OXYGEN BOUND TO HEMOGLOBIN

Hemoglobin, an iron-bearing protein molecule contained within the red blood cells, can form a loose, easily reversible combination with O_2. When not combined with O_2, Hb is referred to as **reduced hemoglobin**, or **deoxyhemoglobin**; when combined with O_2 it is called **oxyhemoglobin** (**HbO_2**):

$$\underset{\text{reduced hemoglobin}}{Hb} + O_2 \rightleftharpoons \underset{\text{oxyhemoglobin}}{HbO_2}$$

P_{O_2} is the primary factor determining the percent Hb saturation

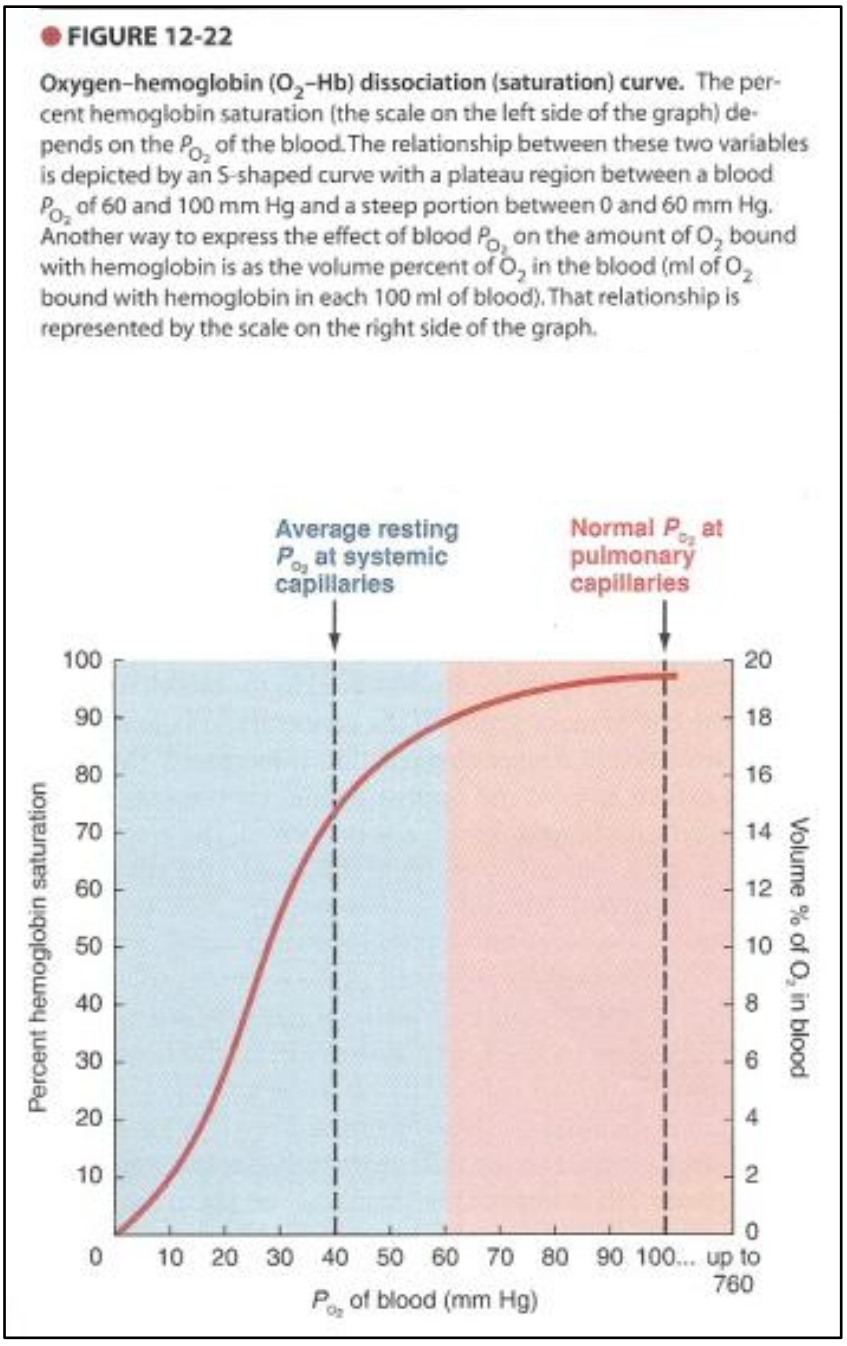
Each of the four atoms of iron within the heme portions of a hemoglobin molecule can combine with an O_2 molecule, so each Hb molecule can carry up to four molecules of O_2 Hemoglobin is considered *fully saturated* when all the Hb present is carrying its maximum O_2 load. The percent hemoglobin (% Hb) saturation, a measure of the extent to which the Hb present is combined with O_2 can vary from 0% to 100%.

The most important factor determining the % Hb saturation is the P_{O_2} of the blood, which in turn is related to the concentration of O_2 physically dissolved in the blood. When blood P_{O_2} increases, as in the pulmonary capillaries, the reaction is driven toward the right side of the equation, increasing formation of HbO_2 (increased % Hb saturation). When blood d P_{O_2} decreases, as in the systemic capillaries, the reaction is driven toward the left side of the equation and oxygen is released from Hb as HbO_2 dissociates (decreased % Hb saturation). Thus because of the difference in P_{O_2} at the lungs and other tissues, Hb automatically "loads up" on O_2 in the lungs, where ventilation is continually providing fresh supplies of O_2 and "unloads" it in the tissues, which are constantly using up O_2.

O_2-Hb DISSOCIATION CURVE

The relationship between blood P_{O_2} and % Hb saturation is not linear, however, a point that is very important physiologically. Doubling the partial pressure does not double the % Hb saturation. Rather, the relationship between these variables follows an S-shaped curve, the O_2-Hb dissociation (or saturation) curve (Figure 12-22). At the upper end, between a blood P_{O_2} of 60 and 100 mm Hg, the curve flattens off, or plateaus. Within this pressure range, a rise in d P_{O_2} produces only a small increase in the extent to which Hb is bound with O_2. In the P_{O_2} range of 0 to 60 mm Hg, in contrast, a small change in P_{O_2} results in a large change in the extent to which Hb is combined with O_2 as shown by the steep lower part of the curve. Both the upper plateau and lower steep portion of the curve have physiological significance.

SIGNIFICANCE OF THE PLATEAU PORTION OF THE O_2-Hb CURVE



The plateau portion of the curve is in the blood P_{O_2} range that exists at the pulmonary capillaries where O_2 is being loaded onto Hb. The systemic arterial blood leaving the lungs, having equilibrated with alveolar P_{O_2} normally has a P_{O_2} of 100 mm Hg. Looking at the O_2-Hb curve, note that at a blood P_{O_2} of 100 mm Hg, Hb is 97.5% saturated. Therefore, the Hb in the systemic arterial blood normally is almost fully saturated.

If the alveolar P_{O_2} and consequently the arterial P_{O_2} fall below normal, there is little reduction in the total amount of O_2 transported by the blood until the P_{O_2} falls below 60 mm Hg, because of the plateau region of the curve. If the arterial P_{O_2} falls 40%, from 100 to 60 mm Hg, the concentration of dissolved O_2 as reflected by the d P_{O_2} is likewise reduced 40%.

