CHAPTER 22

The Control of Ventilation

Rodney A. Rhoades, Ph.D.

CHAPTER OUTLINE

- **GENERATION OF THE BREATHING PATTERN**
- **REFLEXES FROM THE LUNGS AND CHEST WALL**
- **CONTROL OF BREATHING BY H$^+$, CO$_2$, AND O$_2$**
- **THE CONTROL OF BREATHING DURING SLEEP**
- **THE RESPONSE TO HIGH ALTITUDE**

KEY CONCEPTS

1. Ventilation is controlled by negative and positive feedback systems.
2. Normal arterial blood gases are maintained and the work of breathing is minimized despite changes in activity, the environment, and lung function.
3. The basic breathing rhythm is generated by neurons in the brainstem and can be modified by ventilatory reflexes.
4. The rate and depth of breathing are finely regulated by vagal nerve endings that are sensitive to lung stretch.
5. The autonomic nerves and vagal sensory nerves maintain local control of airway function.
6. Mechanical or chemical irritation of the airways and lungs induces coughing, bronchoconstriction, shallow breathing, and excess mucus production.

7. Arterial P_{CO_2} is the most important factor in determining the ventilatory drive in resting individuals.
8. Central chemoreceptors detect changes only in arterial P_{CO_2}; peripheral chemoreceptors detect changes in arterial P_{O_2}, P_{CO_2}, and pH.
9. The hypoxia-induced stimulation of ventilation is not great until the arterial P_{O_2} drops below 60 mm Hg.
10. Sleep is induced by the withdrawal of a wakefulness stimulus arising from the brainstem reticular formation and results in a general depression of breathing.
11. Chronic hypoxemia causes ventilatory acclimatization that increases breathing.

GENERATION OF THE BREATHING PATTERN

The control of breathing is critical for understanding of respiratory responses to activity, changes in the environment, and lung diseases. Breathing is an automatic process that occurs without any conscious effort while we are awake, asleep, or under anesthesia. Breathing is similar to the heartbeat in terms of an automatic rhythm. However, there is no single pacemaker that sets the basic rhythm of breathing and no single muscle devoted solely to the task of tidal air movement. Breathing depends on the cyclic excitation of many muscles that can influence the volume of the thorax. Control of that excitation is the result of multiple neuronal interactions involving all levels of the nervous system. Furthermore, the muscles used for breathing must often be used for other purposes as well. For example, talking while walking requires that some muscles simultaneously attend to the tasks of posturing, walking, phonation, and breathing. Because it is impossible to

study extensively the subtleties of such a complex system in humans, much of what is known about the control of breathing has been obtained from the study of other species. Much, however, remains unexplained.

The control of upper and lower airway muscles that affect airway tone is integrated with control of the muscles that start tidal air movements. During quiet breathing, inspiration is brought about by a progressive increase in activation of inspiratory muscles, most importantly the diaphragm (Fig. 22.1). This nearly linear increase in activity with time causes the lungs to fill at a nearly constant rate until tidal volume has been reached. The end of inspiration is associated with a rapid decrease in excitation of inspiratory muscles, after which expiration occurs passively by elastic recoil of the lungs and chest wall. Some excitation of inspiratory muscles resumes during the first part of expiration, slowing the initial rate of expiration. As more ventilation is required—for example, during exercise—other inspiratory muscles (external intercostals, cervical muscles)
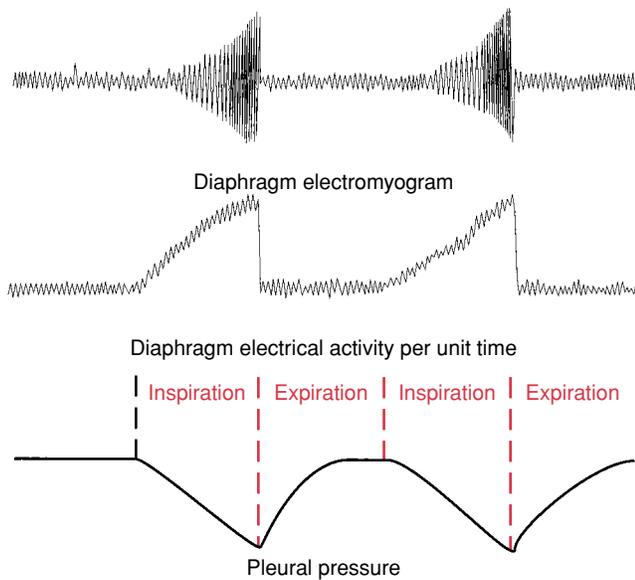
Diaphragm electromyogram

Diaphragm electrical activity per unit time

| Inspiration | Expiration | Inspiration | Expiration |

Pleural pressure

FIGURE 22.1 **Relationship between electrical activity of the diaphragm and pleural pressure during quiet breathing.** During inspiration, the number of active muscle fibers, and the frequency at which each fires, increases progressively, leading to a mirror-image fall in pleural pressure as the diaphragm descends.

FIGURE 22.2 **The general locations of the dorsal respiratory group (DRG) and ventral respiratory group (VRG).** These drawings show the dorsal aspect of the medulla oblongata and a cross section in the region of the fourth ventricle. C1, first cervical nerve; X, vagus nerve; IX, glossopharyngeal nerve.

are recruited. In addition, expiration becomes an active process through the use, most notably, of the muscles of the abdominal wall. The neural basis of these breathing patterns depends on the generation and subsequent tailoring of cyclic changes in the activity of cells primarily located in the medulla oblongata in the brain.

Two Major Cell Groups in the Medulla Oblongata Control the Basic Breathing Rhythm

The central pattern for the basic breathing rhythm has been localized to fairly discrete areas in the medulla oblongata that discharge action potentials in a phasic pattern with respiration. Cells in the medulla oblongata associated with breathing have been identified by noting the correlation between their activity and mechanical events of the breathing cycle. Two different groups of cells have been found, and their anatomic locations are shown in Figure 22.2. The **dorsal respiratory group** (DRG), named for its dorsal location in the region of the nucleus tractus solitarii, predominantly contains cells that are active during inspiration. The **ventral respiratory group** (VRG) is a column of cells in the general region of the nucleus ambiguus that extends caudally nearly to the bulbospinal border and cranially nearly to the bulbopontine junction. The VRG contains both inspiration- and expiration-related neurons. Both groups contain cells projecting ultimately to the bulbospinal motor neuron pools. The DRG and VRG are bilaterally paired, but cross-communication enables them to respond in synchrony; as a consequence, respiratory movements are symmetric.

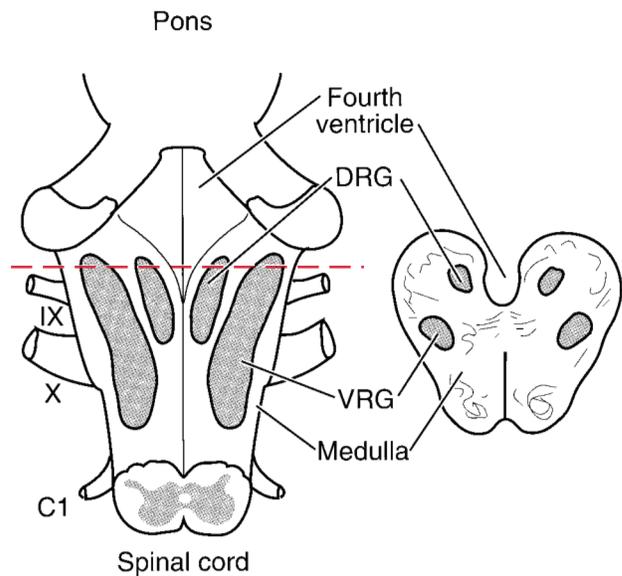The neural networks forming the **central pattern generator for breathing** are contained within the DRG/VRG

complex, but the exact anatomic and functional description remains uncertain. Central pattern generation probably does not arise from a single pacemaker or by reciprocal inhibition of two pools of cells, one having inspiratory- and the other expiratory-related activity. Instead, the progressive rise and abrupt fall of inspiratory motor activity associated with each breath can be modeled by the starting, stopping, and resetting of an integrator of background ventilatory drive. An integrator-based theoretical model, as described below, is suitable for a first understanding of respiratory pattern generation.

