# 25
# Control of Respiration

## LEARNING OBJECTIVES

*Upon completion of this chapter, the student should be able to answer the following questions:*

1. How is ventilation controlled by the central nervous system?
2. How do the central and peripheral chemoreceptors provide feedback for regulation of ventilation?
3. How are chemoreceptors and pulmonary mechanoreceptors similar and different in regulation of respiration?
4. How do circumstances such as exercise or high altitude exposure alter respiratory drive?
5. How does obstructive sleep apnea differ from central sleep apnea?

People breathe without thinking, and they can willingly modify their breathing pattern and even hold their breath. Control of ventilation includes the generation and regulation of rhythmic breathing by the respiratory center in the brainstem. The rhythmic breathing pattern can be altered in response to input from systemic receptors and from higher brain centers. The goals of breathing are, from a mechanical perspective, to minimize work and, from a physiological perspective, to maintain and regulate arterial blood $O_2$ ($Pao_2$) and $CO_2$ ($Paco_2$). Another goal of breathing is to maintain acid-base balance by regulating $Paco_2$. Automatic respiration begins at birth. In utero, the placenta, not the lung, is the organ of gas exchange in the fetus. Its microvilli interdigitate with the maternal uterine circulation, and $Pao_2$ transport and $Paco_2$ removal from the fetus occur by passive diffusion across the maternal circulation.

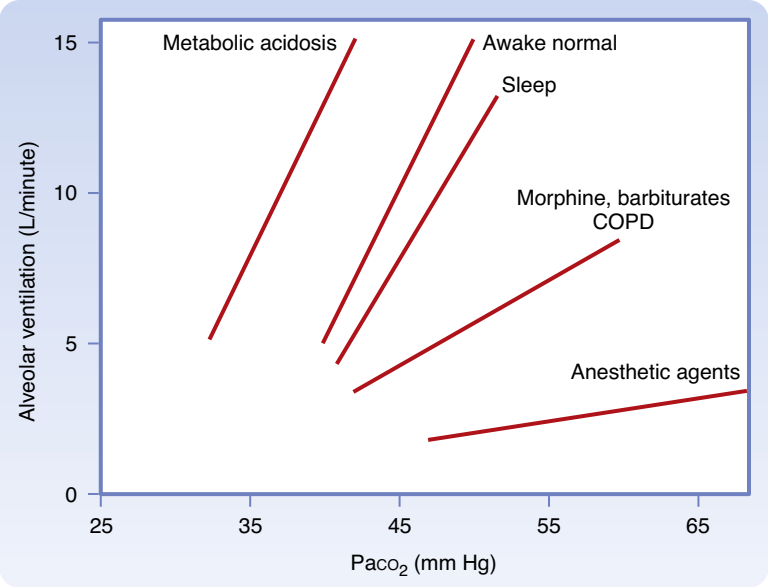
## Ventilatory Control: An Overview

There are four major sites of ventilatory control: (1) the **respiratory control center,** (2) **central chemoreceptors,** (3) **peripheral chemoreceptors,** and (4) **pulmonary mechanoreceptors/sensory nerves.** The respiratory control center is located in the medulla oblongata of the brainstem and is composed of multiple nuclei that generate and modify the basic ventilatory rhythm. This center consists of two main parts: (1) a ventilatory pattern generator, which sets the rhythmic pattern; and (2) an integrator, which controls generation of the pattern, processes input from higher brain centers and chemoreceptors, and controls the rate and amplitude of the ventilatory pattern. Input to the integrator arises from higher brain centers, including the cerebral cortex, hypothalamus, limbic system including the amygdalae, and cerebellum.

Central chemoreceptors are located in the central nervous system just below the ventrolateral surface of the medulla. These central chemoreceptors detect changes in the $Paco_2$ and pH of interstitial fluid in the brainstem, and they modulate ventilation. Peripheral chemoreceptors are located on specialized cells in the aortic arch **(aortic bodies)** and at the bifurcation of the internal and external carotid arteries **(carotid bodies)** in the neck. These peripheral chemoreceptors sense the $Pao_2$, $Paco_2$, and pH of arterial blood. They feed information back to the integrator nuclei in the medulla through the vagus nerves, and by the carotid sinus nerves that are branches of the glossopharyngeal nerves. Pulmonary mechanoreceptors and sensory nerve stimulation, in response to lung inflation or to stimulation by irritants or release of local mediators in the airways, modify the ventilatory pattern.

The collective output of the respiratory control center to motor neurons located in the anterior horn of the spinal column controls the muscles of respiration, and this output determines the automatic rhythmic pattern of respiration. Motor neurons located in the cervical region of the spinal column control the activity of the diaphragm through the **phrenic nerves,** whereas other motor neurons located in the thoracic region of the spine control the intercostal muscles and the accessory muscles of respiration.

In contrast to automatic respiration, voluntary respiration bypasses the respiratory control center in the medulla. The neural activity controlling voluntary respiration originates in the motor cortex and signaling passes directly to motor neurons in the spine through the **corticospinal tracts.** The motor neurons to the respiratory muscles act as the final site of integration of the voluntary (corticospinal tract) and automatic (ventrolateral tracts) control of ventilation. Voluntary control of these muscles competes with automatic influences at the level of the spinal motor neurons, and this competition can be demonstrated by breath holding. At the start of the breath hold, voluntary control dominates the spinal motor neurons. However, as the breath hold continues, the automatic ventilatory control eventually




• **Fig. 25.1** Relationship between partial pressure of arterial carbon dioxide ($Paco_2$) and alveolar ventilation in awake normal states, during sleep, after narcotic ingestion and deep anesthesia, and in the presence of metabolic acidosis. Both the slopes of the response (sensitivity) and the position of the response curves (threshold, the point at which the curve crosses the x-axis [not shown]) are changed, which indicates differences in ventilatory responses and response thresholds. *COPD*, Chronic obstructive pulmonary disease.

overpowers the voluntary effort and limits the duration of the breath hold. Motor neurons also innervate muscles of the upper airway. These neurons are located within the medulla near the respiratory control center. They innervate muscles in the upper airways through the cranial nerves. When activated, they dilate the pharynx and large airways at the initiation of inspiration.