At a blood P_{O_2} of 60 mm Hg, however, the % Hb saturation is still remarkably high at 90%. Accordingly, the total O_2 content of the blood is only slightly decreased despite the 40% reduction in P_{O_2} because Hb is still carrying an almost full load of O_2 and, as mentioned before, the vast majority of O_2 is transported by Hb rather than being dissolved. However, even if the blood P_{O_2} is greatly increased-say, to 600 mm Hg-by breathing pure O_2, very little additional O_2

is added to the blood. A small extra amount of O_2 dissolves, but the % Hb saturation can be maximally increased by only another 2.5%, to 100% saturation. Therefore, in the P_{O_2} range between 60 and 600 mm Hg or even higher, there is only a 10% difference in the amount of O_2 carried by Hb. Thus the plateau portion of the O_2-Hb curve provides a good margin of safety in O_2-carrying capacity of the blood.

SIGNIFICANCE OF THE STEEP PORTION OF THE O_2-Hb CURVE

The steep portion of the curve between 0 and 60 mm Hg is in the blood P_{O_2} range that exists at the systemic capillaries, where O_2 is unloaded from Hb. In the systemic capillaries, the blood equilibrates with the surrounding tissue cells at an average P_{O_2} of 40 mm Hg. Note on Figure 12-22 that at a P_{O_2} of 40 mm Hg, the % Hb saturation is 75%. The blood arrives in the tissue capillaries at a P_{O_2} of 100 mm Hg with 97.5% Hb saturation. Because Hb can only be 75% saturated at the P_{O_2} of 40 mm Hg in the systemic capillaries, nearly 25% of the HbO_2 must dissociate, yielding reduced Hb and O_2. This released O_2 is free to diffuse down its partial pressure gradient from the red blood cells through the plasma and interstitial fluid into the tissue cells.

The Hb in the venous blood returning to the lungs is still normally 75% saturated. If the tissue cells are metabolizing more actively; the P_{O_2} of the systemic capillary blood falls (for example, from 40 to 20 mm Hg) because the cells are consuming O_2 more rapidly. Note on the curve that this drop of 20 mm Hg in P_{O_2} decreases the % Hb saturation from 75% to 30%; that is, about 45% more of the total HbO_2 than normal gives up its O_2 for tissue use. The normal 60 mm Hg drop in P_{O_2} from 100 to 40 mm Hg in the systemic capillaries causes about 25% of the total HbO_2 to unload its O_2. In comparison, a further drop in P_{O_2} of only 20 mm Hg results in an additional 45% of the total HbO_2 unloading its O_2 because the O_2 partial pressures in this range are operating in the steep portion of the curve. In this range, only a small drop in systemic capillary P_{O_2} can automatically make large amounts of O_2 immediately available to meet the O_2 needs of more actively metabolizing tissues. As much as 85% of the Hb may give up its O_2 to actively metabolizing cells during strenuous exercise. In addition to this more thorough withdrawal of O_2 from the blood, even more O_2 is made available to actively metabolizing cells, such as exercising muscles, by circulatory and respiratory adjustments that increase the flow rate of oxygenated blood through the active tissues.

Factors at the tissue level promote the unloading of O_2 from hemoglobin

The P_{O_2} of the blood, other factors can affect the affinity, or bond strength, between Hb and O_2 and, accordingly, can shift the O_2-Hb curve (that is, change the % Hb saturation at a given P_{O2}).

These other factors are CO_2, acidity, temperature, and 2,3-bisphosphoglycerate.

EFFECT OF CO_2 ON % Hb SATURATION

An increase in P_{O_2} shifts the O_2-Hb curve to the right (Figure 12-24). The % Hb saturation still depends on the P_{O2} but for any given P_{O_2} less O_2 and Hb can be combined. This effect is important, because the P_{CO2} of the blood increases in the systemic capillaries as CO_2 diffuses down its gradient from the cells into the blood. The presence of this additional CO_2 in the blood in effect decreases the affinity of Hb for O_2 so Hb unloads even more O_2 at the tissue level than it would if the reduction in P_{O_2} in the systemic capillaries were the only factor affecting % Hb saturation.

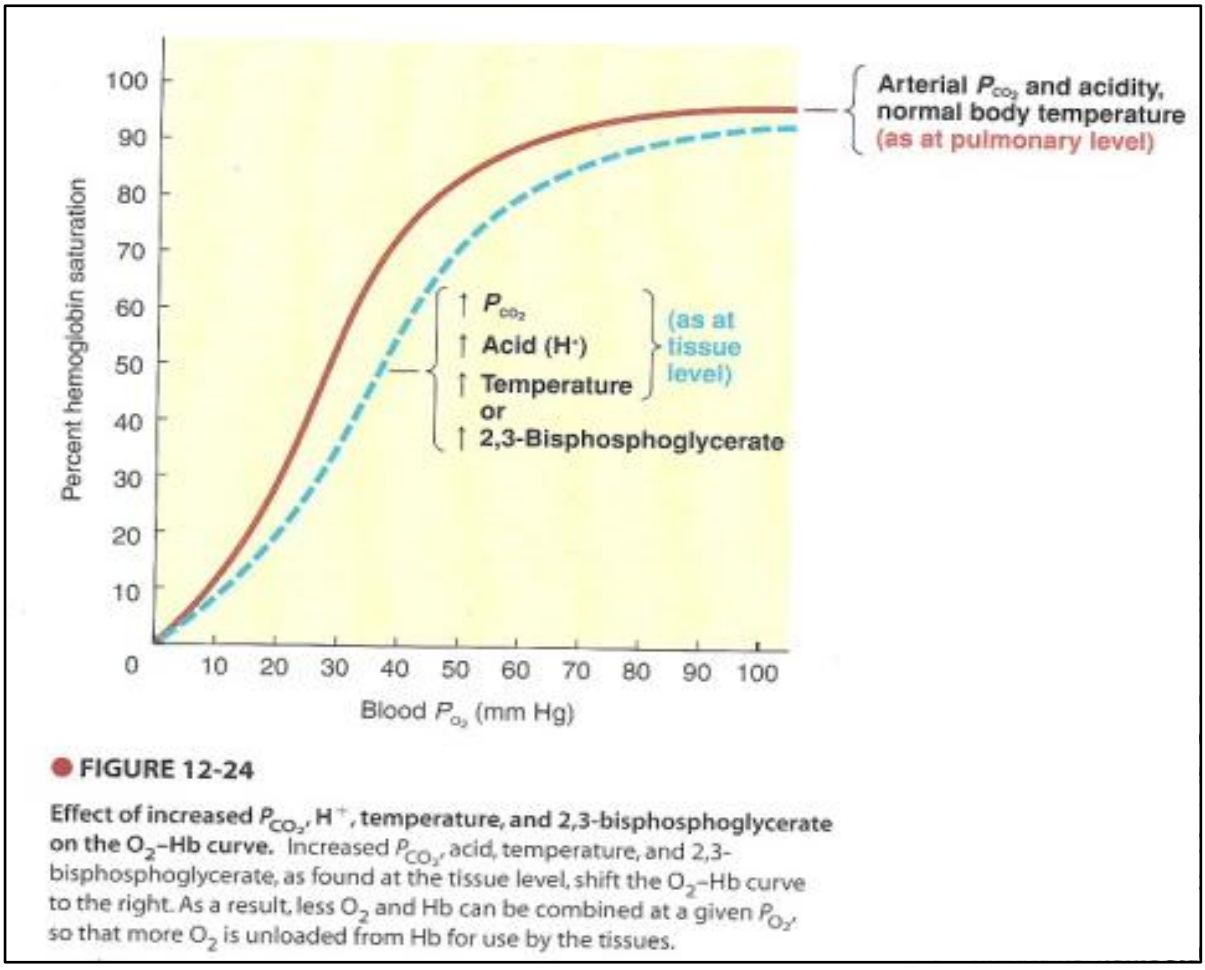


FIGURE 12-24

Effect of increased P_{CO_2}, H^+, temperature, and 2,3-bisphosphoglycerate on the O_2–Hb curve. Increased P_{CO_2}, acid, temperature, and 2,3-bisphosphoglycerate, as found at the tissue level, shift the O_2–Hb curve to the right. As a result, less O_2 and Hb can be combined at a given P_{O_2}, so that more O_2 is unloaded from Hb for use by the tissues.