Integrator Neurons Synchronize the Onset of Inspiration

Many different signals (e.g., volition, anxiety, musculoskeletal movements, pain, chemosensor activity, and hypothalamic temperature) provide a background ventilatory drive to the medulla. Inspiration begins by the abrupt release from inhibition of a group of cells, **central inspiratory activity (CIA) integrator** neurons, located within the medullary reticular formation, that integrate this background drive (see Fig. 22.3). Integration results in a progressive rise in the output of the integrator neurons, which, in turn, excites a similar rise in activity of inspiratory premotor neurons of the DRG/VRG complex. The rate of rising activity of inspiratory neurons and, therefore, the rate of inspiration itself, can be influenced by changing the characteristics of the CIA integrator. Inspiration is ended by abruptly switching off the rising excitation of inspiratory neurons. The CIA integrator is reset before the beginning of each inspiration, so that activity of the inspiratory neurons begins each breath from a low level.
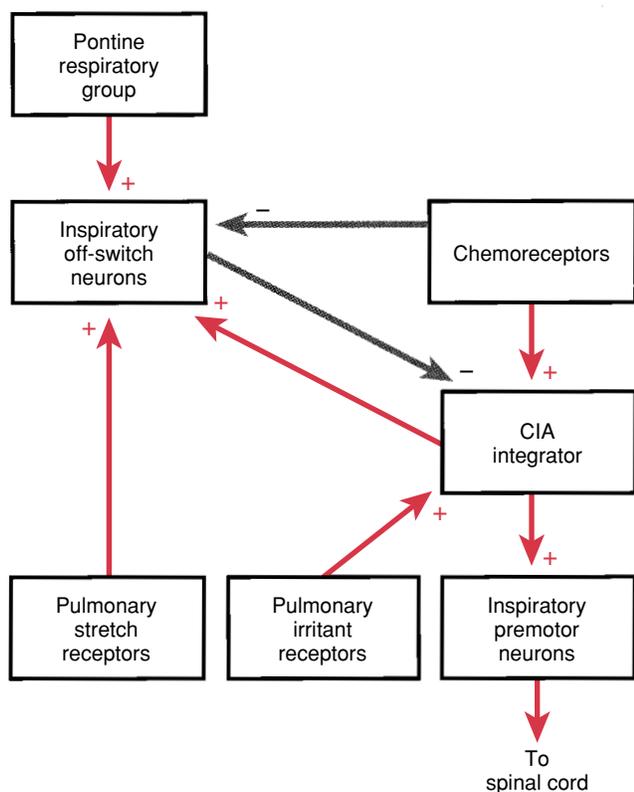
The medullary inspiratory pattern genera-tor. CIA, central inspiratory activity.

may serve to integrate many different autonomic functions in addition to breathing.

Expiration Is Divided Into Two Phases

Shortly after the abrupt termination of inspiration, some activity of inspiratory muscles resumes. This activity serves to control expiratory airflow. This effect is greatest early in expiration and recedes as lung volume falls. Inspiratory muscle activity is essentially absent in the second phase of expiration, which includes continued passive recoil during quiet breathing or activation of expiratory muscles if more than quiet breathing is required.

The duration of expiration is determined by the intensity of inhibition of activity of inspiratory-related cells of the DRG/VRG complex. Inhibition is greatest at the start of expiration and falls progressively until it is insufficient to prevent the onset of inspiration. The progressive fall of inhibition amounts to a decline of threshold for initiating the switch from expiration to inspiration. The rate of decline of inhibition and the occurrence of events that trigger the onset of inspiration are subject to several influences. The duration of expiration can be controlled not only by neural information arriving during expiration but also in response to the pattern of the preceding inspiration. How the details of the preceding inspiration are stored and later recovered is unresolved.

Various Control Mechanisms Adjust Breathing to Meet Metabolic Demands

The basic pattern of breathing generated in the medulla is extensively modified by several control mechanisms. Multiple controls provide a greater capability for regulating breathing under a larger number of conditions. Their interactions modify each other and provide for backup in case of failure. The set of strategies for controlling a given variable, such as minute ventilation, typically includes individual schemes that differ in several respects, including choices of sensors and effectors, magnitudes of effects, speeds of action, and optimum operating points.

The use of multiple control mechanisms in breathing can be illustrated by considering some of the ways breathing changes in response to exercise. Perhaps the simplest strategies are feedforward mechanisms, in which breathing responds to some component of exercise but without recognition of how well the response meets the demand. One such mechanism would be for the central nervous system (CNS) to vary the activity of the medullary pattern generator in parallel with, and in proportion to, the excitation of the muscles used during exercise. Another prospective feedforward scheme involves sensing the magnitude of the carbon dioxide load delivered to the lungs by systemic venous return and then driving ventilation in response to the magnitude of that load. Experimental evidence supports this mechanism, but the identity of the required intrapulmonary sensor remains uncertain. Still another recognized feedforward mechanism is the enhancement of breathing in response to increased receptor activity in skeletal joints as joint motion increases with exercise.

Inspiratory Activity Is Switched Off to Initiate Expiration

Two groups of neurons, probably located within the VRG, seem to serve as an inspiratory off-switch (see Fig. 22.3). Switching occurs abruptly when the sum of excitatory inputs to the off-switch reaches a threshold. Adjustment of the threshold level is one of the ways in which depth of breathing can be varied. Two important excitatory inputs to the off-switch are a progressively increasing activity from the CIA integrator's rising output and an input from lung stretch receptors, whose afferent activity increases progressively with rising lung volume. (The first of these is what allows the medulla to generate a breathing pattern on its own; the second is one of many reflexes that influence breathing.) Once the critical threshold is reached, off-switch neurons apply a powerful inhibition to the CIA integrator. The CIA integrator is thus reset by its own rising activity. Other inputs, both excitatory and inhibitory, act on the off-switch and change its threshold. For example, chemical stimuli, such as hypoxemia and hypercapnia, are inhibitory, raising the threshold and causing larger tidal volumes.

An important excitatory input to the off-switch comes from a group of spatially dispersed neurons in the rostral pons called the **pontine respiratory group.** Electrical stimulation in this region causes variable effects on breathing, dependent not only on the site of stimulation but also on the phase of the respiratory cycle in which the stimulus is applied. It is believed that the pontine respiratory group

Although feedforward methods bring about changes in the appropriate direction, they do not provide control in response to the difference between desired and prevailing conditions, as can be done with feedback control. For example, if $PaCO_2$ deviates from a reference point, say 40 mm Hg, ventilation could be adjusted by feedback control to reduce the discrepancy. This well-known control system, diagrammed according to the principles given in Chapter 1, is shown in Figure 22.4. Unlike feedforward control, feedback control requires a sensor, a reference (set point), and a comparator that together generate an error signal, which drives the effector. Negative-feedback systems provide good control in the presence of considerable variations of other properties of the system, such as lung stiffness or respiratory muscle strength. They can, if sufficiently sensitive, act quickly to reduce discrepancies from reference points to very low levels. Too much sensitivity, however, may lead to instability and undesirable excursions of the regulated variable.

Other mechanisms involve minimization or optimization. For example, evidence indicates that rate and depth of breathing are adjusted to minimize the work expenditure for ventilation of a given magnitude. In other words, the controller decides whether to use a large breath with its attendant large elastic load or more frequent smaller breaths with their associated higher resistive load. This strategy requires afferent neural information about lung volume, rate of volume change, and transpulmonary pressures, which can be provided by lung and chest wall mechanoreceptors. During exercise, such a controller would act in concert with, among other things, the feedback control of carbon dioxide described earlier. As a final example, an optimization model using two pieces of information is illustrated in Figure 22.5. Breathing is adjusted to minimize the sum of the muscle effort and the sensory "cost" of tolerating a raised $PaCO_2$.

Muscles of the Upper Airways Are Also Under Phasic Control

The same rhythm generator that controls the chest wall muscles also controls muscles of the nose, pharynx, and larynx. But unlike the inspiratory ramp-like rise of the stimulation of chest wall muscles, the excitation of upper airway muscles quickly reaches a plateau and is sustained until inspiration is ended. Flattening of the expected ramp excitation waveform probably results from progressive inhibition by the rising afferent activity of airway stretch reflexes as lung volume increases. Excitation during inspiration causes contractions of upper airway muscles, airway widening, and reduced resistance from the nostrils to the larynx.

During the first phase of quiet expiration, when expiration is slowed by renewed inspiratory muscle activity, there is also expiratory braking caused by active adduction of the vocal cords. However, during exercise-induced hyperpnea (increased depth and rate of breathing), the cords are separated during expiration and expiratory resistance is reduced.

REFLEXES FROM THE LUNGS AND CHEST WALL

Reflexes arising from the periphery provide feedback for fine-tuning, which adjusts frequency and tidal volume to minimize the work of breathing. Reflexes from the upper airways and lungs also act as defensive reflexes, protecting the lungs from injury and environmental insults. This section considers reflexes that arise from the lungs and chest wall. Among reflexes influencing breathing, the lung and chest wall mechanoreceptors and the chemoreflexes responding to blood pH and gas tension changes are the most widely recognized. Although many other less well-explored reflexes also influence breathing, most are not covered in this chapter. Examples are reflexes induced by changes in arterial blood pressure, cardiac stretch, epicardial irritation, sensations in the airway above the trachea, skin injury, and visceral pain.