## Response to Carbon Dioxide

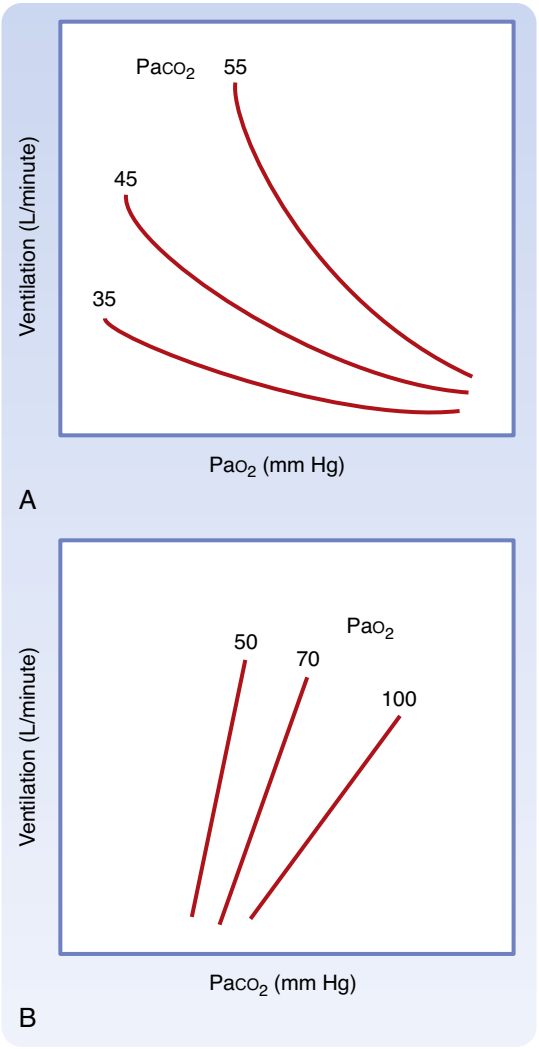
Ventilation is also regulated by $Paco_2$, $Pao_2$, and pH in arterial blood. $Paco_2$ is the most important of these regulators. Both the rate and depth of breathing are controlled to maintain $Paco_2$ close to 40 mm Hg. In a normal awake individual, there is a linear rise in ventilation as $Paco_2$ reaches and exceeds 40 mm Hg (Fig. 25.1). The ventilatory drive or response to changes in $Paco_2$ can be reduced by hyperventilation and by drugs that depress the respiratory center and decrease the ventilatory response to both $CO_2$ and $O_2$. These drugs include opiates, benzodiazepines, barbiturates, and anesthetic agents. In these instances, the stimulus is inadequate to stimulate the motor neurons that innervate the muscles of respiration. It is also depressed during sleep. In addition, the ventilatory response to changes in $Paco_2$ is reduced if the work of breathing is increased, which can occur in individuals with chronic obstructive pulmonary disease (COPD). This effect occurs primarily because the neural output of the respiratory center is less effective in promoting ventilation as a result of the mechanical limitation to ventilation.

Changes in $Paco_2$ are sensed by central and peripheral chemoreceptors, and they transmit this information to the medullary respiratory centers. The respiratory control center then regulates minute ventilation and thereby maintains $Paco_2$ within the normal range. In the presence of a normal $Pao_2$, ventilation increases by approximately 3 L/minute for each 1 mm Hg rise in $Paco_2$. The response to an increase in $Paco_2$ is further increased when the $Pao_2$ is low (Fig. 25.2*A*). With a low $Pao_2$, ventilation is greater for any given $Paco_2$, and the increase in ventilation for a given increment in $Paco_2$ is enhanced. The slope of the minute ventilation response as a function of the inspired $CO_2$ is termed the *ventilatory response* to $CO_2$ and is a test of $CO_2$ sensitivity. It is important to recognize that this relationship is amplified by low $O_2$ (see Fig. 25.2*B*). The responsiveness to low $O_2$ is enhanced because different mechanisms are responsible for sensing $Pao_2$ and $Paco_2$ in the peripheral chemoreceptors. Thus the presence of both hypercapnia-elevated $CO_2$ and hypoxemia-low $O_2$ (often called *asphyxia* when both changes are present) has an additive effect on chemoreceptor output and on the resulting ventilatory stimulation.

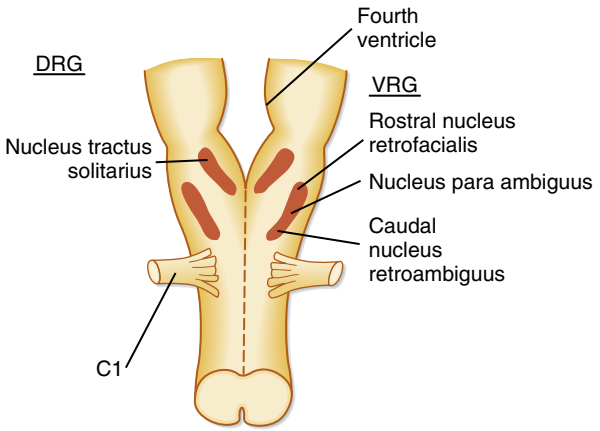
## Control of Ventilation: The Details

### The Respiratory Control Center

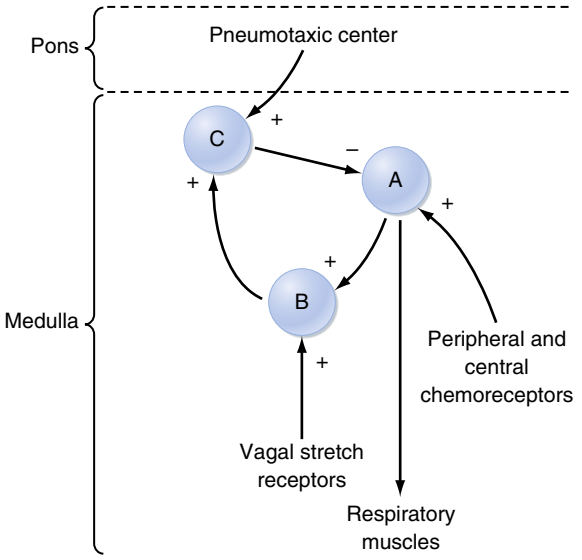
When the brain is transected experimentally between the medulla and the pons, periodic breathing is maintained, thus demonstrating that the inherent rhythmicity of breathing originates in the medulla. Although no single group of neurons in the medulla has been found to be the breathing "pacemaker," two distinct nuclei within the medulla are involved in generation of the respiratory pattern (Fig. 25.3). One nucleus is the **dorsal respiratory group** (DRG), which




