the coexistent respiratory alkalosis.

INCREASING SALICYLATE EXCRETION WITH ACETAZOLAMIDE

- In the proximal convoluted tubule, the effect of acetazolamide is to *increase* (not decrease) the concentration of H^+ of tubular fluid via inhibition of luminal carbonic anhydrase. Hence, the likely mechanism for acetazolamide to increase the excretion of salicylate cannot be a result of lowering the H•SA concentration in luminal fluid.
- We suggest that there is a direct effect of HCO_3^- to inhibit the reabsorption of salicylate in the proximal convoluted tubule; hence, an increase in luminal HCO_3^- resulting from the effect of acetazolamide may explain its effect to increase salicylate excretion if salicylates are a substrate for a transport system.

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

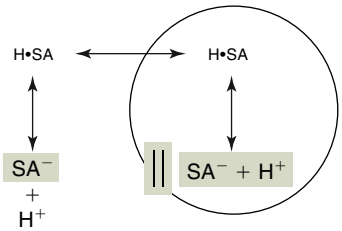


FIGURE 8-3 Nonionic diffusion of salicylic acid versus salicylate anions. The *circle* represents the cell membrane or the luminal membrane of the proximal convoluted tubule. The assumption made is that the organic acid form of salicylate (H•SA) can cross cell membranes by diffusion because it is uncharged, 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 HCO_3^- 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.

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.

PART C
INTEGRATIVE PHYSIOLOGY

PHYSIOLOGY OF O_2

The vast majority of O_2 in blood is bound to hemoglobin (4 mmol of O_2 per mmol of hemoglobin). Because blood contains 2 mmol/L of hemoglobin, the content of O_2 in blood is 8 mmol/L (*see margin note*). The affinity of hemoglobin for O_2 is high, but it can be reduced by elevated concentrations of H^+, CO_2, 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 O_2 is extracted, there is a higher P_{O_2}, which aids in diffusion of oxygen to cells (Fig. 8-5).

O_2 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 O_2.
- The rate of consumption of O_2 is 12 mmol/min.
- With a cardiac output of 5 L/min, 40 mmol/min of O_2 are delivered to body tissues. Therefore, even if the hemoglobin concentration in blood is decreased appreciably, organs can still extract sufficient O_2 to perform their work because each liter of blood has a threefold surplus of O_2. Hence, anemia is virtually never the *sole* cause of hypoxia-induced L-lactic acidosis at rest.

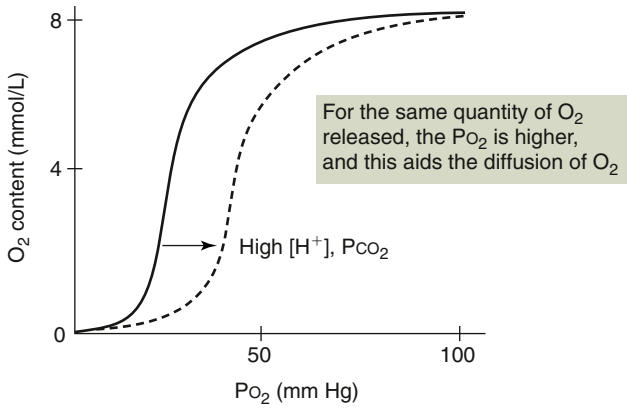


FIGURE 8-4 Relationship between the content and concentration of O_2 in 1 liter of blood. The content of O_2 in each liter of blood (shown on the y-axis) has a sigmoid relationship to the arterial P_{O_2} (shown on x-axis). When the concentration of H^+ and/or the P_{CO_2} rises in capillaries, the S-shaped curve is shifted to the right, so the affinity of hemoglobin for O_2 is diminished and the P_{O_2} rises. Therefore, there is a higher P_{O_2}, which aids the diffusion of O_2.

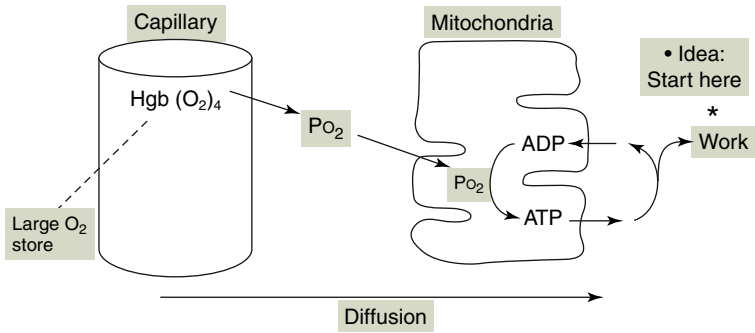


FIGURE 8-5 Delivery of O_2 to mitochondria by diffusion. *The structure on the left* is a capillary and the *structure on the right* is a mitochondrion. A large quantity of O_2 must be delivered to mitochondria in exercise to have a high rate of regeneration of ATP. Both a high P_{O_2} in capillaries and "stirring of the interstitial compartment" are needed for rapid rates of diffusion of O_2 to muscle cells. Nevertheless, the P_{O_2} in mitochondria needs to be only a few mm Hg to regenerate ATP at maximal rates. Hgb, hemoglobin.