Three Classes of Receptors Are Associated With Lung Reflexes

Pulmonary receptors can be divided into three groups: slowly adapting receptors, rapidly adapting receptors, and C fiber endings. Afferent fibers of all three types lie predominantly in the vagus nerves, although some pass with the sympathetic nerves to the spinal cord. The role of the sympathetic afferents is uncertain and is not considered further.
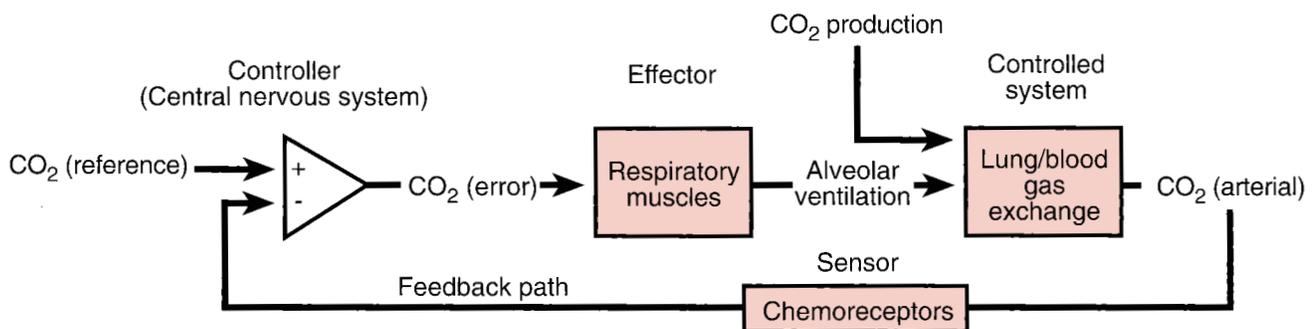

FIGURE 22.4 **Negative-feedback control of arterial CO_2.** Variations in CO_2 production lead to changes in arterial CO_2 that are sensed by chemoreceptors. The chemoreceptor signal is subtracted from a reference value. The absolute value of the difference is taken as an input by the CNS and passed on to respiratory muscles as new minute ventilation. The loop is completed as the new ventilation alters blood gas composition through the mechanism of lung-blood gas exchange.
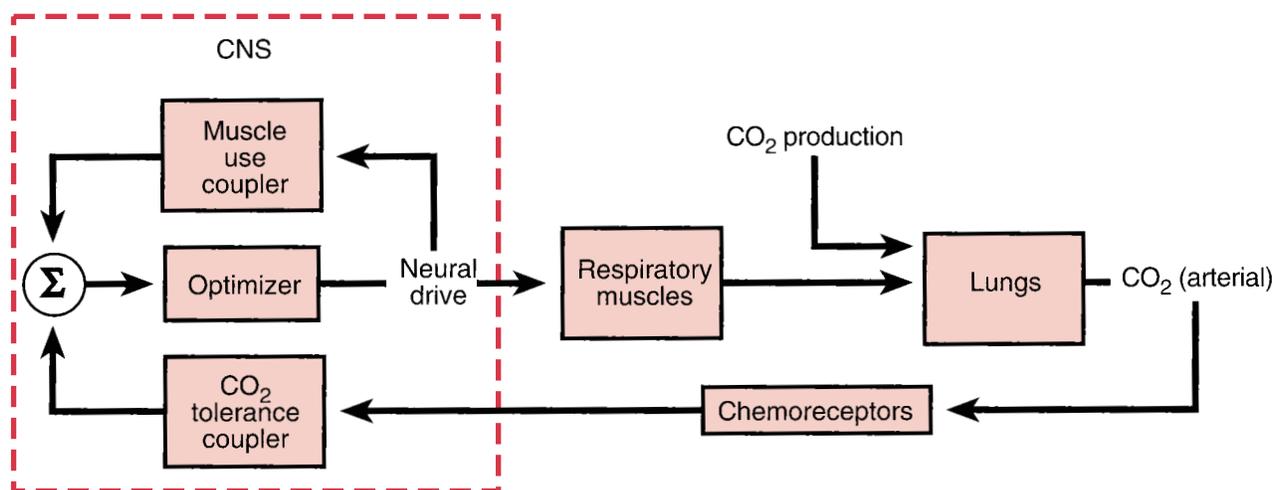
FIGURE 22.5 **An optimization controller.** The components inside the dashed box constitute the controller. In this strategy for breathing, the conflicting needs to maintain chemical homeostasis and to minimize respiratory effort are resolved by selecting an optimal ventilation. The muscle use and CO_2 tolerance couplers convert neural drive and the output of the chemoreceptors to a form interpreted by the neural optimizer as a cost to be minimized. (Modified from Poon CS. Ventilatory control in hypercapnia and exercise: Optimization hypothesis. J Appl Physiol 1987;62:2447–2459.)

Slowly Adapting Receptors. The **slowly adapting receptors** are sensory terminals of myelinated afferent fibers that lie within the smooth muscle layer of conducting airways. Because they respond to airway stretch, they are also called **pulmonary stretch receptors.** Slowly adapting receptors fire in proportion to applied airway transmural pressure, and their usual role is to sense lung volume. When stimulated, an increased firing rate is sustained as long as stretch is imposed; that is, they adapt slowly. Stimulation of these receptors causes an excitation of the inspiratory off-switch and a prolongation of expiration. Because of these two effects, inflating the lungs with a sustained pressure at the mouth terminates an inspiration in progress and prolongs the time before a subsequent inspiration occurs. This sequence is known as the **Hering-Breuer reflex** or **lung inflation reflex**.

The Hering-Breuer reflex probably plays a more important role in infants than in adults. In adults, particularly in the awake state, this reflex may be overwhelmed by more prominent central control. Because increasing lung volume stimulates slowly adapting receptors, which then excite the inspiratory off-switch, it is easy to see how they could be responsible for a feedback signal that results in cyclic breathing. However, as already mentioned, feedback from vagal afferents is not necessary for cyclic breathing to occur. Instead, feedback modifies a basic pattern established in the medulla. The effect may be to shorten inspiration when tidal volume is larger than normal. The most important role of slowly adapting receptors is probably their participation in regulating expiratory time, expiratory muscle activation, and functional residual capacity (FRC). Stimulation of slowly adapting receptors also relaxes airway smooth muscle, reduces systemic vasomotor tone, increases heart rate, and, as previously noted, influences laryngeal muscle activity.

Rapidly Adapting Receptors. The **rapidly adapting receptors** are sensory terminals of myelinated afferent fibers that are found in the larger conducting airways. They are frequently called **irritant receptors** because these nerve endings, which lie in the airway epithelium, respond to irritation of the airways by touch or by noxious substances, such as smoke and dust. Rapidly adapting receptors are stimulated by histamine, serotonin, and prostaglandins released locally in response to allergy and inflammation. They are also stimulated by lung inflation and deflation, but their firing rate rapidly declines when a volume change is sustained. Because of this rapid adaptation, bursts of activity occur that are in proportion to the change of volume and the rate at which that change occurs. Acute congestion of the pulmonary vascular bed also stimulates these receptors but, unlike the effect of inflation, their activity may be sustained when congestion is maintained.

Background activity of rapidly adapting receptors is inversely related to lung compliance, and they are thought to serve as sensors of compliance change. These receptors are probably nearly inactive in normal quiet breathing. Based on what stimulates them, their role would seem to be to sense the onset of pathological events. In spite of considerable information about what stimulates them, the effect of their stimulation remains controversial. As a general rule, stimulation causes excitatory responses such as coughing, gasping, and prolonged inspiration time.

C Fiber Endings. C fiber endings belong to unmyelinated nerves. These nerve endings are classified into two populations in the lungs. One group, **pulmonary C fibers**, is located adjacent to alveoli and is accessible from the pulmonary circulation. They are sometimes called **juxtapulmonary capillary receptors** or **J receptors**. A second group, **bronchial C fibers**, is accessible from the bronchial circulation and, consequently, is located in airways. Like rapidly adapting receptors, both groups play a protective role. They are both stimulated by lung injury, large inflation, acute pulmonary vascular congestion, and certain chemical agents.

Pulmonary C fibers are sensitive to mechanical events (e.g., edema, congestion, and pulmonary embolism), but are not as sensitive to products of inflammation, whereas the opposite is true of bronchial C fibers. Their activity excites breathing, and they probably provide a background excitation to the medulla. When stimulated, they cause rapid shallow breathing, bronchoconstriction, increased airway secretion, and cardiovascular depression (bradycardia, hypotension). **Apnea** (cessation of breathing) and a marked fall in systemic vascular resistance occur when they are stimulated acutely and severely. An abrupt reduction of skeletal muscle tone is an intriguing effect that follows intense stimulation of pulmonary C fibers, the homeostatic significance of which remains unexplained.

Chest Wall Proprioceptors Provide Information About Movement and Muscle Tension

Joint, tendon, and muscle spindle receptors—collectively called **proprioceptors**—may play a role in breathing, particularly when more than quiet breathing is called for or when breathing efforts are opposed by increased airway resistance or reduced lung compliance. Muscle spindles are present in considerable numbers in the intercostal muscles but are rare in the diaphragm. It has been proposed, but not fully verified, that muscle spindles may adjust breathing effort by sensing the discrepancy between tensions of the intrafusal and extrafusal fibers of the intercostal muscles. If a discrepancy exists, information from the spindle receptor alters the contraction of the extrafusal fiber, thereby minimizing the discrepancy. This mechanism provides increased motor excitation when movement is opposed. Evidence also shows that chest wall proprioceptors play a major role in the perception of breathing effort, but other sensory mechanisms may also be involved.

CONTROL OF BREATHING BY H^+, P_{CO_2}, and P_{O_2}

Breathing is profoundly influenced by the hydrogen ion concentration and respiratory gas composition of the arterial blood. The general rule is that breathing activity is inversely related to arterial blood P_{O_2} but directly related to P_{CO_2} and H^+. Figures 22.6 and 22.7 show the ventilatory responses of a typical person when alveolar P_{CO_2} and P_{O_2} are individually varied by controlling the composition of inspired gas. Responses to carbon dioxide and, to a lesser extent, blood pH depend on sensors in the brainstem and sensors in the carotid arteries and aorta. In contrast, responses to hypoxia are brought about only by the stimulation of arterial receptors.