EFFECT OF ACID ON % Hb SATURATION

An increase in acidity also shifts the curve to the right. Because CO_2 generates carbonic acid (H_2CO_3), the blood becomes more acidic at the systemic capillary level as it picks up CO_2 from the tissues. The resulting reduction in Hb affinity for O_2 in the presence of increased acidity aids

in releasing even more O_2 at the tissue level for a given P_{O_2}. In actively metabolizing cells, such as exercising muscles, not only is more carbonic acid-generating CO_2 produced, but lactic acid also may be produced if the cells resort to anaerobic metabolism. The resultant local elevation of acid in the working muscles facilitates further unloading of O_2 in the very tissues that need the most O_2.

EFFECT OF TEMPERATURE ON % Hb SATURATION

In a similar manner, a rise in temperature shifts the O_2-Hb curve to the right, resulting in more unloading of O_2 at a given P_{O2}. An exercising muscle or other actively metabolizing cell produces heat. The resulting local rise in temperature enhances O_2 release from Hb for use by more active tissues

EFFECT OF 2,3-BISPHOSPHOGLYCERATE ON % Hb SATURATION

The preceding changes take place in the environment of the red blood cells, but a factor inside the red blood cells can also affect the degree of O_2-Hb binding: 2,3-bisphosphoglycerate (BPG). This erythrocyte constituent, which is produced during red blood cell metabolism, can bind reversibly with Hb and reduce its affinity for O_2 just as CO_2 and H^+ do. Thus an increased level of BPG, like the other factors, shifts the O_2-Hb curve to the right, enhancing O_2 unloading as the blood flows through the tissues.

BPG production by red blood cells gradually increases whenever Hb in the arterial blood is chronically undersaturated-that is, when arterial HbO_2 is below normal. This condition may occur in people living at high altitudes or in those suffering from certain types of circulatory or respiratory diseases or anemia. By helping unload O_2 from Hb at the tissue level, increased BPG helps maintain O_2 availability for tissue use even though arterial O_2 supply is chronically reduced.

Hemoglobin has a much higher affinity for carbon monoxide than for O_2

Carbon monoxide (CO) and O_2 compete for the same binding sites on Hb, but Hb's affinity for CO is 240 times that of its affinity for O_2. The combination of CO and Hb is known as carboxyhemoglobin (HbCO).

Because Hb preferentially binds CO, even small amounts of CO can tie up a large share of Hb, making Hb unavailable for O_2 transport. Even though the Hb concentration and P_{O_2} are normal, the O_2 content of the blood is seriously reduced.

Fortunately, CO is not a normal constituent of inspired air. It is a poisonous gas produced during the incomplete combustion (burning) of carbon products such as automobile gasoline, coal, wood, and tobacco. Carbon monoxide is especially dangerous because it is so insidious. If CO is being produced in a closed environment so that its concentration continues to increase (for example, in a parked car with the motor running and windows closed), it can reach lethal levels without the victim ever being aware of the danger. Because it is odorless, colorless, tasteless, and nonirritating, CO is not detectable. Furthermore, the victim has no sensation of breathlessness and makes no attempt to increase ventilation, even though the cells are O_2-starved.

Most CO_2 is transported in the blood as bicarbonate

When arterial blood flows through the tissue capillaries, CO diffuses down its partial pressure gradient from the tissue cells into the blood. Carbon dioxide is transported in the blood in three ways (Figure 12-25 and Table 12-3)