THE ALVEOLAR-ARTERIAL P_{O_2} DIFFERENCE

- Calculation of the alveolar-arterial (A-a) P_{O_2} difference is used clinically to assess the cause of hypoxemia (*see margin note*).

ALVEOLAR-ARTERIAL P_{O_2} DIFFERENCE
The difference in P_{O_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 P_{O_2} OF INSPIRED AIR
Room air is 21% O_2, barometric pressure is 760 mm Hg, and water vapor pressure is 47 mm Hg. Therefore, the P_{O_2} of inspired air is 0.21 × (760 – 47), or close to 150 mm Hg.

The arterial P_{O_2} is determined by both the P_{O_2} of alveolar air and the ability of O_2 to diffuse across the alveolar capillary membrane. The A-a P_{O_2} difference is useful to estimate how much of the fall in the arterial P_{O_2} is the result of a change in alveolar P_{O_2} (ventilation) and how much is the result of reduced transfer of O_2 from alveolus to blood (intrinsic lung disease). One must, however, be able to estimate the P_{O_2} of the inspired air to calculate the A-a difference (*see margin note*). In the alveoli, CO_2 is part of the "non-nitrogen" gases. Therefore, as the P_{CO_2} of alveolar air rises, the P_{O_2} falls. One can calculate the alveolar P_{O_2} using the abbreviated alveolar gas equation (see equations).

$$\begin{aligned}\text{Alveolar air } P_{O_2} &= \text{inspired air } P_{O_2} - (\text{arterial } P_{CO_2})/\text{RQ} \\ &= \text{inspired air } P_{O_2} - (\text{arterial } P_{CO_2})/0.8\end{aligned}$$

Two major types of pulmonary lesions cause the arterial P_{O_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 P_{O_2} (i.e., a shunt). Second, there may be a barrier to diffusion of O_2 from alveolar air to the capillaries in lungs (e.g., inflammation, pulmonary edema).

The usual value for the A-a P_{O_2} difference is up to 10 mm Hg, and higher values are observed with increasing age. The usual value for the A-a P_{O_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 P_{O_2} instead of the O_2 saturation, which reflects the content of O_2.

The pitfalls are the following:

1. The same reduction in O_2 content has a different impact on the P_{O_2} 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 O_2 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 P_{O_2} despite a very small change in O_2 saturation or the content of oxygen. A similar decrease in its content of O_2 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 P_{O_2} is strongly influenced by the content of O_2 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 P_{O_2}, one must estimate the amount of O_2 removed and replaced by CO_2. To do so, one uses the arterial P_{CO_2} 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*).

CONTROL OF THE RELEASE OF ERYTHROPOIETIN

- The central issue is that the P_{O_2} 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 O_2 sensor that regulates the release of erythropoietin because they allow the concentration of hemoglobin to be the only variable that influences the P_{O_2} at the site of the O_2 sensor (*see margin note*).

Fall in P_{O_2} 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 O_2 is extracted from each liter of blood. When the same amount of O_2 is extracted from blood that has a lower content of O_2 because of a lower hemoglobin concentration, the drop in P_{O_2} 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 O_2 to delivery of O_2 in renal cortex must be constant to ensure that sensor for O_2 is exposed to near-constant P_{O_2} unless blood has lower hemoglobin concentration

- O_2 is consumed when work is performed.

LOW P_{O_2} IN CELLS

- One might think that a very low P_{O_2} in cells might limit ATP regeneration. Nevertheless, the large amount of O_2 bound to myoglobin and a high affinity of cytochrome C for O_2 avoids the difficulty of not having enough O_2 during exercise.
- Having a low P_{O_2} in cells at rest (due to slow diffusion owing to poor mixing) prevents the development of too high a P_{O_2} in cells, and thereby, an excessive formation of reactive oxygen species.

IMPACT OF THE CONTENT OF O_2 IN SHUNTED BLOOD ON THE ALVEOLAR-ARTERIAL DIFFERENCE

Assume that arterial blood has 8 mmol/L of O_2 and that 10% of the blood in the pulmonary artery bypasses aerated alveoli via a shunt into the pulmonary vein.