Neuronal Cells of the Medulla Respond to Local H^+

Ventilatory drive is exquisitely sensitive to P_{CO_2} of blood perfusing the brain. The source of this chemosensitivity has been localized to bilaterally paired groups of cells just below the surface of the ventrolateral medulla immediately caudal to the pontomedullary junction. Each side contains a rostral and a caudal chemosensitive zone, separated by an
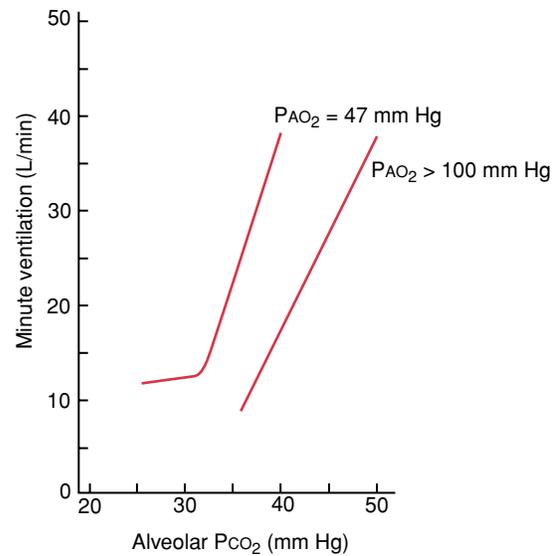

FIGURE 22.6 **Ventilatory responses to increasing alveolar CO_2 tension.** The line on the right represents the response when alveolar P_{O_2} was held at 100 mm Hg or greater to essentially eliminate O_2-dependent activity of the chemoreceptors. The line on the left represents the response when alveolar P_{O_2} was held at 47 mm Hg to provide an overlying hypoxic stimulus. Note that hypoxia increases the slope of the line in addition to changing its location. (Based on Nielsen M, Smith H. Studies on the regulation of respiration in acute hypoxia. Acta Physiol Scand 1952;24:293–313.)

intermediate zone in which the activities of the caudal and rostral groups converge and are integrated together with other autonomic functions. Exactly which cells exhibit chemosensitivity is unknown, but they are not the same as those of the DRG/VRG complex. Although specific cells have not been identified, the chemosensitive neurons that respond to the H^+ of the surrounding interstitial fluid are referred to as **central chemoreceptors**. The H^+ concentration in the interstitial fluid is a function of P_{CO_2} in the cerebral arterial blood and the bicarbonate concentration of cerebrospinal fluid.

CSF pH Depends on Its Bicarbonate Concentration and P_{CO_2}

Cerebrospinal fluid (CSF) is formed mainly by the **choroid plexuses** of the ventricular cavities of the brain. The epithelium of the choroid plexus provides a barrier between blood and CSF that severely limits the passive movement of large molecules, charged molecules, and inorganic ions. However, choroidal epithelium actively transports several substances, including ions, and this active transport participates in determining the composition of CSF. Cerebrospinal fluid formed by the choroid plexuses is exposed to brain interstitial fluid across the surface of the brain and spinal cord, with the result that the composition of CSF away from the choroid plexuses is closer to that of interstitial fluid than it is to CSF as first formed. Brain interstitial fluid is also separated from blood
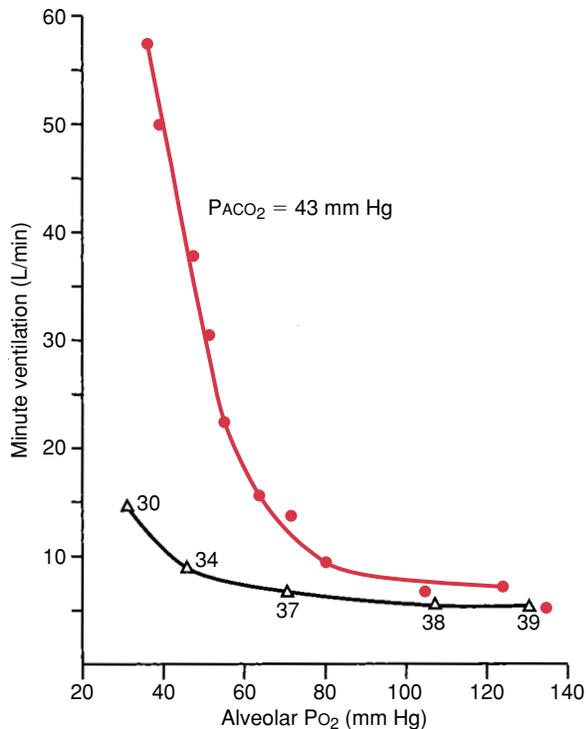
Ventilatory responses to hypoxia. Inspired oxygen was lowered while PaO$_2$ was held at 43 mm Hg by adding CO$_2$ to the inspired air. If this had not been done (lower curve), hypocapnia secondary to the hypoxic hyperventilation would have reduced the ventilatory response. The numbers next to the lower curve are PaO$_2$ values measured at each point on the curve. (Based on Loeschke HH, Gertz KH. Einfluss des O$_2$-Druckes in der Einatmungsluft auf die Atemtätigkeit des Menschen, geprüft unter Konstanthaltung des alveolaren CO$_2$-Druckes. Pflugers Arch Gesamte Physiol Menschen Tiere 1958;267:460–477.)

by the **blood-brain barrier** (capillary endothelium), which has its own transport capability.

Because of the properties of the limiting membranes, CSF is essentially protein-free, but it is not just a simple ultrafiltrate of plasma. CSF differs most notably from an ultrafiltrate by its lower bicarbonate and higher sodium and chloride ion concentrations. Potassium, magnesium, and calcium ion concentrations also differ somewhat from plasma; moreover they change little in response to marked changes in plasma concentrations of these cations. Bicarbonate serves as the only significant buffer in CSF, but the mechanism that controls bicarbonate concentration is controversial.

Most proposed regulatory mechanisms invoke the active transport of one or more ionic species by the epithelial and endothelial membranes. Because of the relative impermeabilities of the choroidal epithelium and capillary endothelium to H$^+$, changes in H$^+$ concentration of blood are poorly reflected in CSF. By contrast, molecular carbon dioxide diffuses readily; therefore, blood PCO$_2$ can influence the pH of CSF. The pH of CSF is primarily determined by its bicarbonate concentration and PCO$_2$. The relative ease of movement of molecular carbon dioxide in contrast to hydrogen ions and bicarbonate is depicted in Figure 22.8.
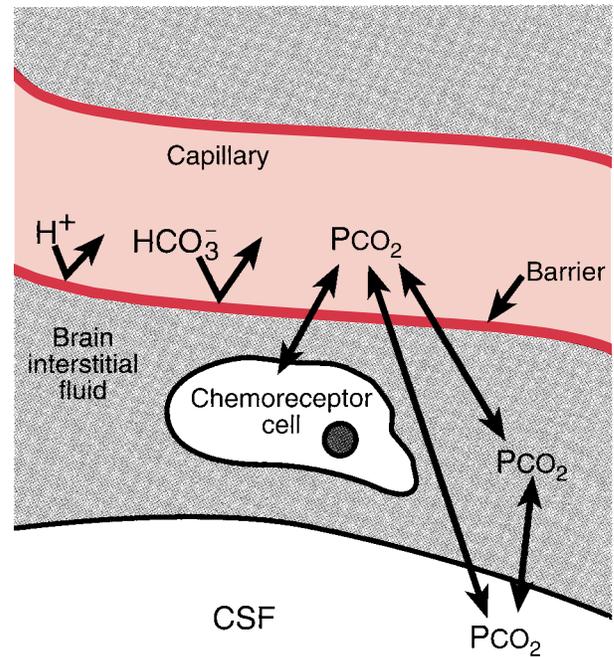

Movement of H$^+$, HCO$_3^-$, and molecular CO$_2$ between capillary blood, brain interstitial fluid, and CSF. The acid-base status of the chemoreceptors can be quickly changed only by changing PaCO$_2$.

In healthy people, the PCO$_2$ of CSF is about 6 mm Hg higher than that of arterial blood, approximating that of brain tissue. The pH of CSF, normally slightly below that of blood, is held within narrow limits. Cerebrospinal fluid pH changes little in states of metabolic acid-base disturbances (see Chapter 25)—about 10% of that in plasma. In respiratory acid-base disturbances, however, the change in pH of the CSF may exceed that of blood. During chronic acid-base disturbances, the bicarbonate concentration of CSF changes in the same direction as in blood, but the changes may be unequal. In metabolic disturbances, the CSF bicarbonate changes are about 40% of those in blood but, with respiratory disturbances, CSF and blood bicarbonate changes are essentially the same. When acute acid-base disturbances are imposed, CSF bicarbonate changes more slowly than does blood bicarbonate, and it may not reach a new steady state for hours or days. As already noted, the mechanism of bicarbonate regulation is unsettled. Irrespective of how it occurs, the bicarbonate regulation that occurs with acid-base disturbances is important because, by changing buffering, it influences the response to a given PCO$_2$.