• **Fig. 25.2** The effects of hypoxia and hypercapnia on ventilation as the other respiratory gas partial pressures are varied. **A,** At a given partial pressure of arterial carbon dioxide *($Paco_2$)*, ventilation increases more and more as partial pressure of arterial oxygen *($Pao_2$)* decreases. When $Paco_2$ is allowed to decrease (the normal condition) during hypoxia, there is little stimulation of breathing until $Pao_2$ falls below 60 mm Hg. The hypoxic response is mediated through the carotid body chemoreceptors. **B,** The sensitivity of the ventilatory response to $CO_2$ is enhanced by hypoxia.




• **Fig. 25.3** The respiratory control center is located in the medulla, the most primitive portion of the brain. The neurons are mainly in two areas: the dorsal respiratory group *(DRG)*, which consists of the nucleus tractus solitarius; and the ventral respiratory group *(VRG)*, which consists of the rostral nucleus retrofacialis, nucleus para-ambiguus, and the caudal nucleus retroambiguus. *C1* refers to the first cervical signal segment to the caudal border of the pons. The fourth ventricle of the brain is located below the cerebellum and above, and between, the pons and the medulla.




• **Fig. 25.4** Diagram of the basic wiring of the brainstem ventilatory controller. The signs of the main output *(arrows)* of the neuron pools indicate whether the output is excitatory (+) or inhibitory (–). Pool A provides tonic inspiratory stimuli to the muscles of breathing. Pool B is stimulated by pool A and provides additional stimulation to the muscles of breathing, and pool B stimulates pool C. Other brain centers feed into pool C (inspiratory cutoff switch), which sends inhibitory impulses to pool A. Afferent information (feedback) from various sensors acts at different locations: Chemoreceptors act on pool A, and intrapulmonary sensory fibers act via the vagus nerves on pool B. A pneumotaxic center in the anterior pons receives input from the cerebral cortex, and it acts on pool C.

is composed of cells in the **nucleus tractus solitarius** and is located in the dorsomedial region of the medulla. Cells in the DRG receive afferent input from cranial nerves IX and X, which originate from airways and the lungs and constitute the initial intracranial processing station for this afferent input. The second group of medullary cells is the **ventral respiratory group** (VRG), located in the ventrolateral region of the medulla. The VRG is composed of three cell groups: the **rostral nucleus retrofacialis,** the **caudal nucleus retroambiguus,** and the **nucleus para-ambiguus.** The VRG contains both inspiratory and expiratory neurons. The nucleus retrofacialis and the caudally located cells of the nucleus retroambiguus are active during exhalation, whereas the rostrally located cells of the nucleus retroambiguus are active during inspiration. The nucleus para-ambiguus has inspiratory and expiratory neurons that travel in the vagus nerve to the laryngeal and pharyngeal muscles. Discharges from cells in these areas excite some cells and inhibit other cells.

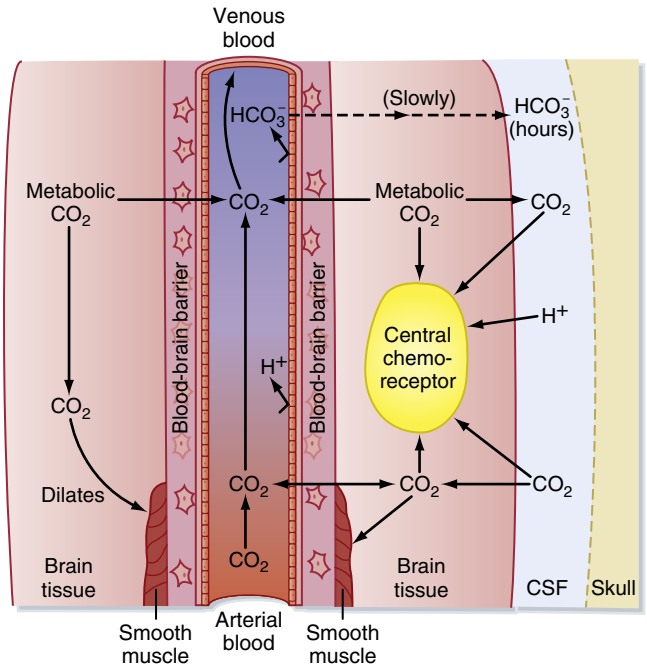
At the level of the respiratory control center, inspiration and exhalation involve three phases: one inspiratory and two expiratory (Fig. 25.4). Inspiration begins with an

abrupt increase in discharge from cells in the nucleus tractus solitarius, the nucleus retroambiguus, and the nucleus para-ambiguus, followed by a steady, ramp-like increase in firing rate throughout inspiration. This leads to progressive contraction of the respiratory muscles during automatic breathing. At the end of inspiration, an "off-switch" event causes neuron firing to decrease markedly, at which point exhalation begins. At the start of exhalation (phase I of expiration), a paradoxical increase in inspiratory neuron firing slows the expiratory phase down by increasing inspiratory muscle tone and expiratory neuron firing. This inspiratory neuron firing decreases and stops during phase II of exhalation. Although many different neurons in the DRG and VRG are involved in ventilation, each cell type appears to have a specific function. For example, the **Hering-Breuer reflex** is an inspiratory-inhibitory reflex that arises from afferent stretch receptors located in the smooth muscles of the airways. Increasing lung inflation stimulates these stretch receptors and results in early exhalation by stimulating the neurons associated with the off-switch phase of inspiratory muscle control. Thus rhythmic breathing depends on a continuous (tonic) inspiratory drive from the DRG and an intermittent (phasic) expiratory drive from the cerebrum, thalamus, cranial nerves, and ascending sensory tracts in the spinal cord.