- In one example, assume that the content of O_2 in the blood in the pulmonary artery is 6 mmol/L. After this 10% shunt, arterial blood would contain 7.8 mmol of O_2/L (0.9 L with 8 mmol/L + 0.1 L with 6 mmol/L).
- In another example, assume that blood in the pulmonary artery contains 3 mmol/L of O_2. After the 10% shunt, the arterial blood would have 7.5 mmol/L of O_2 (0.9 L with 8 mmol/L + 0.1 L with 3 mmol/L). As a result, the new arterial P_{O_2} in the first instance would be 95 mm Hg and it would be 65 mm Hg in the second example. The corresponding A-a differences would be 5 and 35 mm Hg.

EFFECT OF THE RESPIRATORY QUOTIENT ON THE ALVEOLAR-ARTERIAL DIFFERENCE

- Assume an RQ of 0.8:

$$\text{Alveolar } O_2 = 150 - (40/0.8) = 100 \text{ mm Hg}$$

- Assume an RQ of 1:

$$\text{Alveolar } O_2 = 150 - (40/1) = 110 \text{ mm Hg}$$

Therefore, the A-a increases by 10 mm Hg.

ERYTHROPOIETIN AND THE KIDNEY

The hypothesis presented here may improve our understanding of why erythropoietin is synthesized in the renal cortex and why having both a high GFR and a very large renal blood flow rate are essential components of this efficient control system.

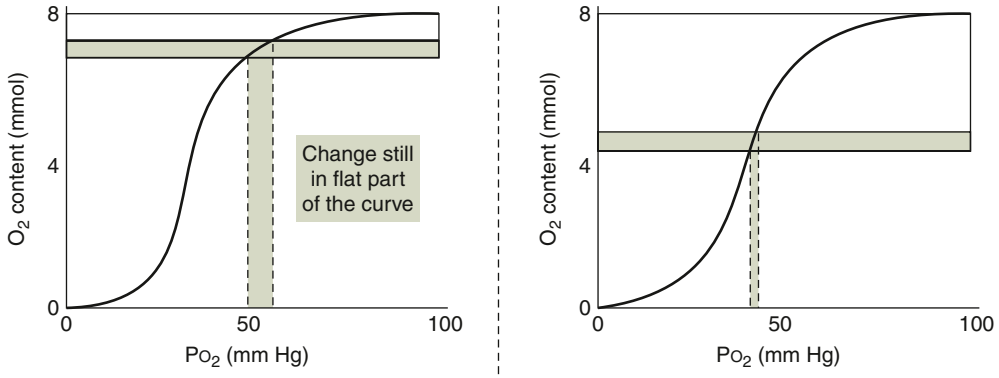


FIGURE 8-6 Importance of the renal blood flow in determining the sensitivity of the receptor for erythropoietin synthesis. The arterial P_{O_2} is depicted on the x-axis and the quantity of O_2 in 1 liter of blood is depicted on the y-axis. The *clear portion of the horizontal rectangle* represents the total quantity of O_2 extracted per liter of blood flow when the hemoglobin concentration in blood is in the upper normal range. In contrast, the *green rectangle* represents the extra quantity of O_2 extracted per liter of blood flow when the hemoglobin concentration in blood is in the lower normal range. The *vertical dashed lines* indicate the change in arterial P_{O_2} as a result of this extra extraction of O_2 per liter of blood flow. The drop in P_{O_2} would be larger if one is still operating near the flat part of the sigmoid-shaped oxygen-hemoglobin dissociation curve; compare the *right* with the *left portion of the figure*, where in other organs, there is more work per O_2 delivery.

NEED FOR A HIGH GFR
Because a high renal blood flow rate is needed to increase the sensitivity of the P_{O_2} signal for the release of erythropoietin, there is also a need for a high GFR to have enough extraction of O_2, independent of other demands of renal physiology.

FILTRATION FRACTION
To calculate the filtration fraction, the renal plasma flow is used. Conversely, the renal blood flow is substituted for the renal plasma flow for this concept because we are assessing the signal system in terms of oxygen.

Filtration fraction = GFR ÷ renal plasma flow
(O_2 consumption ÷ O_2 delivery)

- 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 P_{Na}. Because there is little variation in the P_{Na} in healthy subjects, renal work (or O_2 consumption) is directly related to the GFR. Moreover, the *ratio* between the GFR (O_2 consumption) and renal plasma flow rate (O_2 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. If the filtration fraction does not vary appreciably, the sensor for O_2 should be exposed to a near-constant P_{O_2} unless blood has a lower hemoglobin concentration.