Peripheral Chemoreceptors Respond to PO$_2$, PCO$_2$, and pH

Peripheral chemoreceptors are located in the carotid and aortic bodies and detect changes in arterial blood PO$_2$, PCO$_2$, and pH. **Carotid bodies** are small ($\sim$ 2 mm wide) sensory organs located bilaterally near the bifurcations of the common carotid arteries near the base of the skull. Afferent nerves travel to the CNS from the carotid bodies in the glos-

sopharyngeal nerves. **Aortic bodies** are located along the ascending aorta and are innervated by vagal afferents.

As with the medullary chemoreceptors, increasing $PaCO_2$ stimulates peripheral receptors. H^+ formed from H_2CO_3 within the peripheral chemoreceptors (glomus cells) is the stimulus and not molecular CO_2. About 40% of the effect of $PaCO_2$ on ventilation is brought about by peripheral chemoreceptors, while central chemoreceptors bring about the rest. Unlike the central sensor, peripheral chemoreceptors are sensitive to rising arterial blood H^+ and falling PO_2. They alone cause the stimulation of breathing by hypoxia; hypoxia in the brain has little effect on breathing unless severe, at which point breathing is depressed.

Carotid chemoreceptors play a more prominent role than aortic chemoreceptors; because of this and their greater accessibility, they have been studied in greater detail. The discharge rate of carotid chemoreceptors (and the resulting minute ventilation) is approximately linearly related to $PaCO_2$. The linear behavior of the receptor is reflected in the linear ventilatory response to carbon dioxide illustrated in Figure 22.6. When expressed using pH, the response curve is no longer linear but shows a progressively increasing effect as pH falls below normal. This occurs because pH is a logarithmic function of $[H^+]$, so the absolute change in $[H^+]$ per unit change in pH is greater when brought about at a lower pH.

The response of peripheral chemoreceptors to oxygen depends on arterial PaO_2, and *not* oxygen content. Therefore, anemia or carbon monoxide poisoning, two conditions that exhibit reduced oxygen content but have normal PaO_2, have little effect on the response curve. The shape of the response curve is not linear; instead, hypoxia is of increasing effectiveness as PO_2 falls below about 90 mm Hg. The behavior of the receptors is reflected in the ventilatory response to hypoxia illustrated in Figure 22.7. The shape of the curve relating ventilatory response to PO_2 resembles that of the oxyhemoglobin equilibrium curve when plotted upside down (see Chapter 21). As a result, the ventilatory response is inversely related in an approximately linear fashion to arterial blood oxygen saturation.

The nonlinearities of the ventilatory responses to PO_2 and pH, and the relatively low sensitivity across the normal ranges of these variables, cause ventilatory changes to be apparent only when PO_2 and pH deviate significantly from the normal range, especially toward hypoxemia or acidemia. By contrast, ventilation is sensitive to PCO_2 within the normal range, and carbon dioxide is normally the dominant chemical regulator of breathing through the use of both central and peripheral chemoreceptors (compare Figs. 22.6 and 22.7).

There is a strong interaction among stimuli, which causes the slope of the carbon dioxide response curve to increase if determined under hypoxic conditions (see Fig. 22.6), causing the response to hypoxia to be directly related to the prevailing PCO_2 and pH (see Fig. 22.7). As discussed in the next section, these interactions, and interaction with the effects of the central carbon dioxide sensor, profoundly influence the integrated chemoresponses to a primary change in arterial blood composition.

Carotid and aortic bodies also can be strongly stimulated by certain chemicals, particularly cyanide ion and other poisons of the metabolic respiratory chain. Changes in blood pressure have only a small effect on chemoreceptor activity, but responses can be stimulated if arterial pressure falls below about 60 mm Hg. This effect is more prominent in aortic bodies than in carotid bodies. Afferent activity of peripheral chemoreceptors is under some degree of efferent control capable of influencing responses by mechanisms that are not clear. Afferent activity from the chemoreceptors is also centrally modified in its effects by interactions with other reflexes, such as the lung stretch reflex and the systemic arterial baroreflex (see Chapter 18). Although the breathing interactions are not well understood in humans, they serve as examples of the complex interactions of cardiorespiratory regulation. Interactions among chemoreflexes, however, are easily demonstrated.

Significant Interactions Occur Among the Chemoresponses

The effect of PO_2 on the response to carbon dioxide and the effect of carbon dioxide on the response to PO_2 have already been noted. By virtue of this interdependence, a response to hypoxia is blunted by the subsequent increased ventilation, unless $PaCO_2$ is somehow maintained, because $PaCO_2$ ordinarily falls as ventilation is stimulated (see Fig 22.7). The stimulating effect of hypoxia is blunted mainly by the central chemoreceptors, which respond more potently than the peripheral receptors to low $PaCO_2$.

The sequence of events in the response to hypoxia (e.g., ascent to high altitude) exemplifies interactions among chemoresponses. For example, if 100% oxygen is given to an individual newly arrived at high altitude, ventilation is quickly restored to its sea level value. During the next few days, ventilation in the absence of supplemental oxygen progressively rises further, but it is no longer restored to sea level value by breathing oxygen. Rising ventilation while acclimatizing to altitude could be explained by a reduction of blood and CSF bicarbonate concentrations. This would reduce the initial increase in pH created by the increased ventilation, and allow the hypoxic stimulation to be less strongly opposed. However, this mechanism is not the full explanation of altitude acclimatization. Cerebrospinal fluid pH is not fully restored to normal, and the increasing ventilation raises PaO_2 while further lowering $PaCO_2$, changes that should inhibit the stimulus to breathe. In spite of much inquiry, the reason for persistent hyperventilation in altitude-acclimatized subjects, the full explanation for altitude acclimatization, and the explanation for the failure of increased ventilation in acclimatized subjects to be relieved promptly by restoring a normal PaO_2 are still unknown.

Metabolic acidosis is caused by an accumulation of nonvolatile acids. The increase in blood $[H^+]$ initiates and sustains hyperventilation by stimulating the peripheral chemoreceptors. Because of the restricted movement of H^+ into CSF, the fall in blood pH cannot directly stimulate the central chemoreceptors. The central effect of the hyperventilation, brought about by decreased pH via the peripheral chemoreceptors, results in a paradoxical rise of CSF pH (i.e., an alkalosis as a result of reduced $PaCO_2$) that actually restrains the hyperventilation. With time, CSF bicarbonate concentration is adjusted downward, although it changes

less than does that of blood, and the pH of CSF remains somewhat higher than blood pH. Ultimately, ventilation increases more than it did initially as the paradoxical CSF alkalosis is removed.

Respiratory acidosis (accumulation of carbon dioxide) is rarely a result of elevated environmental CO_2, although this occurs in submarine mishaps, while exploring wet limestone caves, and in physiology laboratories where responses to carbon dioxide are measured. Under these conditions, the response is a vigorous increase in minute ventilation proportional to the $PaCO_2$; PaO_2 actually rises slightly and arterial pH falls slightly, but these have relatively little effect. If mild hypercapnia can be sustained for a few days, the intense hyperventilation subsides, probably as CSF bicarbonate is raised. More commonly, respiratory acidosis results from failure of the controller to respond to carbon dioxide (e.g., during anesthesia, following brain injury, and in some patients with chronic obstructive lung disease). Another cause of respiratory acidosis is a failure of the breathing apparatus to provide adequate ventilation at an acceptable effort, as may be the case in some patients with obstructive lung disease. When these subjects breathe room air, hypercapnia caused by reduced alveolar ventilation is accompanied by significant hypoxia and acidosis. If the hypoxic component alone is corrected—for example, by breathing oxygen-enriched air—a significant reduction in the ventilatory stimulus may result in greater underventilation, causing further hypercapnia and more severe acidosis. A more appropriate treatment is providing mechanical assistance for restoring adequate ventilation.

THE CONTROL OF BREATHING DURING SLEEP

We spend about one third of our lives asleep. Sleep disorders and disordered breathing during sleep are common and often have physiological consequences (see Clinical Focus Box 22.1). Chapter 7 described the two different neurophysiological sleep states: rapid eye movement (REM) sleep and slow-wave sleep. Sleep is a condition that results from withdrawal of the wakefulness stimulus that arises from the brainstem reticular formation. This wakefulness stimulus is one component of the tonic excitation of brainstem respiratory neurons, and one would predict correctly that sleep results in a general depression of breathing. There are, however, other changes, and the effects of REM and slow-wave sleep on breathing differ.

Sleep Changes the Breathing Pattern

During slow-wave sleep, breathing frequency and inspiratory flow rate are reduced, and minute ventilation falls. These responses partially reflect the reduced physical activity that accompanies sleep. However, because of the small rise in $PaCO_2$ (about 3 mm Hg), there must also be a change in either the sensitivity or the set point of the carbon dioxide controller. In the deepest stage of slow-wave sleep (stage 4), breathing is slow, deep, and regular. But in stages 1 and 2, the depth of breathing sometimes varies periodically. The explanation is that during light sleep, withdrawal of the wakefulness stimulus varies over time in a periodic fashion. When the stimulus is removed, sleep is deepened and breathing is depressed; when returned, breathing is excited not only by the wakefulness stimulus but also by the carbon dioxide retained during the interval of sleep. This periodic pattern of breathing is known as **Cheyne-Stokes breathing** (Fig. 22.9).