## Central Chemoreceptors

A chemoreceptor is a receptor that responds to a change in the chemical composition of blood or other fluid around it. Central chemoreceptors are specialized cells on the ventrolateral surface of the medulla. Chemoreceptors are sensitive to the pH of the surrounding extracellular fluid. Because this extracellular fluid is in contact with cerebrospinal fluid (CSF), changes in the pH of CSF affect ventilation by acting on these chemoreceptors.

CSF is an ultrafiltrate of plasma that is secreted continuously by the **choroid plexus** and is reabsorbed by the arachnoid villi. Because it is in contact with the extracellular fluid in the brain, the composition of CSF is influenced by the metabolic activity of the cells in the surrounding area and the composition of the blood. Although the origin of CSF is plasma, the composition of CSF is not the same as that of plasma because the **blood-brain barrier** exists between the two sites (Fig. 25.5). The blood-brain barrier is composed of endothelial cells, smooth muscle, and the **pial** and **arachnoid membranes,** and it regulates the movement of ions between blood and CSF. In addition, the choroid plexus also determines the ionic composition of CSF by transporting ions into and out of CSF. The blood-brain barrier is relatively impermeable to $H^+$ and $HCO_3^-$ ions, but it is very permeable by $CO_2$. Thus the $P_{CO_2}$ in CSF parallels the arterial $P_{CO_2}$. $CO_2$ is also produced by cells of the brain as a product of metabolism. As a consequence, the $P_{CO_2}$ in CSF is usually a few millimeters of mercury higher than that in arterial blood, and so the pH is slightly more acidic (7.33) in CSF than in plasma (Table 25.1).




• **Fig. 25.5** Carbon dioxide and the blood-brain barrier. $P_{aCO_2}$ crosses the blood-brain barrier and rapidly equilibrates with $CO_2$ in cerebrospinal fluid *(CSF)*. $H^+$ and $HCO_3^-$ ions cross the barrier slowly. The partial pressure of arterial carbon dioxide ($P_{aCO_2}$) combines with $CO_2$ generated by metabolism to dilate the smooth muscle. In comparison with arterial blood, the pH of CSF is lower and the $P_{CO_2}$ is higher, with little protein buffering.

**TABLE 25.1 Normal Values for the Composition of Cerebrospinal Fluid and Arterial Blood**

| Parameter | Cerebrospinal Fluid | Arterial Blood |
|---|---|---|
| pH | 7.33 | 7.40 |
| $P_{CO_2}$ (mm Hg) | 44 | 40 |
| $HCO_3^-$ (mEq/L) | 22 | 24 |

*$P_{CO_2}$*, Partial pressure of carbon dioxide.

## Peripheral Chemoreceptors

The **carotid** and **aortic bodies** are peripheral chemoreceptors that respond to changes in $P_{aO_2}$ (the $O_2$ dissolved in plasma, not the total $O_2$ content of blood), $P_{aCO_2}$, and pH, and they transmit afferent information to the central respiratory control center. The peripheral chemoreceptors are the only chemoreceptors that respond to changes in $P_{aO_2}$. The peripheral chemoreceptors are also responsible for approximately 40% of the ventilatory response to $P_{aCO_2}$. These chemoreceptors are small, highly vascularized structures. They consist of type I **(glomus)** cells that are rich in mitochondria and endoplasmic reticulum. They also have several types of cytoplasmic granules (synaptic vesicles) that contain various neurotransmitters, including dopamine, acetylcholine, norepinephrine, and neuropeptides. Afferent nerve fibers synapse with type I cells, and they transmit information to the brainstem through the carotid sinus nerve (carotid

## AT THE CELLULAR LEVEL

The **Henderson-Hasselbalch equation** relates the pH of CSF to the concentration of bicarbonate ($[HCO_3^-]$) and $P_{CO_2}$:

$$pH = pK + \frac{\log[HCO_3^-]}{\alpha \times P_{CO_2}}$$

where α is the solubility coefficient (0.03 mmol/L per mm Hg) and pK is the negative logarithm of the dissociation constant for carbonic acid (6.1). The Henderson-Hasselbalch equation demonstrates that an increase in CSF $P_{CO_2}$ causes the pH of CSF to decrease at any given $[HCO_3^-]$. The decrease in pH stimulates the central chemoreceptors and thereby increases ventilation. Thus $CO_2$ in blood regulates ventilation by its effect on the pH of CSF. The resulting hyperventilation reduces the $P_{aCO_2}$, and therefore the $P_{CO_2}$ of CSF, and returns the pH of CSF toward a normal value. Furthermore, cerebral vasodilation accompanies an increase in $P_{aCO_2}$, and this enhances the diffusion of $CO_2$ into CSF. In contrast, an increase in CSF $[HCO_3^-]$ causes an increase in the pH of CSF at any given $P_{aCO_2}$.

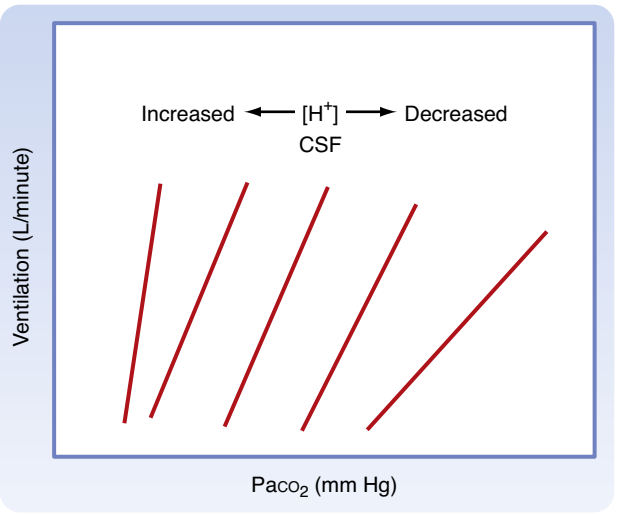
Changes in $P_{aCO_2}$ that result from alterations in pH activate homeostatic mechanisms that return the pH back toward a normal value. The blood-brain barrier regulates the pH of CSF by adjusting the ionic composition and $[HCO_3^-]$ of CSF. These changes in CSF $[HCO_3^-]$, however, occur slowly, over a period of several hours, whereas changes in CSF $P_{CO_2}$ can occur within minutes. Thus compensation for changes in the pH of CSF requires hours to develop fully.