A high renal cortical blood flow rate speeds up the diffusion of O_2 from its capillaries to the receptor for O_2 deep in the renal cortex

The high cortical blood flow eliminates another variable, the slow speed of diffusion of O_2. 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 P_{O_2} signal is not influenced by other factors that may influence this shift. In fact, this is achieved by having a high P_{CO_2} 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?*

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.

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_{HCO3} (15 mmol/L) indicate that he has metabolic acidosis. Because the P_{HCO3} 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."

Think of ventilation controlling the arterial P_{CO_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 P_{CO_2} is high and therefore the tissue P_{CO_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 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 P_{CO_2} in brachial and femoral venous blood will fall. This permits more H^+ removal by the bicarbonate buffer system in skeletal muscles, which in turn diminishes the binding of 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 P_{O_2} in capillary blood?*

Because O_2 is poorly soluble in water, virtually 100% of O_2 is transported in blood bound to hemoglobin in red blood cells. It is important to ensure that the P_{O_2} is high in capillary blood so that the diffusion of O_2 into mitochondria can proceed at a sufficiently rapid rate (see Fig. 8-5). There are three issues to consider.

1. *Raise the P_{O_2} in capillaries during vigorous exercise*: To have O_2 delivery at a *high* P_{O_2} (O_2 concentration), the kinetics of O_2 binding to hemoglobin must have special properties. Hence, the shape of the curve relating the content of O_2 in 1 liter of blood to its P_{O_2} is S-shaped (see Fig. 8-4). When the objective is to have a large off-loading of O_2 from hemoglobin at the highest P_{O_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 O_2 is maximal—vigorous exercise. Therefore, the signals that cause this rightward shift are the products associated with high rates of ATP turnover (CO_2, 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 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 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 O_2 is tiny, having 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 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 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.

ADVANTAGE OF SPORTS ANEMIA

- **Blood in the vascular tree is in three locations: arteries, veins, and capillaries.**
- **The capacity of the capillaries to "hold" blood is enormous. Therefore, the capillary volume cannot expand appreciably, as this would cause a hemodynamic emergency.**
- **During vigorous exercise, there is more blood in capillaries in skeletal muscles and in the skin. This extra capillary volume cannot exceed the "extra" volume contained in the circulation (due to contraction of capacitance vessels and the decrease in capillary volume elsewhere in the body) if hemodynamics are to be preserved during vigorous exercise. Hence, having a higher blood volume is an advantage.**

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 P_{O_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 P_{O_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

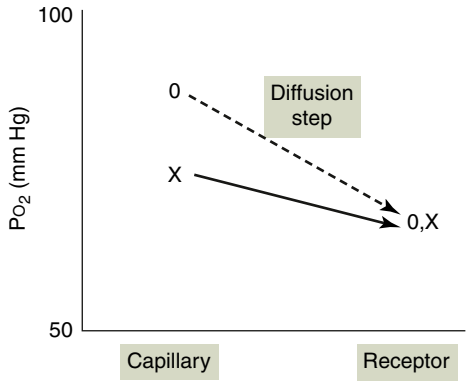


FIGURE 8-7 Possible independent role of the renal blood flow rate on the P_{O_2} near the receptor for O_2 deep in the renal cortex. The graph depicts the P_{O_2} that is likely to be present in capillary blood deep in the renal cortex (*points to the **left of the line*** depict diffusion) and its fall 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 P_{O_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 P_{O_2} during diffusion. As a result, the P_{O_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 (O_2 consumption) without influencing the renal blood flow to a major extent. Thus, there is a higher P_{O_2} 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.

absolute value for the renal blood flow rate that may influence the renal cortical P_{O_2} in steady state. When less O_2 is extracted *per liter* of renal blood flow, the P_{O_2} in the interstitial compartment near the O_2 sensor is higher and less erythropoietin is released. The result could be the development of chronic anemia. Perhaps, one example of this pathophysiology could be the chronic anemia associated with the use of an angiotensin-converting enzyme inhibitor. To identify which patient with chronic anemia has this functional form of erythropoietin deficiency, the GFR and renal plasma flow could be measured to reveal the low filtration fraction, and the absolute value for the renal blood flow rate should be examined as well (*see margin note*).

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 P_{O_2} 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 P_{O_2} in the slow diffusion step between capillaries and the receptor for O_2 deep in the renal cortex, there may not be a lower P_{O_2} 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 P_{O_2} may be deep in the renal cortex.