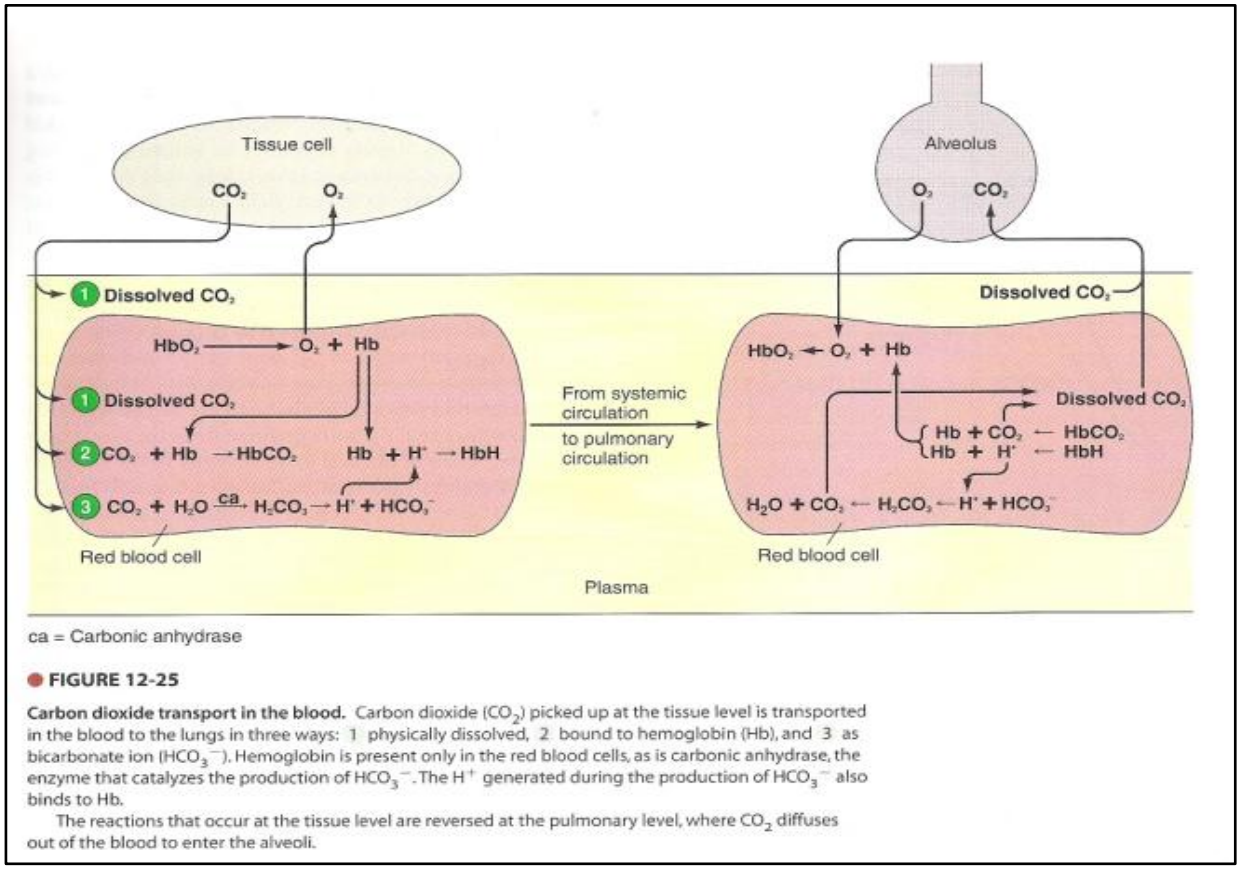


FIGURE 12-25

Carbon dioxide transport in the blood. Carbon dioxide (CO_2) picked up at the tissue level is transported in the blood to the lungs in three ways: 1 physically dissolved, 2 bound to hemoglobin (Hb), and 3 as bicarbonate ion (HCO_3^-). Hemoglobin is present only in the red blood cells, as is carbonic anhydrase, the enzyme that catalyzes the production of HCO_3^-. The H^+ generated during the production of HCO_3^- also binds to Hb.

The reactions that occur at the tissue level are reversed at the pulmonary level, where CO_2 diffuses out of the blood to enter the alveoli.

1. Physically dissolved. As with dissolved O_2, the amount of CO_2 physically dissolved in the blood depends on the P_{CO_2}. Because CO_2 is more soluble than O_2 in plasma water, a greater proportion of the total CO_2 in the blood is physically dissolved compared to O_2. Even so, only 10% of the blood's total CO_2 content is carried this way at the normal

systemic venous P_{CO_2} level.

2. Bound to hemoglobin. Another 30% of the CO_2 combines with Hb to form carbamino hemoglobin ($HbCO_2$). Carbon dioxide binds with the globin portion of Hb in contrast to O_2, which combines with the heme portions. Reduced Hb has a greater affinity for CO_2 than HbO_2 does. The unloading of O_2 from Hb in the tissue capillaries therefore facilitates the picking up of CO_2 by Hb.

3. As bicarbonate. By far the most important means of CO_2 transport is as bicarbonate (HCO_3^-), with 60% of the CO; being converted into HCO_3^- by the following chemical reaction, which takes place within the red blood cells:

$$CO_2 + H_2O \xrightleftharpoons{\text{Carbonic anhydrase}} H_2CO_3 \rightleftharpoons H^+ + HCO_3^-$$

In the first step, CO_2 combines with H_2O to form carbonic acid (H_2CO_3). This reaction can occur very slowly in plasma, but it proceeds swiftly within the red blood cells because of the presence of the erythrocyte enzyme carbonic anhydrase which catalyzes (speeds up) the reaction. As is characteristic of acids, some of the carbonic acid molecules spontaneously dissociate into hydrogen ions (H^+) and bicarbonate ions (HCO_3^-). The one carbon and two oxygen atoms of the original CO_2 molecule are thus present in the blood as an integral part of HCO_3^-. This is beneficial because HCO_3^- is more soluble in the blood than CO_2 is.

Note how hemoglobin's unloading of O_2 and its uptake of CO_2 and CO_2-generated H^+ at the tissue level work in synchrony. Increased CO_2 and H^+ cause increased O_2 release from Hb, and increased O_2 release from Hb in turn causes increased CO_2 and H^+ uptake by Hb. The entire process is very efficient. Reduced Hb must be carried back to the lungs to refill on O_2 anyway. Meanwhile, after O_2 is released Hb picks up new passengers-CO_2 and H^+ -that are going in the same direction to the lungs.

Various respiratory states are characterized by abnormal blood-gas levels

Table 12-4 is a glossary of terms used to describe various states associated with respiratory abnormalities.

ABNORMALITIES IN ARTERIAL P_{O_2}

The term **hypoxia** refers to the condition of having insufficient O_2 at the cell level. There are four general categories of hypoxia:

1. *Hypoxic hypoxia* is characterized by a low arterial blood P_{O_2} accompanied by inadequate Hb saturation. It is caused by (a) a respiratory malfunction involving inadequate gas exchange, typified by (a) normal alveolar P_{O_2} but a reduced arterial P_{O_2} or (b) exposure to high altitude or to a suffocating environment where atmospheric d P_{O_2} is reduced so that alveolar and arterial d P_{O_2} are likewise reduced.

2. *Anemic hypoxia* is a reduced O_2-carrying capacity of the blood. It can result from (a) a decrease in circulating red blood cells, (b) an inadequate amount of Hb within the red blood cells, or (c) CO poisoning. In all cases of anemic hypoxia, the arterial P_{O_2} is normal, but the O_2 content of the arterial blood is lower than normal because of the reduction in available Hb.

TABLE 12-4

Miniglossary of Clinically Important Respiratory States

Apnea Transient cessation of breathing

Asphyxia O_2 starvation of tissues, caused by a lack of O_2 in the air, respiratory impairment, or inability of the tissues to use O_2

Cyanosis Blueness of the skin resulting from insufficiently oxygenated blood in the arteries

Dyspnea Difficult or labored breathing

Eupnea Normal breathing

Hypercapnia Excess CO_2 in the arterial blood

Hyperpnea Increased pulmonary ventilation that matches increased metabolic demands, as in exercise

Hyperventilation Increased pulmonary ventilation in excess of metabolic requirements, resulting in decreased P_{CO_2} and respiratory alkalosis

Hypocapnia Below-normal CO_2 in the arterial blood

Hypoventilation Underventilation in relation to metabolic requirements, resulting in increased P_{CO_2} and respiratory acidosis

Hypoxia Insufficent O_2 at the cellular level

- ***Anemic hypoxia*** Reduced O_2-carrying capacity of the blood
- ***Circulatory hypoxia*** Too little oxygenated blood delivered to the tissues; also known as *stagnant hypoxia*
- ***Histotoxic hypoxia*** Inability of the cells to use O_2 available to them
- ***Hypoxic hypoxia*** Low arterial blood P_{O_2} accompanied by inadequate Hb saturation

Respiratory arrest Permanent cessation of breathing (unless clinically corrected)

Suffocation O_2 deprivation as a result of an inability to breathe oxygenated air

3. *Circuiaiory hypoxia* arises when too little oxygenated blood is delivered to the tissues. The arterial P_{O_2} and O_2 content are typically normal, but too little oxygenated blood reaches the cells.
4. *In histotoxic hypoxia,* O_2 delivery to the tissues is normal, but the cells cannot use the O_2 available to them. The classic example is *cyanide poisoning.* Cyanide blocks cellular enzymes essential for internal respiration.