body) and vagus nerve (aortic body). Type I cells are the cells primarily responsible for sensing $P_{aO_2}$, $P_{aCO_2}$, and pH. In response to even small decreases in $P_{aO_2}$, there is an increase in chemoreceptor discharge, which enhances respiration. The response is robust when $P_{aO_2}$ decreases below 75 mm Hg. Thus ventilation is regulated by changes in arterial and CSF pH through effects on peripheral and central chemoreceptors (Fig. 25.6).

## Pulmonary Mechanoreceptors

### *Chest Wall and Lung Reflexes*

Several reflexes that arise from the chest wall and lungs affect ventilation and ventilatory patterns (Table 25.2). The **Hering-Breuer inspiratory-inhibitory reflex** is stimulated by increases in lung volume, especially those associated with an increase in both ventilatory rate and tidal volume. This stretch reflex is mediated by vagal fibers, and when elicited, it results in cessation of inspiration by




• **Fig. 25.6** The ventilatory response to partial pressure of arterial carbon dioxide ($P_{aCO_2}$) is affected by the concentration of hydrogen *([H⁺])* in cerebrospinal fluid *(CSF)* and brainstem interstitial fluid. During chronic metabolic acidosis (e.g., diabetic ketoacidosis), the $[H^+]$ in CSF is increased, and the ventilatory response to inspired $P_{aCO_2}$ is increased (steeper slope). Conversely, during chronic metabolic alkalosis (a relatively uncommon condition), the $[H^+]$ in CSF is decreased and the ventilatory response to inspired $P_{aCO_2}$ is decreased (reduced slope). The positions of the response lines are also shifted, which indicates altered thresholds.

**TABLE 25.2 Reflexes in the Respiratory Tract**

| Reflex | Stimuli | Site of Activation | Receptor Type | Effect |
|---|---|---|---|---|
| Hering-Breuer Inflation | Lung inflation (maximal) | Airway smooth muscles (bronchi, bronchioles) | Stretch receptor, vagal afferent | Inhibition of medullary and pontine apenustic center, inhibiting active inspiration |
| Hering-Breuer Deflation | Lung deflation (maximal) | Airway smooth muscles (bronchi, bronchioles) | Stretch receptor or proprioceptor, vagal afferent | Inhibition of respiratory center inhibatory signal |
| Diving | Cold water, possibly pressure | Face and anterior nasal mucosa | Chemesthetic chemoreceptor, trigeminal afferent | Apnea, bradycardia, increased peripheral vascular resistance |
| Cough | Inhaled irritant (acid, dust, noxious gas, capscacin), mechanical irritant | Trachea, main carina, brancing points of larger airways, proximal conducting airways | Chemical and probably mechanical receptors, vagal afferent | Sequence of inspiration, brief glottic closure with expiratory muscle activation, quick glottic opening releasing forceful exhalation |
| Sneeze | Chemical or mechanical irritant | Nasal cavity | Chemical and probably mechanical receptors, trigeminal afferent | Eye closing, deep inhalation, glottic closure during forced exhalation, abrupt glotic opening with forceful airflow through nose and mouth. |

## IN THE CLINIC

Imagine flying from New York City to Denver. The barometric pressure in New York is approximately 760 mm Hg, whereas in the mountains surrounding Denver, Colorado, it is 600 mm Hg. At sea level, the $P_{AO_2}$ is approximately 95 mm Hg and $P_{AO_2}$ = [(760 – 47) × 0.21] – [40/0.8] = 100 mm Hg (according to the alveolar air equation; see Chapter 23). If the alveolar-arterial $P_{O_2}$ difference [$A_aD_{O_2}$] is 5 mm Hg, then $P_{aO_2}$ = 100 mm Hg – 5 mm Hg = 95 mm Hg. In the CSF, pH would be approximately 7.33, $P_{aCO_2}$ would be 44 mm Hg ($P_{aCO_2}$ + $CO_2$ produced by metabolism of brain cells), and $HCO_3^-$ would be approximately 22 mEq/L.

When you arrive in Denver, there is an abrupt decrease in the partial pressure of inspired $O_2$ ($P_{IO_2}$): $P_{IO_2}$ = (600 – 47) × 0.21 = 116 mm Hg; there are also decreases in the partial pressures of alveolar and arterial $O_2$: $P_{AO_2}$ = 116 – (40/0.8) = 66 mm Hg, and $P_{aO_2}$ = 61 mm Hg (if there is no change in $A_aD_{O_2}$). This decrease in arterial $O_2$ stimulates the peripheral chemoreceptors and thereby increases ventilation. The increase in ventilation decreases $P_{aCO_2}$ and elevates arterial pH. The result of this increase in ventilation is to minimize the hypoxemia by increasing $P_{AO_2}$. For example, assume that $P_{ACO_2}$ decreases to 30 mm Hg. Then $P_{AO_2}$ = [(600 – 47) × 0.21] – [30/0.8] = 78 mm Hg, a 12-mm Hg increase in $P_{AO_2}$.