In REM sleep, breathing frequency varies erratically while tidal volume varies little. The net effect on alveolar ventilation is probably a slight reduction, but this is achieved by averaging intervals of frank tachypnea (excessively rapid breathing) with intervals of apnea. Unlike slow-wave sleep, the variations during REM sleep do not reflect a changing wakefulness stimulus but instead represent responses to increased CNS activity of behavioral, rather than autonomic or metabolic, control systems.

CLINICAL FOCUS BOX 22.1

Sleep Apnea Syndrome

The analysis of multiple physiological variables recorded during sleep, known as **polysomnography**, is an important method for research into the control of breathing that has had increasing use in clinical evaluations of sleep disturbances. In normal sleep, reduced dilatory upper-airway muscle tone may be accompanied with brief intervals with no breathing movements. Some people, typically overweight and predominantly men, exhibit more severe disruption of breathing, referred to as **sleep apnea syndrome.** Sleep apnea is classified into two broad groups: obstructive and central.

In **central sleep apnea**, breathing movements cease for a longer than normal interval. In **obstructive sleep apnea**, the fault seems to lie in a failure of the pharyngeal muscles to open the airway during inspiration. This may be the result of decreased muscle activity, but the obstruction is worsened by an excessive amount of neck fat with which the muscles must contend. With obstructive sleep apnea, progressively larger inspiratory efforts eventually overcome the obstruction and airflow is temporarily resumed, usually accompanied by loud snoring.

Some patients exhibit both central and obstructive sleep apneas. In both types, hypoxemia and hypercapnia develop progressively during the apnea intervals. Frequent episodes of repeated hypoxia may lead to pulmonary and systemic hypertension and to myocardial distress; the accompanying hypercapnia is thought to be a cause of the morning headache these patients often experience. There may be partial arousal at the end of the periods of apnea, leading to disrupted sleep and resulting in drowsiness during the day. Daytime sleepiness, often leading to dangerous situations, is probably the most common and most debilitating symptom. The cause of this disorder is multivariate and often obscure, but mechanically assisted ventilation during sleep often results in significant symptomatic improvement.
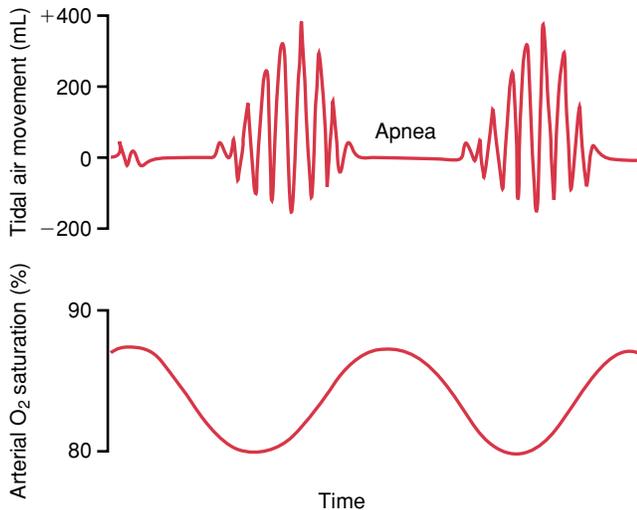
FIGURE 22.9 **Cheyne-Stokes breathing and its effect on arterial O_2 saturation.** Cheyne-Stokes breathing occurs frequently during sleep, especially in subjects at high altitude, as in this example. In the presence of preexisting hypoxemia secondary to high altitude or other causes, the periods of apnea may result in further falls of O_2 saturation to dangerous levels. Falling P_{O_2} and rising P_{CO_2} during the apnea intervals ultimately induce a response and breathing returns, reducing the stimuli and leading to a new period of apnea.

Sleep Changes the Responses to Respiratory Stimuli

Responsiveness to carbon dioxide is reduced during sleep. In slow-wave sleep, the reduction in sensitivity seems to be secondary to a reduction in the wakefulness stimulus and its tonic excitation of the brainstem rather than to a suppression of the chemosensory mechanisms. It is important to note that breathing remains responsive to carbon dioxide during slow-wave sleep, although at a less sensitive level, and that carbon dioxide stimulus may provide the major background brainstem excitation in the absence of the wakefulness stimulus or behavioral excitation. Hence, pathological alterations in the carbon dioxide chemosensory system may profoundly depress breathing during slow-wave sleep.

During intervals of REM sleep in which there is little sign of increased activity, the breathing response to carbon dioxide is slightly reduced, as in slow-wave sleep. However, during intervals of increased activity, responses to carbon dioxide during REM sleep are significantly reduced, and breathing seems to be regulated by the brain's behavioral control system. It is interesting that regulation of breathing during REM sleep by the behavioral control system, rather than by carbon dioxide, is similar to the way breathing is controlled during speech.

Ventilatory responses to hypoxia are probably reduced during both slow-wave and REM sleep, especially in individuals who have high sensitivity to hypoxia while awake. There does not seem to be a difference between the effects of slow-wave and REM sleep on hypoxic responsiveness, and the irregular breathing of REM sleep is unaffected by hypoxia.

Both slow-wave and REM sleep cause an important change in responses to airway irritation. Specifically, a stimulus that causes cough, tachypnea, and airway constriction during wakefulness will cause apnea and airway dilation during sleep unless the stimulus is sufficiently intense to cause arousal. The lung stretch reflex appears to be unchanged or somewhat enhanced during arousal from sleep, but the effect of stretch receptors on upper airways during sleep may be important.

Arousal Mechanisms Protect the Sleeper

Several stimuli cause arousal from sleep; less intense stimuli cause a shift to a lighter sleep stage without frank arousal. In general, arousal from REM sleep is more difficult than from slow-wave sleep. In humans, hypercapnia is a more potent arousal stimulus than hypoxia, the former requiring a Pa_{CO_2} of about 55 mm Hg and the latter requiring a Pa_{O_2} less than 40 mm Hg. Airway irritation and airway occlusion induce arousal readily in slow-wave sleep but much less readily during REM sleep.

All of these arousal mechanisms probably operate through the activation of a reticular arousal mechanism similar to the wakefulness stimulus. They play an important role in protecting the sleeper from airway obstruction, alveolar hypoventilation of any cause, and the entrance into the airways of irritating substances. Recall that coughing depends on the aroused state and without arousal airway irritation leads to apnea. Obviously, wakefulness altered by other than natural sleep—such as during drug-induced sleep, brain injury, or anesthesia—leaves the individual exposed to risk because arousal from those states is impaired or blocked. From a teleological point of view, the most important role of sensors of the respiratory system may be to cause arousal from sleep.

Upper Airway Tone May Be Compromised During Sleep

A prominent feature during REM sleep is a general reduction in skeletal muscle tone. Muscles of the larynx, pharynx, and tongue share in this relaxation, which can lead to obstruction of the upper airways. Airway muscle relaxation may be enhanced by the increased effectiveness of the lung inflation reflex.

A common consequence of airway narrowing during sleep is snoring. In many people, usually men, the degree of obstruction may at times be sufficient to cause essentially complete occlusion. In these people, an intact arousal mechanism prevents suffocation, and this sequence is not in itself unusual or abnormal. In some people, obstruction is more complete and more frequent, and the arousal threshold may be raised. Repeated obstruction leads to significant hypercapnia and hypoxemia, and repeated arousals cause sleep deprivation that leads to excessive daytime sleepiness, often interfering with normal daily activity.

THE RESPONSE TO HIGH ALTITUDE

Changes in activity and the environment initiate integrated ventilatory responses that involve changes in the car-

diopulmonary system. Examples include the response to exercise (see Chapter 30) and the response to the low inspired oxygen tension at high altitudes. The importance of understanding integrated ventilatory responses is that similar interactions occur under pathophysiological conditions in patients with respiratory illnesses.

How the body responds to high altitude has fascinated physiologists for centuries. The French physiologist Paul Bert first recognized that the harmful effects of high altitude are caused by low oxygen tension. Recall from Chapter 21 that the percentage of oxygen does not change at high altitude but the barometric pressure decreases (see Fig 21.1). So the hypoxic response at high altitude is caused by a decrease in inspired oxygen tension (PIO_2). At high altitude, when the PIO_2 decreases and oxygen supply in the body is threatened, several compensations are made in an effort to deliver normal amounts of oxygen to the tissues. Chief among these responses to altitude is hyperventilation. Figure 22.7 shows, that hypoxia-induced hyperventilation is not significantly increased until the alveolar PO_2 decreases below 60 mm Hg. In a healthy adult, a drop in alveolar PO_2 to 60 mm Hg occurs at an altitude of approximately 4,500 m (14,000 feet).