Hyperoxia, an above-normal arterial P_{O_2} cannot occur when a person is breathing atmospheric air at sea level. However, breathing supplemental O_2 can increase alveolar and consequently arterial P_{O_2}. Because more of the inspired air is O_2, more of the total pressure of the inspired air is attributable to the O_2 partial pressure, so more O_2 dissolves in the blood before arterial P_{O_2} equilibrates with alveolar P_{O_2}. Even though arterial P_{O_2} increases, the total blood O_2 content does not significantly increase, because Hb is nearly fully saturated at the normal arterial $\boldsymbol{P_{O_2}}$. In certain pulmonary diseases associated with a reduced arterial $\boldsymbol{P_{O_2}}$, however, breathing supplemental O_2 can help establish a larger alveoli-to-blood driving gradient, improving arterial d $\boldsymbol{P_{O_2}}$. Far from being advantageous, in contrast, a markedly elevated arterial $\boldsymbol{P_{O_2}}$ can be dangerous. If the arterial $\boldsymbol{P_{O_2}}$ is too high, oxygen toxicity occur. Even though the total O_2 content of the blood is only slightly increased, exposure to a high $\boldsymbol{P_{O_2}}$ can damage some cells. In particular, brain damage and blindness-causing damage to the retina are associated with O_2 toxicity. Therefore, O_2 therapy must be administered cautiously.

ABNORMALITIES IN ARTERIAL $\boldsymbol{P_{CO_2}}$

The term **hypercapnia** refers to the condition of having excess CO_2 in arterial blood; it is caused by hypoventilation (ventilation inadequate to meet metabolic needs for O_2 delivery and CO_2 removal). With most lung diseases, CO_2 accumulates in arterial blood concurrently with an O_2 deficit.

Hypocapnia, below-normal arterial $\boldsymbol{P_{CO_2}}$ levels, is brought about by **hyperventilation**. Hyperventilation occurs when a person "overbreathes," that is, when the rate of ventilation exceeds the body's metabolic needs for CO_2 removal. As a result, CO_2 is blown off to the atmosphere more rapidly than it is produced in the tissues, and arterial $\boldsymbol{P_{CO_2}}$ falls. Hyperventilation can be triggered by anxiety states, fever, and aspirin poisoning. Alveolar $\boldsymbol{P_{O_2}}$ increases during hyperventilation as more fresh O_2 is delivered to the alveoli from the atmosphere than the blood extracts from the alveoli for tissue consumption, and arterial $\boldsymbol{P_{O_2}}$ increases correspondingly. However, because Hb is almost fully saturated at the normal arterial $\boldsymbol{P_{O_2}}$ very little additional O_2 is added to the blood. Except for the small extra amount of dissolved O_2, blood O_2 content remains essentially unchanged during hyperventilation.

Increased ventilation is not synonymous with hyperventilation. Increased ventilation that matches an increased metabolic demand, such as the increased need for O_2 delivery and CO_2 elimination during exercise, is termed hyperpnea. During exercise, alveolar $\boldsymbol{P_{O_2}}$ and $\boldsymbol{P_{CO_2}}$ remain constant, with the increased atmospheric exchange just keeping pace with the increased O_2 consumption and CO_2 production.

CONSEQUENCES OF ABNORMALITIES IN ARTERIAL BLOOD GASES

The consequences of reduced O_2 availability to the tissues during hypoxia are apparent. The cells need adequate O_2 supplies to sustain energy-generating metabolic activities. The consequences of abnormal blood CO_2 levels are less obvious. Changes in blood CO_2 concentration primarily affect acid-base balance. Hypercapnia elevates production of carbonic acid. The subsequent generation of excess H^+ produces an acidic condition termed *respiratory acidosis.* Conversely, less-than-normal amounts of H^+ are generated through carbonic acid formation in conjunction with hypocapnia. The resultant condition is called *respiratory alkalosis.*

CONTROL OF RESPIRATION

Like the heartbeat, breathing must occur in a continuous, cyclic pattern to sustain life processes. Cardiac muscle must rhythmically contract and relax to alternately empty blood from the heart and fill it again. Similarly, inspiratory muscles must rhythmically contract and relax to alternately fill the lungs with air and empty them. Both these activities are accomplished automatically, without conscious effort. However, the underlying mechanisms and control of these two systems are remarkably different.

Respiratory centers in the brain stem establish a rhythmic breathing pattern

Whereas the heart can generate its own rhythm by means of its intrinsic pacemaker activity, the respiratory muscles, being skeletal muscles, require nervous stimulation to induce contraction. The rhythmic pattern of breathing is established by cyclic neural activity to the respiratory muscles. In other words, the pacemaker activity that establishes breathing rhythm resides in the respiratory control centers in the brain, not in the lungs or respiratory muscles themselves. The nerve supply to the heart, not being needed to initiate the heartbeat, only modifies the rate and strength of cardiac contraction. In contrast, the nerve supply to the respiratory system is absolutely essential in maintaining breathing and in reflexly adjusting the level of ventilation to match changing needs for O_2 uptake and CO_2 removal. Furthermore, unlike cardiac activity, which is not subject to voluntary control, respiratory activity can be voluntarily modified to accomplish speaking, singing, whistling, playing a wind instrument, or holding one's breath while swimming.

COMPONENTS OF NEURAL CONTROL OF RESPIRATION

Neural control of respiration involves three distinct components: (1) factors that generate

the alternating inspiration/expiration rhythm, (2) factors that regulate the magnitude of ventilation (that is, the rate and depth of breathing) to match body needs, and (3) factors that modify respiratory activity to serve other purposes. The latter modifications may be either voluntary, as in the breath control required for speech, or involuntary, as in the respiratory maneuvers involved in a cough or sneeze.

Respiratory control centers housed in the brain stem generate the rhythmic pattern of breathing. The primary respiratory control center, the *medullary respiratory center*, consists of several aggregations of neuronal cell bodies within the medulla that provide output to the respiratory muscles. In addition, two other respiratory centers lie higher in the brain stem in the pons -the *apneustic center* and *pneumotaxic center*. These centers influence output from the medullary respiratory center **(**Figure 12-26). Here is a description of how these various regions interact to establish respiratory rhythmicity.