The decrease in $P_{aCO_2}$ also causes a reduction in the $P_{CO_2}$ of CSF. Because [$HCO_3^-$] is unchanged, the pH of CSF increases. This increase in the pH of CSF attenuates the rate of discharge of the central chemoreceptors and decreases their contribution to the ventilatory drive. Over the next 12 to 36 hours, [$HCO_3^-$] in CSF decreases as acid-base transporter proteins in the blood-brain barrier reduce [$HCO_3^-$]. As a consequence, the pH of CSF returns toward normal. Central chemoreceptor discharge increases, and minute ventilation is further increased. At the same time that [$HCO_3^-$] in CSF decreases, $HCO_3^-$ is gradually excreted from plasma by the kidneys. This results in a gradual return of arterial pH toward normal values. Peripheral chemoreceptor stimulation increases further as arterial pH becomes normal (peripheral chemoreceptors are inhibited by the elevated arterial pH). Finally, within 36 hours of arriving at high altitude, minute ventilation increases significantly. This delayed response is greater than the immediate effect of the hypoxemia on ventilation. This further increase in ventilation is due to both central and peripheral chemoreceptor stimulation. Thus after 36 hours, both arterial pH and CSF pH are approaching normal values; minute ventilation is increased, $P_{aO_2}$ is decreased, and $P_{aCO_2}$ is decreased.

You now return home. When you land in New York, the $P_{IO_2}$ returns to a normal value, and the hypoxic stimulus to ventilation is removed. $P_{aO_2}$ returns to a normal value, and the peripheral chemoreceptor stimulation to ventilation decreases. This causes an increase in arterial [$CO_2$] toward normal values, which in turn causes an increase in CSF [$CO_2$]. This increase is associated with a decrease in the pH of CSF as [$HCO_3^-$] in CSF is reduced and ventilation is augmented. Over the next 12 to 36 hours, the acid-base transporters in the blood-brain barrier transport $HCO_3^-$ back into CSF, and the pH of CSF gradually returns toward normal values. Similarly, the pH of blood decreases as $P_{aCO_2}$ rises because arterial [$HCO_3^-$] falls. This stimulates the peripheral chemoreceptors, and minute ventilation remains augmented. Over the next 12 to 36 hours, [$HCO_3^-$] excretion by the kidneys increases (see Chapter 36), arterial pH returns to a normal value, and minute ventilation returns to a normal level.

stimulating the off-switch neurons in the medulla. This reflex is inactive during quiet breathing and appears to be most important in newborns. Stimulation of nasal or facial receptors with cold water initiates the **diving reflex.** When this reflex is elicited, **apnea,** or cessation of breathing, and bradycardia occur. This reflex protects individuals from aspirating water in the initial stages of drowning. Activation of receptors in the nose is responsible for the **sneeze reflex.**

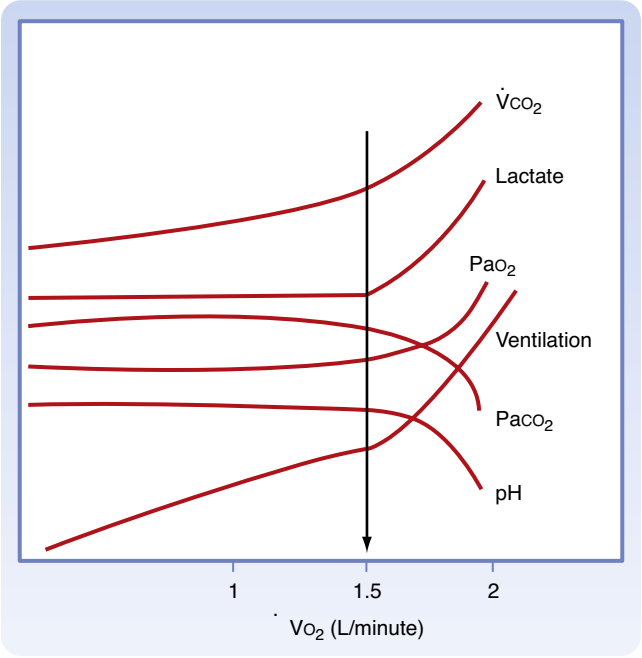
The **aspiration** or **sniff reflex** can be elicited by stimulation of mechanical receptors in the nasopharynx and pharynx. This is a strong, short-duration inspiratory effort that brings material from the nasopharynx to the pharynx, where it can be swallowed or expectorated. The mechanical receptors responsible for the sniff reflex are also important in swallowing by inhibiting respiration and causing laryngeal closure. For anatomical reasons, only newborns can breathe and swallow simultaneously, which allows more rapid ingestion of nutrients.

The larynx contains both superficial and deep receptors. Activation of the superficial receptors results in apnea, cough, and expiratory movements that protect the lower respiratory tract from aspirating foreign material. The deep receptors are located in the skeletal muscles of the larynx, and they control muscle fiber activation, as in other skeletal muscles.

### *Sensory Receptors and Reflexes*

Three major types of sensory receptors located in the tracheobronchial tree respond to a variety of different stimuli, and those responses result in changes in the lung's mechanical properties, alterations in the respiratory pattern, and the development of respiratory symptoms. Inhaled dust, noxious gases, and cigarette smoke stimulate **irritant receptors** in the trachea and large airways that transmit information through myelinated vagal afferent fibers. Stimulation of these receptors results in an increase in airway resistance, reflex apnea, and coughing. These receptors are also known as **rapidly adapting pulmonary stretch receptors. Slowly adapting pulmonary stretch receptors** respond to mechanical stimulation, and they are activated by lung inflation. They also transmit information through myelinated, vagal afferent fibers. The increase in lung volume in people with COPD stimulates these pulmonary stretch receptors and delays the onset of the next inspiratory effort. This explains the long, slow expiratory effort in affected individuals, and it is essential to minimize dynamic, expiratory airway compression.

In addition, specialized sensory receptors located in the lung parenchyma respond to chemical or mechanical stimulation in the lung interstitium. These receptors are called **juxta-alveolar,** (or **J**) **receptors.** They transmit their afferent input through unmyelinated, vagal C fibers. They may be responsible for the sensation of **dyspnea** (abnormal shortness of breath) and the rapid, shallow ventilatory patterns that occur in interstitial lung edema and some inflammatory lung states.




• **Fig. 25.7** Oxygen consumption *($\dot{V}o_2$)* as a function of the metabolic changes that occur during exercise. The anaerobic threshold *(arrow)* is the point at which the illustrated variables change and is due to lactic acidosis. *$Paco_2$*, Partial pressure of arterial carbon dioxide; *$Pao_2$*, partial pressure of arterial oxygen; *$\dot{V}co_2$*, carbon dioxide consumption.