Figure 22.10 shows how ventilation and alveolar PCO_2 change with hypoxia. The hypoxia-induced hyperventilation appears in two stages. First, there is an immediate increase in ventilation, which is primarily a result of hypoxia-induced stimulation via the carotid bodies. However, the increase in ventilation seen in the first stage is small compared with the second stage, in which ventilation continues to rise slowly over the next 8 hours. After 8 hours of hypoxia, minute ventilation is sustained. The reason for the smal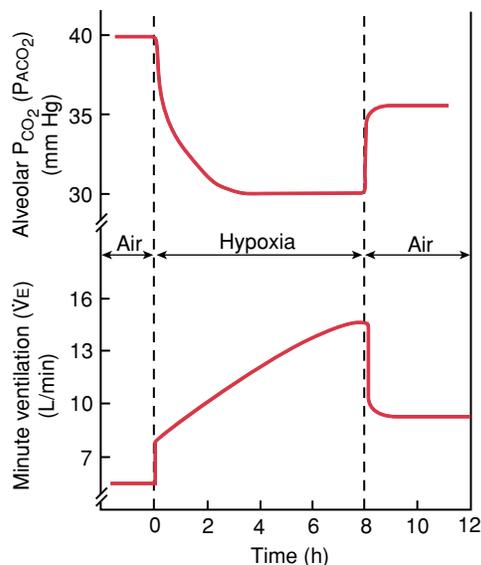l rise in ventilation seen in the first stage is that the hypoxic stimulation is strongly opposed by the decrease in arterial PCO_2 as a result of excess carbon dioxide blown off with altitude-induced hyperventilation. The hypoxia-induced hyperventilation results in an increase in arterial pH. The decrease in arterial PCO_2 (hypocapnia) and the rise in blood pH work in concert to blunt the hypoxic drive.

Ventilatory Acclimatization Results in a Sustained Increase in Ventilation

The increased ventilation seen in the second stage is referred to as **ventilatory acclimatization**. Acclimatization occurs during prolonged exposure to hypoxia and is a physiological response, as opposed to a genetic or evolutionary change over generations leading to a permanent adaptation. Ventilatory acclimatization is defined as a time-dependent increase in ventilation that occurs over hours to days of continuous exposure to hypoxia. After 2 weeks, the hypoxia-induced hyperventilation reaches a stable plateau.

Although the physiological mechanisms responsible for ventilatory acclimatization are not completely understood, it is clear that two mechanisms are involved. One involves the chemoreceptors, and the second involves the kidneys. CSF pH, which becomes more alkaline when ventilation is stimulated by hypoxia, is brought closer to normal by the movement of bicarbonate out of the CSF. Also, during prolonged hypoxia, the carotid bodies increase their sensitivity to arterial PO_2. These changes result in a further increase in ventilation.

The second mechanism responsible for ventilatory acclimatization involves the kidneys. The alkaline blood pH resulting from the hypoxia-induced hyperventilation is antagonistic to the hypoxic drive. Blood pH is regulated by both the lungs and the kidneys (see Chapter 25). The kidneys compensate by excreting more bicarbonate, which lowers the blood pH towards normal over 2 to 3 days; therefore, the antagonistic effect resulting from the hyperventilation-induced alkaline pH is minimized, allowing the hypoxic drive to increase minute ventilation further.

Cardiovascular Acclimatization Improves the Delivery of Oxygen to the Tissues

In addition to ventilatory acclimatization, the body undergoes other physiological changes to acclimatize to low oxygen levels. These include increased pulmonary blood flow, increased red cell production, and improved oxygen and carbon dioxide transport. There is an increase in cardiac output at high altitude resulting in increased blood flow to the lungs and other organs of the body. The increase in pulmonary blood flow reduces capillary transit time and results in an increase in oxygen uptake by the lungs. Low PO_2 causes vasodilation in the systemic circulation. The increase in blood flow resulting from the combined increased vasodilation and increased cardiac output sustains oxygen delivery to the tissues at high altitude.

Red cell production is also increased at high altitude, which improves oxygen delivery to the tissues. Hypoxia stimulates the kidneys to produce and release **erythropoietin**, a hormone that stimulates the bone marrow to produce erythrocytes, which are released into the circulation.

FIGURE 22.10 **Effect of hypoxia on minute ventilation and alveolar PCO_2.** Hypoxia was induced by having a healthy subject breath 12% O_2 for 8 hours. With hypoxia-induced hyperventilation, excess CO_2 is blown off, resulting in a decrease in alveolar PCO_2. Minute ventilation remains elevated for a while after the subject returns to room air.

The increased hematocrit resulting from the hypoxia-induced **polycythemia** enables the blood to carry more oxygen to the tissues. However, the increased viscosity, as a result of the elevated hematocrit, increases the workload on the heart. In some cases, the polycythemia becomes so severe (hematocrit > 70%) at high altitude that blood has to be withdrawn periodically to permit the heart to pump effectively. Oxygen delivery to the cells is also favored by an increased concentration of 2,3-DPG in the red cells, which shifts the oxyhemoglobin equilibrium curve to the right, and favors the unloading of oxygen in the tissues (see Chapter 21).

Although the body undergoes many beneficial changes that allow acclimatization to high altitude, there are some undesirable effects. One of these is **pulmonary hypertension** (abnormally high pulmonary arterial blood pressure). Alveolar hypoxia causes pulmonary vasoconstriction. In addition, prolonged hypoxia causes vascular remodeling in which pulmonary arterial smooth muscle cells undergo hypertrophy and hyperplasia. The vascular remodeling results in narrowing of the small pulmonary arteries and leads to a significant increase in pulmonary vascular resistance and hypertension. With severe hypoxia, the pulmonary veins are also constricted. The increase in venous pressure elevates the filtration pressure in the alveolar capillary beds, leading to pulmonary edema. Pulmonary hypertension also increases the workload of the right heart, causing right heart hypertrophy, which, if severe enough, may lead to death.

REVIEW QUESTIONS

DIRECTIONS: Each of the numbered items or incomplete statements in this section is followed by answers or by completions of the statement. Select the ONE lettered answer or completion that is BEST in each case.

1. Generation of the basic cyclic pattern of breathing in the CNS requires participation of
   (A) The pontine respiratory group
   (B) Vagal afferent input to the pons
   (C) Vagal afferent input to the medulla
   (D) An inhibitory loop in the medulla
   (E) An intact spinal cord
2. Quiet expiration is associated with
   (A) A brief early burst by inspiratory neurons
   (B) Active abduction of the vocal cords
   (C) An early burst of activity by expiratory muscles
   (D) Reciprocal inhibition of inspiratory and expiratory centers
   (E) Increased activity of slowly adapting receptors
3. The ventilatory response to hypoxia
   (A) Is independent of Pa_{CO_2}
   (B) Is more dependent on aortic than carotid chemoreceptors
   (C) Is exaggerated by hypoxia of the medullary chemoreceptors
   (D) Bears an inverse linear relationship to arterial oxygen content
   (E) Is a sensitive mechanism for controlling breathing in the normal range of blood gases
4. Which of the following is *not* a consequence of stimulation of lung C fiber endings?
   (A) Bronchoconstriction
   (B) Apnea

(C) Rapid shallow breathing
(D) Systemic vasoconstriction
(E) Skeletal muscle relaxation
5. Which of the following is true about cerebrospinal fluid?
   (A) Its protein concentration is equal to that of plasma
   (B) Its P_{CO_2} equals that of systemic arterial blood
   (C) It is freely accessible to blood hydrogen ions
   (D) Its composition is essentially that of a plasma ultrafiltrate
   (E) Its pH is a function of Pa_{CO_2}
6. Slow-wave sleep is characterized by
   (A) A fall in Pa_{CO_2}
   (B) A tendency for breathing to vary in a periodic fashion
   (C) Facilitation of the cough reflex
   (D) Heightened ventilatory responsiveness to hypoxia
   (E) Greater skeletal muscle relaxation than REM sleep
7. Which of the following is *not* true during sleep?
   (A) Airway irritation evokes apnea
   (B) Airway irritation evokes coughing
   (C) Airway irritation evokes arousal
   (D) Airway occlusion evokes arousal
   (E) Hypercapnia evokes arousal
8. Negative-feedback control systems
   (A) Would not apply to the regulation of Pa_{CO_2}
   (B) Anticipate future events
   (C) Give the best control when most sensitive
   (D) Are ineffective if the properties of the controlled system change
   (E) Are not necessarily stable
9. With regard to the control of minute ventilation by carbon dioxide
   (A) About 80% of the effect of Pa_{O_2} is mediated by the peripheral chemoreceptors

(B) Central effects are mediated by direct effects on cells of the DRG/VRG complex
(C) Sensitivity of the control system is inversely related to the prevailing Pa_{O_2}
(D) This mechanism is less sensitive than control in response to oxygen
(E) Transection of cranial nerves IX and X at the skull would have no effect
10. Which of the following relationships can be represented by a straight line sloping downward from left to right?
    (A) Minute ventilation as a function of arterial pH
    (B) Minute ventilation as a function of arterial oxygen percent saturation
    (C) Carotid chemoreceptor firing frequency as a function of Pa_{CO_2}
    (D) Minute ventilation as a function of Pa_{O_2} while Pa_{CO_2} is held constant
    (E) Arterial pH as a function of arterial $[H^+]$

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CASE STUDIES FOR PART V ● ● ●

CASE STUDY FOR CHAPTER 19

Emphysema

A 65-year-old man went to the university hospital emergency department because of a 5-day history of shortness of breath and dyspnea on exertion. He also complained of a cough productive of green sputum. He appeared pale and said he felt feverish at home, but denied any shaking chills, sore throat, nausea, vomiting, or diarrhea. Having smoked two packs of cigarettes a day for the past 30 years, he had recently decreased his habit to one pack a day. He had not been previously hospitalized. He is a retired cab driver and lives with his wife; they have no pets. Although he has had dyspnea upon exertion for the last 2 years, he continues to maintain an active lifestyle. He still mows his lawn without much difficulty, and can walk 1 to 2 miles on a flat surface at a moderate pace. The patient said he rarely drinks alcohol. He denied having had any other significant past medical problems, including heart disease, hypertension, edema, childhood asthma, or any allergies. He did state that his father, also a heavy smoker, died of emphysema at age 55.