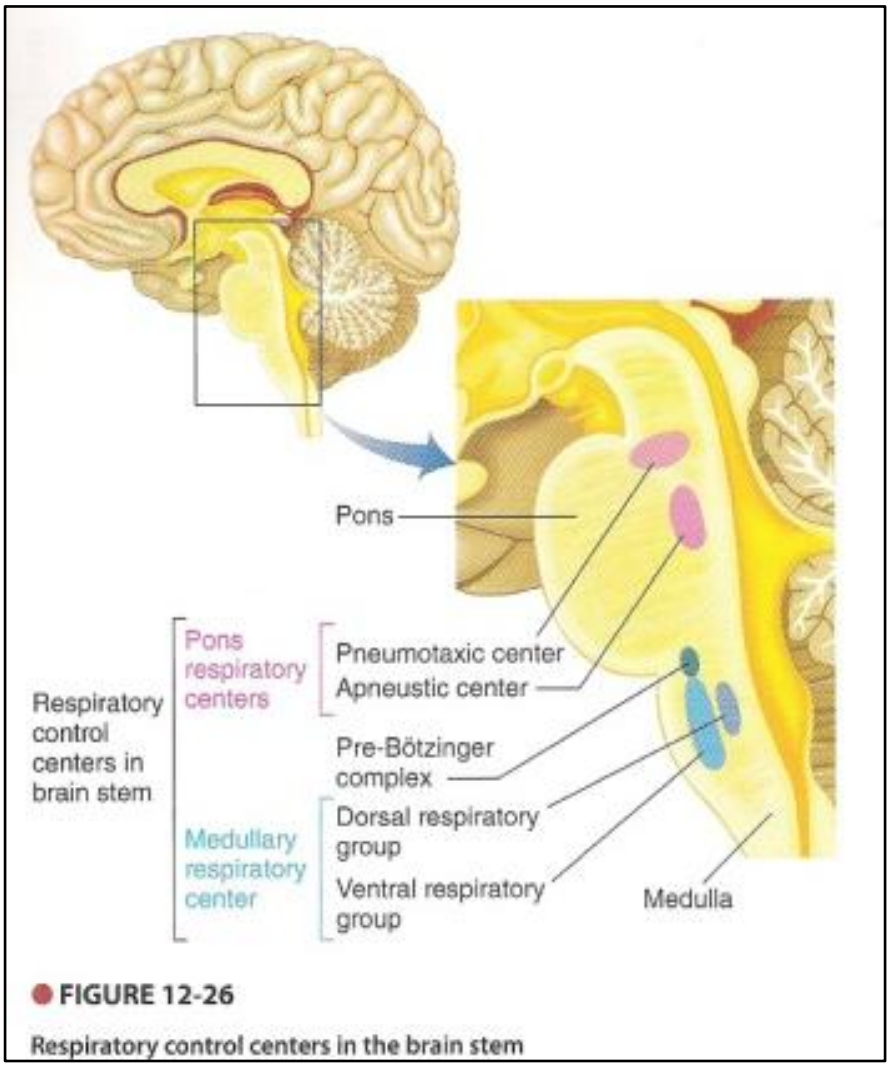


FIGURE 12-26
Respiratory control centers in the brain stem

INSPIRATORY AND EXPIRATORY NEURONS IN THE MEDULLARY CENTER

We rhythmically breathe in and out during quiet breathing because of alternate contraction and relaxation of the inspiratory muscles, namely the diaphragm and external intercostal muscles, supplied by the phrenic nerve and intercostal nerves. Respectively. The cell bodies for the neuronal fibers composing these nerves are located in the spinal

cord. Impulses originating in the medullary center end on these motor-neuron cell bodies. When these motor neurons are activated, they in turn stimulate the inspiratory muscles, leading to inspiration; when these neurons are not firing, the inspiratory muscles relax, and expiration takes place. The **medullary respiratory center** consists of two neuronal clusters known as the *dorsal respiratory group* and the *ventral respiratory group* **(**Figure 12-26).

- The **dorsal respiratory group (DRG)** consists mostly of *inspiratory neurons* whose descending fibers terminate on the motor neurons that supply the inspiratory muscles. When the DRG inspiratory neurons fire, inspiration takes place; when they cease firing, expiration occurs. Expiration is brought to an end as the inspiratory neurons once again reach threshold and fire, The DRG has important interconnections with the ventral respiratory group.

- The **ventral respiratory group (VRG)** is composed of in*spiratory neurons* and *expiratory neurons,* both of which remain inactive during normal quiet breathing. This region is called into play by the DRG as an "overdrive" mechanism during periods when demands for ventilation are increased. It is especially important in active expiration. No impulses are generated in the descending pathways from the expiratory neurons during quiet breathing, Only during active expiration do the expiratory neurons stimulate the motor neurons supplying the expiratory muscles (the abdominal and internal intercostal muscles). Furthermore, the VRG inspiratory neurons, when stimulated by the DRG, rev up inspiratory activity when demands for ventilation are high.

GENERATION OF RESPIRATORY RHYTHM

Until recently, the DRG was generally thought to generate the basic rhythm of ventilation, However, generation of respiratory rhythm is now widely believed to lie in the pre-Botzinger complex, a region located near the upper (head) end of the medullary respiratory center **(**Figure 12-26), A network of neurons in this region display pacemaker activity, undergoing self-induced action potentials similar to the SA node of the heart. Scientists believe the rate at which the DRG inspiratory neurons rhythmically fire is driven by synaptic input from this complex.

INFLUENCES FROM THE PNEUMOTAXIC AND APNEUSTIC CENTERS

These centers exert "fine-tuning" influences over the medullary center to help produce normal, smooth inspirations and expirations, The pneumotaxic center sends impulses to the DRG that help "switch off" the inspiratory neurons, limiting the duration of

inspiration, In contrast, the apneustic center prevents the inspiratory neurons from being switched off, thus providing an extra boost to the inspiratory drive, In this check-and-balance system, the pneumotaxic center dominates over the apneustic center, helping halt inspiration and letting expiration occur normally. Without the pneumotaxic brakes, the breathing pattern consists of prolonged inspiratory gasps abruptly interrupted by very brief expirations. This abnormal pattern of breathing is known as apneusis; hence, the center that promotes this type of breathing is the apneustic center. Apneusis occurs in certain types of severe brain damage,

The magnitude of ventilation is adjusted in response to three chemical factors: P_{O_2}, P_{CO_2} and H^+

No matter how much O_2 is extracted from the blood or how much CO_2 is added to it at the tissue level, the P_{O_2} and P_{CO_2} of the systemic arterial blood leaving the lungs are held remarkably constant, indicating that arterial blood gas content is precisely regulated. Arterial blood gases are maintained within the normal range by varying the magnitude of ventilation (rate and depth of breathing) to match the body's needs for O_2 uptake and CO_2 removal. If more O_2 is extracted from the alveoli and more CO_2 is dropped off by the blood because the tissues are metabolizing more actively, ventilation increases correspondingly to bring in more fresh O_2 and blow off more CO_2 (Table 12-5).

TABLE 12-5
Influence of Chemical Factors on Respiration

CHEMICAL FACTOR	EFFECT ON THE PERIPHERAL CHEMORECEPTORS	EFFECT ON THE CENTRAL CHEMORECEPTORS
↓ P_{O_2} in the Arterial Blood	Stimulates only when the arterial P_{O_2} has fallen to the point of being life-threatening (<60 mm Hg); an emergency mechanism	Directly depresses the central chemoreceptors and the respiratory center itself when <60mm Hg
↑ P_{CO_2} in the Arterial Blood (↑ H^+ in the Brain ECF)	Weakly stimulates	Strongly stimulates; is the dominant control of ventilation (Levels >70–80 mm Hg directly depress the respiratory center and central chemoreceptors)
↑ H^+ in the Arterial Blood	Stimulates; important in acid–base balance	Does not affect; cannot penetrate the blood–brain barrier

Decreased arterial P_{O_2} increases ventilation only as an emergency mechanism

Arterial P_{O_2} is monitored by **peripheral chemoreceptors** known as the **carotid bodies** and **aortic bodies**, which lie at the fork of the common carotid arteries on both the right and left sides and in the arch of the aorta, respectively (Figure 12-27). These chemoreceptors respond to specific changes in the chemical content of the arterial blood that bathes them.