**Somatic receptors** are also located in the intercostal muscles, rib joints, accessory muscles of respiration, and tendons, and they respond to changes in the length and tension of the respiratory muscles. Although they do not directly control respiration, they do provide information about lung volume and play a role in terminating inspiration. They are especially important in individuals with increased airway resistance and decreased pulmonary compliance because they can augment muscle force within the same breath. Somatic receptors also help minimize the chest wall distortion during inspiration in newborns, who have very compliant rib cages.

## Exercise

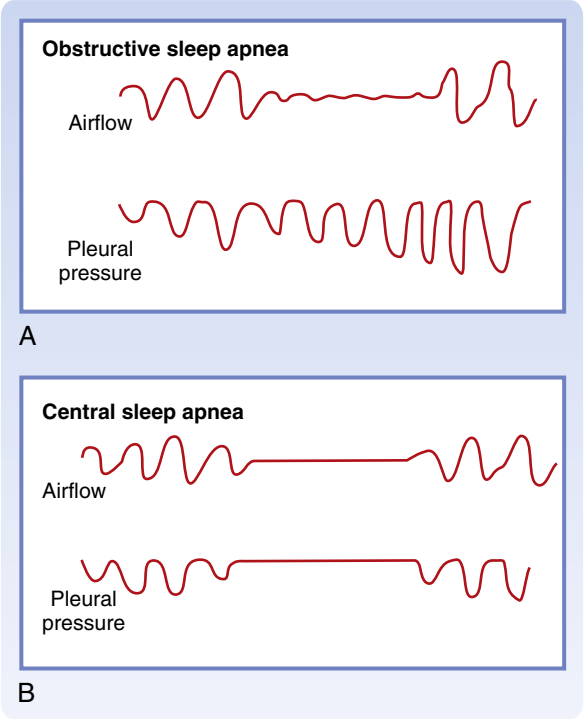
The ability to exercise depends on the capacity of the cardiac and respiratory systems to increase delivery of $O_2$ to tissues and remove $CO_2$ from the body. Ventilation increases immediately when exercise begins, and this increase in minute ventilation closely matches the increases in $O_2$ consumption and $CO_2$ production that accompany exercise (Fig. 25.7). Ventilation is linearly related to both $CO_2$ production and $O_2$ consumption at low to moderate levels (see Fig. 25.7). During maximal exercise, a physically fit individual can achieve an $O_2$ consumption of 4 L/minute with a minute ventilation volume of 120 L/minute, which is almost 15 times the resting level.

Exercise is remarkable because of the lack of significant changes in blood gases. Except at maximal exertion, changes in $Paco_2$ and $Pao_2$ are minimal during exercise. Arterial pH remains within normal values during moderate exercise. During strenuous exercise, arterial pH begins to fall as lactic acid is liberated from muscles during anaerobic metabolism. This decrease in arterial pH stimulates ventilation that is out of proportion to the level of exercise. The level of exercise at which sustained metabolic (lactic) acidosis begins is called the **anaerobic threshold** (see Fig. 25.7).

## Abnormalities in the Control of Breathing

Changes in the ventilatory pattern can occur for both primary and secondary reasons. During sleep, approximately one-third of healthy individuals have brief episodes of apnea or hypoventilation that have no significant effects on $Pao_2$ or $Paco_2$. The apnea usually lasts less than 10 seconds, and it occurs in the lighter stages of slow-wave and rapid eye movement (REM) sleep. In **sleep apnea** syndromes, the duration of apnea is abnormally prolonged, and it changes $Pao_2$ and $Paco_2$. There are two major categories of sleep apnea (Fig. 25.8). The first, **obstructive sleep apnea** (OSA), is the most common of the sleep apnea syndromes, and it occurs when the upper airway (generally the hypopharynx) closes during inspiration. Although the process is similar to what happens during snoring, it is more severe, inasmuch as it obstructs the airway and causes cessation of airflow.

The second sleep apnea syndrome is **central sleep apnea.** This variant of apnea occurs when the ventilatory drive to



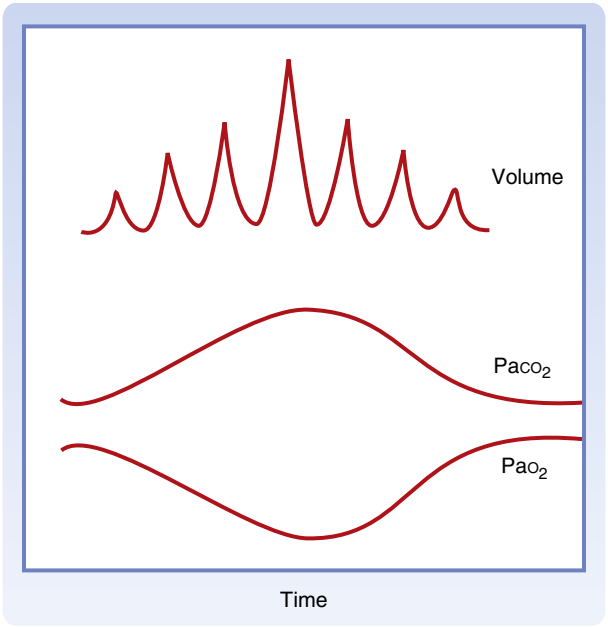

• **Fig. 25.8** The two main categories of sleep apnea. **A,** Obstructive sleep apnea, the pleural pressure oscillations increase as $CO_2$ level rises. This indicates that resistance to airflow is very high as a result of upper airway obstruction. **B,** Central sleep apnea is characterized by no attempt to breathe, as demonstrated by no oscillations in pleural pressure.