An initial exam shows that the patient is thin but has a large chest. He is in moderate respiratory distress. His blood pressure is 130/80 mm Hg; respiratory rate, 28 to 32 breaths/min; heart rate, 92/minute; and oral temperature, 37.9°C. His trachea is midline, and his chest expands symmetrically. He has decreased but audible breath sounds in both lung fields, with expiratory wheezing and a prolonged expiratory phase. Head, eyes, ears, nose, and throat findings are unremarkable. A pulse oximetry reading reveals his blood hemoglobin oxygen saturation is 91% when breathing room air.

Pulmonary function tests reveal severe limitation of airflow rates, particularly expiratory airflow. The patient is diagnosed with pulmonary emphysema.

Questions

1. What are the common spirometry findings associated with emphysema?
2. What are the mechanisms of airflow limitation in emphysema?
3. What is the most commonly held theory explaining the development of emphysema?

Answers to Case Study Questions for Chapter 19

1. The hallmark of emphysema is the limitation of airflow out of the lungs. In emphysema, expiratory flow rates (FVC, FEV_1, and FEV_1/FVC ratio) are significantly decreased. However, some lung volumes (TLC, FRC, and RV) are increased, and the increase is a result of the loss of lung elastic recoil (increased compliance).
2. The mechanisms that limit expiratory airflow in emphysema include hypersensitivity of airway smooth muscle, mucus hypersecretion, and bronchial wall inflammation and increased dynamic airway compression as a result of increased compliance.
3. Many of the pathophysiological changes in emphysema are a result of the loss of lung elastic recoil and destruction of the alveolar-capillary membrane. This is thought to be a result of an imbalance between the proteases and antiproteases (α_1-antitrypsin) in the lower respiratory tree. Normally, proteolytic enzyme activity is inactivated by antiproteases. In emphysema, excess proteolytic activity destroys elastin and collagen, the major extracellular matrix proteins responsible for maintaining the integrity of the alveolar-capillary membrane and the elasticity of the lung. Cigarette smoke increases proteolytic activity, which may arise through an increase in protease levels, a decrease in antiprotease activity, or a combination of the two.

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CASE STUDY FOR CHAPTER 20

Chest Pain

A 27-year-old accountant recently drove cross-country to start a new job in Denver, Colorado. A week after her move, she started to experience chest pains. She drove to the emergency department after experiencing 24 hours of right-sided chest pain, which was worse with inspiration. She also experienced shortness of breath and stated that she felt warm. She denied any sputum production, hemoptysis, coughing, or wheezing. She is active and walks daily and never has experienced any swelling in her legs. She has never been treated for any respiratory problems and has never undergone any surgical procedures. Her medical history is negative, and she has no known drug allergies. Oral contraceptives are her only medication. She smokes a pack of cigarettes a day and consumes wine occasionally. She does not use intravenous drugs and has no other risk factors for HIV disease. Her family history is negative for asthma and any cardiovascular diseases.

Physical examination reveals a mildly obese woman in moderate respiratory distress. Her respiratory rate is 24 breaths/min and her pulse is 115 beats/min. Her blood pressure is 140/80 mm Hg, and no jugular vein distension is observed. Heart rate and rhythm are regular, with normal heart sounds and no murmurs. Her chest is clear, and her temperature is 38°C. Her extremities show signs of cyanosis, but no clubbing or edema is detected. Blood gases, obtained while she was breathing room air, reveal a P_{O_2} of 60 mm Hg and a P_{CO_2} of 32 mm Hg; her arterial blood pH is 7.49. Her alveolar-arterial (A-a)$_{O_2}$ gradient is 40 mm Hg. A Gram's stain sputum specimen exhibited a normal flora. A chest X-ray study reveals a normal heart shadow and clear lung fields, except for a small peripheral infiltrate in the left lower lobe. A lung scan reveals an embolus in the left lower lobe.

Case Study Questions

1. What is the cause of a widened alveolar-arterial gradient in patients with pulmonary embolism?
2. What causes the decreased arterial P_{CO_2} and elevated arterial pH?
3. Why do oral contraceptives induce hypercoagulability?

Answers to Case Study Questions for Chapter 20

1. A normal A-a$_{O_2}$ gradient is 5 to 15 mm Hg. A pulmonary embolus will cause blood flow to be shunted to another region of the lung. Because cardiac output is unchanged, the shunting of blood causes overperfusion, which causes an abnormally low A/ ratio in another region of the lungs.

Thus, blood leaving the lungs has a low Po_2, resulting in hypoxemia (a low arterial Po_2). The decrease in arterial Po_2 accounts in part for the increase in the $A\text{-}ao_2$ gradient. However, ventilation is also stimulated as a compensatory mechanism to hypoxemia, which leads to hyperventilation with a concomitant increase in alveolar Po_2. The $A\text{-}ao_2$ gradient is, therefore, further increased because of the increased alveolar Po_2 caused by hyperventilation.

2. The decreased Pco_2 and increased pH are the result of hyperventilation as a result of the hypoxic drive (low Po_2) that stimulates ventilation.

3. The mechanisms by which oral contraceptives increase the risk of thrombus formation are not completely understood. The risk appears to be correlated best with the estrogen content of the pills. Hypotheses include increased endothelial cell proliferation, decreased rates of venous blood flow, and increased coagulability secondary to changes in platelets, coagulation factors, and the fibrinolytic system. Furthermore, there are changes in serum lipoprotein levels with an increase in LDL and VLDL and a variable effect on HDL. Driving cross-country, with long sedentary periods, may have exacerbated the patient's condition.

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CASE STUDY FOR CHAPTER 21

Anemia

A 68-year-old widow is seen by her physician because of complaints of fatigue and mild memory loss. The patient does not abuse alcohol and has not had a history of surgery in the last 5 years. Blood gases (Sao_2, Po_2, Pco_2, and pH) are normal. Blood analysis shows a white cell count of 5,200 cells/mm^3; Hb, 9.0 gm/dL; and a hematocrit of 27%. Her serum vitamin B_{12} is low, but her serum folate, thyroxin-stimulating hormone (TSH), and liver enzymes are normal. Her peripheral blood smear is unremarkable.

Questions

1. Why are Sao_2 and arterial Po_2 normal in anemic patients who have hypoxemia?
2. How does anemia affect the oxygen diffusing capacity of the lungs?
3. Why might this patient be deficient in vitamin B_{12}?

Answers to Case Study Questions for Chapter 21

1. Hemoglobin increases the oxygen carrying capacity of the blood, but has no effect on arterial Po_2. By way of illustration, if 100 mL of blood are exposed to room air, the Po_2 in the blood will equal atmospheric Po_2 after equilibration. Removing the red cells, leaving only plasma, will not affect Po_2. An otherwise healthy patient with anemia will have a normal Sao_2 because both O_2 content and capacity are reduced proportionately. Hypoxemia in anemic patients is a result of low oxygen content, not a low Po_2.

2. DL_{CO} decreases with anemia because there is less hemoglobin available to bind CO.

3. There are several causes of vitamin B_{12} deficiency. In older individuals, especially those who live alone, insufficient dietary intake of animal protein may be the cause; other causes include loss of gastric mucosa or regional enteritis.

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CASE STUDY FOR CHAPTER 22.

Pickwickian Syndrome

A 45-year-old man was referred to the pulmonary function laboratory because of polycythemia (hematocrit of 57%). At the time of referral, he weighs 142 kg (312 pounds) and his height is 175 cm (5 feet, 9 inches). A brief history reveals that he frequently falls asleep during the day. His blood gas values are Pao_2, 69 mm Hg; Sao_2, 94%; Pco_2, 35 mm Hg; and pH, 7.44. A few days later, he is admitted as an outpatient in the hospital's sleep center. He is connected to an ear oximeter and to a portable heart monitor. Within 30 minutes, the patient falls asleep and, within another 30 minutes, his Sao_2 decreases from 92% to 47% and his heart rate increases from 92 to 108 beats/min, with two premature ventricular contractions. During this time, his chest wall continues to move, but airflow at the mouth and nose is not detected.

Questions

1. How would this patient's test results be interpreted?
2. What is the cause of the polycythemia?
3. How does hypoxia accelerate heart rate?

Answers to Case Study Questions for Chapter 22

1. This patient is suffering from what has been known as pickwickian syndrome, a disorder that occurs with severely obese individuals because of their excessive weight. The pickwickian syndrome was named after Joe, the fat boy who was always falling asleep in Charles Dickens' novel *The Pickwick Papers.* Pickwickian patients suffer from hypoventilation and often suffer from sleep apnea as well. Pickwickian syndrome is no longer an appropriate name because it does not indicate what type of sleep disorder is involved. About 80% of sleep apnea patients are obese and 20% are of relatively normal weight.

2. Polycythemia is the result of chronic hypoxemia from hypoventilation, as well as from sleep apnea.

3. An increase in sympathetic discharge is often associated with sleep apnea and is responsible for the accelerated heart rate.

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