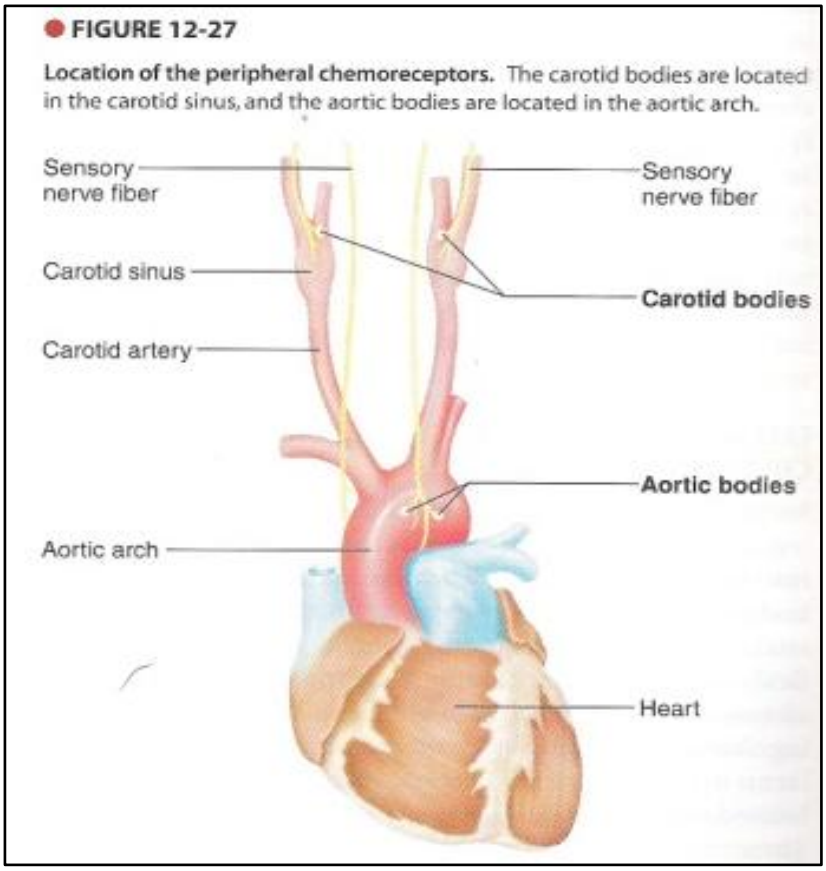


FIGURE 12-27

Location of the peripheral chemoreceptors. The carotid bodies are located in the carotid sinus, and the aortic bodies are located in the aortic arch.

EFFECT OF A LARGE DECREASE IN P_{O_2} ON THE PERIPHERAL CHEMORECEPTORS

The peripheral chemoreceptors are not sensitive to modest reductions in arterial P_{O_2}. The arterial P_{O_2} must fall below 60 mm Hg (>40% reduction) before the peripheral chemoreceptors respond by sending afferent impulses to the medullary inspiratory neurons, thereby reflexly increasing ventilation. Because arterial P_{O_2} only falls below 60 mm Hg in the unusual circumstances of severe pulmonary disease or reduced atmospheric P_{O_2} it does not play a role in the normal ongoing regulation of respiration. This fact may seem surprising at first, because a primary function of ventilation is to provide enough O_2

for uptake by the blood. However, there is no need to increase ventilation until the arterial P02 falls below 60 mm Hg, because of the safety margin in % Hb saturation afforded by the plateau portion of the O_2-Hb curve. Hemoglobin is still 90% saturated at an arterial P_{O_2} of 60 mm Hg, but the % Hb saturation drops precipitously when the P_{O_2} falls below this level. Therefore, reflex stimulation of respiration by the peripheral chemoreceptors serves as an important emergency mechanism in dangerously low arterial P_{O_2} states. Indeed, this reflex mechanism is a lifesaver, because a low arterial P_{O_2} tends to directly depress the respiratory center, as it does all the rest of the brain.

Because the peripheral chemoreceptors respond to the P_{O_2} of the blood, not the total O_2 content of the blood, O_2 content in the arterial blood can fall to dangerously low or even fatal levels without the peripheral chemoreceptors ever responding to reflexly stimulate respiration. Remember that only physically dissolved O_2 contributes to blood P_{O_2}. The total O_2 content in the arterial blood can be reduced in anemic states, in which O_2-carrying Hb is reduced, or in CO poisoning, when Hb is preferentially bound to this molecule rather than to O_2. In both cases, arterial P_{O_2} is normal, so respiration is not stimulated, even though O_2 delivery to the tissues may be so reduced that the person dies from cellular O_2 deprivation.

DIRECT EFFECT OF A LARGE DECREASE IN P_{O_2} ON THE RESPIRATORY CENTER

Except for the peripheral chemoreceptors, the level of activity in all nervous tissue falls in O_2 deprivation. Direct depression of the respiratory center by the markedly low arterial P_{O_2} would further reduce ventilation, leading to an even greater fall in arterial P_{O_2} which would even further depress the respiratory center until ventilation ceased and death occurred.

Carbon dioxide-generated H^+ in the brain is normally the main regulator of ventilation

In contrast to arterial P_{O_2} which does not contribute to the minute-to-minute regulation of respiration, arterial P_{CO_2} is the most important input regulating the magnitude of ventilation under resting conditions. This role is appropriate, because changes in alveolar ventilation have an immediate and pronounced effect on arterial P_{CO_2}. By contrast, changes in ventilation have little effect on % Hb saturation and O_2 availability to the tissues until the arterial P_{O_2} falls by more than 40%. Even slight alterations from normal in arterial d P_{CO_2} induce a significant reflex effect on ventilation. An increase in arterial P_{CO_2} reflexly stimulates the respiratory center, with the resultant increase in ventilation promoting elimination of the excess CO_2 to the atmosphere. Conversely, a fall in arterial P_{CO_2} reflexly reduces the respiratory drive. The subsequent decrease in ventilation lets metabolically produced CO_2 accumulate so that P_{CO_2} can be returned to normal.