## IN THE CLINIC

The clinical histories of individuals with OSA are very similar. A spouse usually reports that the affected individual snores. The snoring becomes louder and louder and then stops while the individual continues to make vigorous respiratory efforts (see Fig. 25.8). The individual then awakens, falls back to sleep, and continues the same process repetitively throughout the night. Individuals with OSA awaken when the arterial hypoxemia and hypercapnia stimulate both peripheral and central chemoreceptors. Respiration is restored briefly before the next apneic event occurs. Individuals with OSA can have hundreds of these events each night that interrupt sleep. Complications of OSA include sleep deprivation, polycythemia, right-sided cardiac failure (cor pulmonale), and pulmonary hypertension secondary to the recurrent, hypoxic events. OSA is common in individuals with obesity and in those with excessive compliance of the hypopharynx, upper airway edema, and structural abnormalities of the upper airway.

the respiratory motor neurons decreases. Individuals with central sleep apnea have repeated episodes of apnea, during which time they make no respiratory effort, every night (see Fig. 25.8). The degree of hypercapnia and hypoxemia in individuals with central sleep apnea is less than that in individuals with OSA, but the same complications (e.g., polycythemia) can occur when central sleep apnea is recurrent and severe.

**Cheyne-Stokes ventilation** is another abnormality of breathing that is characterized by varying tidal volume and ventilatory frequency (Fig. 25.9). After a period of apnea, tidal volume and respiratory frequency increase progressively over several breaths, and then they progressively decrease until apnea recurs. This irregular breathing pattern is seen in some individuals with central nervous system diseases, head trauma, and increased intracranial pressure. It is also present on occasion in healthy individuals during sleep at high altitude. The mechanism underlying Cheyne-Stokes respiration is not known. In some individuals, it appears to be due to slow blood flow in the brain in association with periods of overshooting and undershooting ventilatory effort in response to changes in $P_{CO_2}$.

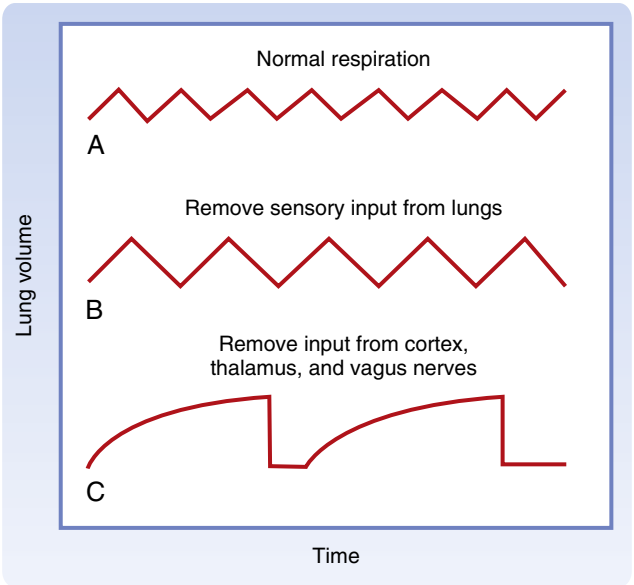



• **Fig. 25.9** In Cheyne-Stokes breathing, tidal volume and, as a consequence, arterial blood gas levels wax and wane. In general, Cheyne-Stokes breathing is a sign of vasomotor instability, particularly low cardiac output. *$Paco_2$*, Partial pressure of arterial carbon dioxide; *$Pao_2$*, partial pressure of arterial oxygen.

## IN THE CLINIC

**Central alveolar hypoventilation,** also known as *Ondine's curse,* is a rare disease in which voluntary breathing is intact but abnormalities in automaticity exist. It is the most severe of the central sleep apnea syndromes. As a result, people with central alveolar hypoventilation can breathe as long as they do not fall asleep. For these individuals, mechanical ventilation or, more recently, bilateral diaphragmatic pacing (similar to a cardiac pacemaker) can be lifesaving.

**Apneustic breathing** is another abnormal breathing pattern that is characterized by sustained periods of inspiration




• **Fig. 25.10** Some patterns of breathing. **A,** Normal rate of breathing is in the range of 12 to 20 breaths per minute. **B,** When sensory input is removed from various lung receptors (mainly stretch), each breathing cycle is lengthened and tidal volume is increased, so that alveolar ventilation is not significantly affected. **C,** When input from the cerebral cortex and thalamus is also eliminated, together with vagal blockade, the result is prolonged inspiratory activity broken after several seconds by brief expirations (apneusis).

separated by brief periods of exhalation (Fig. 25.10*C*). The mechanism underlying this ventilatory pattern appears to be a loss of inspiratory-inhibitory activities that results in augmentation of the inspiratory drive. The pattern sometimes occurs in individuals with central nervous system injury.

## IN THE CLINIC

**Sudden infant death syndrome** (SIDS) is the most common cause of death in infants in the first year of life after the perinatal period. Although the cause of SIDS is not known, abnormalities in ventilatory control, particularly in $CO_2$ responsiveness, have been implicated. Placing infants on their backs to sleep (which reduces the potential for $CO_2$ rebreathing) has dramatically decreased (but not eliminated) the rate of death from this syndrome.

## Key Points

1. Ventilatory control is composed of the respiratory control center, central chemoreceptors, peripheral chemoreceptors, and pulmonary mechanoreceptors/sensory nerves. $Paco_2$ is the major factor that influences ventilation.
2. The respiratory control center is composed of the dorsal respiratory group and the ventral respiratory group. Rhythmic breathing depends on a continuous (tonic) inspiratory drive from the dorsal respiratory group and on intermittent (phasic) expiratory input from the cerebrum, thalamus, cranial nerves, and ascending spinal cord sensory tracts. The peripheral and central chemoreceptors respond to changes in $Paco_2$ and pH. The peripheral chemoreceptors (carotid and aortic bodies) are the only chemoreceptors that respond to changes in $Pao_2$.
3. Acute hypoxia and chronic hypoxia affect breathing differently because the slow adjustments in CSF $[H^+]$ in chronic hypoxia alter sensitivity to $CO_2$.
4. Irritant receptors protect the lower respiratory tract from particles, chemical vapors, and physical factors, primarily by inducing cough. C fiber J receptors in the terminal respiratory units are stimulated by distortion of the alveolar walls (by lung congestion or edema).
5. The two most important clinical abnormalities of breathing are obstructive and central sleep apnea.
6. $Pao_2$, $Paco_2$, and pH remain within normal limits during moderate exercise; however, during strenuous exercise, pH falls, which stimulates ventilation, whereas $Pao_2$ and $Paco_2$ remain relatively normal.