EFFECT OF INCREASED P_{CO_2} ON THE CENTRAL CHEMORECEPTORS

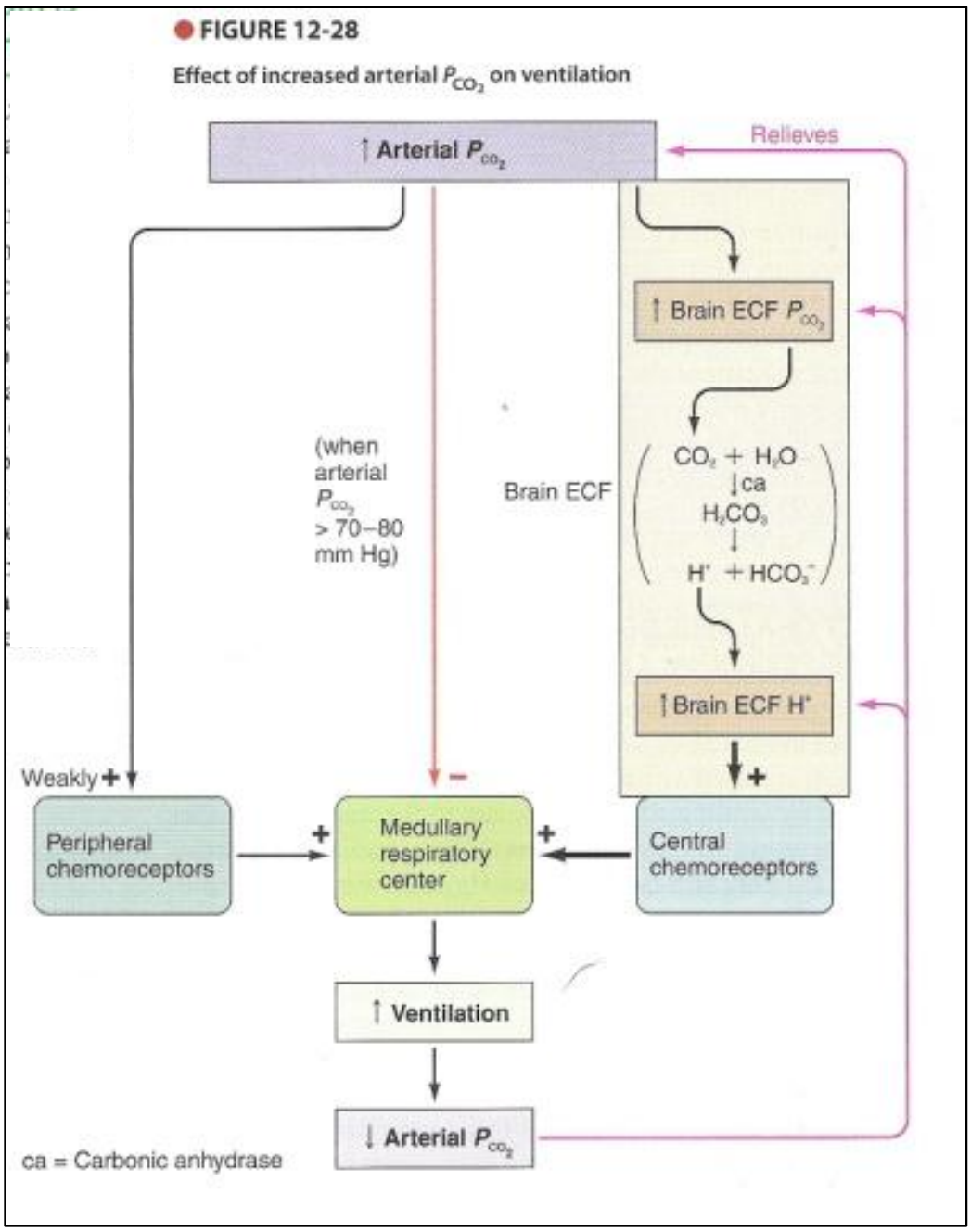
Surprisingly, given the key role of arterial P_{CO_2} in regulating respiration, no important receptors monitor arterial P_{CO_2} per se. The carotid and aortic bodies are only weakly responsive to changes in arterial P_{CO_2}, so they play only a minor role in reflexly stimulating ventilation in response to an elevation in arterial P_{CO_2}. More important in linking changes in arterial P_{CO_2} to compensatory adjustments in ventilation are the central chemoreceptors, located in the medulla near the respiratory center. These central chemoreceptors do not monitor CO_2 itself; however, they are sensitive to changes in CO_2-induced H^+ concentration in the brain extracellular fluid (ECF) that bathes them.

Movement of materials across the brain capillaries is restricted by the blood-brain barrier. Because this barrier is readily permeable to CO_2, any increase in arterial P_{CO_2} causes a similar rise in brain ECF P_{CO_2} as CO_2 diffuses down its pressure gradient from the cerebral blood vessels into the brain ECE The increased P_{e02} within the brain ECF correspondingly raises the concentration of H^+ according to the law of mass action as it applies to this reaction:

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

An elevation in H^+ concentration in the brain ECF directly stimulates the central chemoreceptors, which in turn increase ventilation by stimulating the respiratory center through synaptic connections **(**Figure 12-28). As the excess CO_2 is subsequently blown off, the arterial and the P_{CO_2} and H^+ concentration of the brain ECF return to normal. Conversely, a decline in arterial P_{CO_2} below normal is paralleled by a fall in P_{CO_2} and H^+ in the brain ECF, the result of which is a central chemoreceptor-mediated decrease in ventilation. As CO_2 produced by cell metabolism is consequently allowed to accumulate, arterial P_{CO_2} and P_{CO_2} and H^+ of the brain ECF are restored toward normal.

Unlike CO_2, H+ cannot readily permeate the blood-brain barrier, so H^+ in the plasma cannot gain access to the central chemoreceptors. Accordingly, the central chemoreceptors respond only to H+ generated within the brain ECF itself as a result of CO_2 entry. Thus the major mechanism controlling ventilation under resting conditions is specifically aimed at regulating the brain ECF H^+ concentration, which in turn directly reflects the arterial P_{CO_2}.



The powerful influence of the central chemoreceptors on the respiratory center is responsible for your inability to deliberately hold your breath for more than about a minute. While you hold your breath, metabolically produced CO_2 continues to accumulate in your blood and then to build up the H^+ concentration in your brain ECF Finally, the increased P_{CO_2}-H^+ stimulant to respiration becomes so powerful that central-chemoreceptor excitatory input overrides voluntary inhibitory input to respiration, so breathing resumes despite deliberate attempts to prevent it. Breathing resumes long before arterial P_{CO_2} falls to the threateningly low levels that trigger the peripheral chemoreceptors. Therefore, you cannot

deliberately hold your breath long enough to create a dangerously high level of CO_2 or low level of O_2 in the arterial blood.

DIRECT EFFECT OF A LARGE INCREASE IN P_{CO_2} ON THE RESPIRATORY CENTER

A further increase in P_{CO_2} beyond 70 to 80 mm Hg, however, does not further increase ventilation but actually depresses the respiratory neurons. Otherwise, CO_2 could reach lethal levels, not only because it depresses respiration but also because it produces severe respiratory acidosis

Adjustments in ventilation in response to changes in arterial H^+ are important in acid-base balance

the aortic and carotid body peripheral chemoreceptors are highly responsive to fluctuations in arterial H+ concentration, in contrast to their weak sensitivity to deviations in arterial P_{CO_2} and their unresponsiveness to arterial P_{O_2} until it falls 40% below normal arterial H^+ concentration increases during diabetes mellitus because excess H^+ -generating keto acids are abnormally produced and added to the blood. A rise in arterial H^+ concentration reflexly stimulates ventilation by means of the peripheral chemoreceptors. Changes in ventilation by this mechanism are extremely important in regulating body's acid-base balance

During apnea, a person "forgets to breathe"; during dyspnea, a person feels "short of breath."

Apnea is the transient interruption of ventilation, with breathing resuming spontaneously. If breathing does not resume, the condition is called **respiratory arrest**. Because ventilation is normally decreased and the central chemoreceptors are less sensitive to the arterial P_{CO_2} drive during sleep, especially paradoxical sleep, apnea is most likely to occur during this time. Victims of **sleep apnea** may stop breathing for a few seconds or up to one or two minutes as many as 500 times a night

SUDDEN INFANT DEATH SYNDROME

In exaggerated cases of sleep apnea, the victim may be unable to recover from an apneic period, and death results. This is the case in **sudden infant death syndrome (SlDS),** or "crib death." With this tragic form of sleep apnea, a previously healthy 2- to 4-month-old infant is found dead in his or her crib for no apparent reason. The underlying cause of SIDS is the subject of intense investigation. Most evidence suggests that the baby "forgets to

breathe" because the respiratory control mechanisms are immature, either in the brain stem or in the chemoreceptors that monitor the body's respiratory status.

Infants whose mothers smoked during pregnancy of who breathe cigarette smoke in the home are three times more likely to die of SIDS than those not exposed to smoke.