Breathing, similar to the heartbeat, is an automatic activity requiring no conscious awareness. In contrast to the heartbeat, breathing patterns can be consciously changed, although powerful neural control mechanisms overwhelm conscious control soon after one willfully stops breathing. The normal unconscious cycle of breathing is regulated by complex mechanisms that are still not completely understood. The rhythmic cycle of breathing comes from the brainstem, mainly from neurons located in the medulla. Higher brain centers and many systemic receptors and reflexes change the output of the medulla. These different structures function in harmony, precisely controlling ventilatory rate and depth to meet the gas exchange needs of the body. This chapter helps the respiratory therapist (RT) understand basic physiologic mechanisms that regulate breathing. With this knowledge, the RT and other members of the patient care team can help predict the effects that various therapies and disease processes have on ventilation.

MEDULLARY RESPIRATORY CENTER

Animal experiments show that cutting through the brainstem just below the medulla (Figure 15-1, *level IV*) stops all ventilatory activity. However, breathing continues rhythmically after the brainstem is cut just above the pons (see Figure 15-1, *level I*). Physiologists used to believe that separate inspiratory and expiratory neuron "centers" in the medulla were responsible for the cyclic pattern of breathing. Researchers believed that inspiratory and expiratory neurons fired by self-excitation and that they mutually inhibited one another. More recent evidence shows that inspiratory and expiratory neurons are anatomically mixed together and do not inhibit one another.[1] No clearly separate inspiratory and expiratory centers exist. Instead, the medulla contains widely scattered groups of respiratory-related neurons, as shown in Figure 15-1. The **dorsal respiratory groups (DRGs)** contain mainly inspiratory neurons, whereas the **ventral respiratory groups (VRGs)** contain both inspiratory and expiratory neurons.

Dorsal Respiratory Groups

As shown in Figure 15-1, DRG neurons are mainly inspiratory neurons located on both sides of the medulla. These neurons send the major inspiratory stimuli to the motor nerves of the diaphragm and external intercostal muscles.[1] Many DRG nerves extend into the VRGs, but few VRG nerve fibers extend into the DRGs. Mutual inhibition is an unlikely explanation for rhythmic, spontaneous breathing.[1]

The vagus and glossopharyngeal nerves transmit many sensory impulses to the DRGs from the lungs, airways, peripheral chemoreceptors, and joint proprioceptors. These impulses change the basic breathing pattern generated in the medulla.

Ventral Respiratory Groups

VRG neurons are located bilaterally in the medulla in two different nuclei and contain inspiratory and expiratory neurons (see Figure 15-1). Some inspiratory VRG neurons send motor impulses through the vagus nerve to the laryngeal and pharyngeal muscles, abducting the vocal cords and increasing the diameter of the glottis. Other VRG inspiratory neurons transmit impulses to the diaphragm and external intercostal muscles. Still other VRG neurons have mostly expiratory discharge patterns and send impulses to the internal intercostal and abdominal expiratory muscles.

The exact origin of the basic rhythmic pattern of ventilation is unknown. No single group of pacemaker cells has been identified. Two predominant theories of rhythm generation are

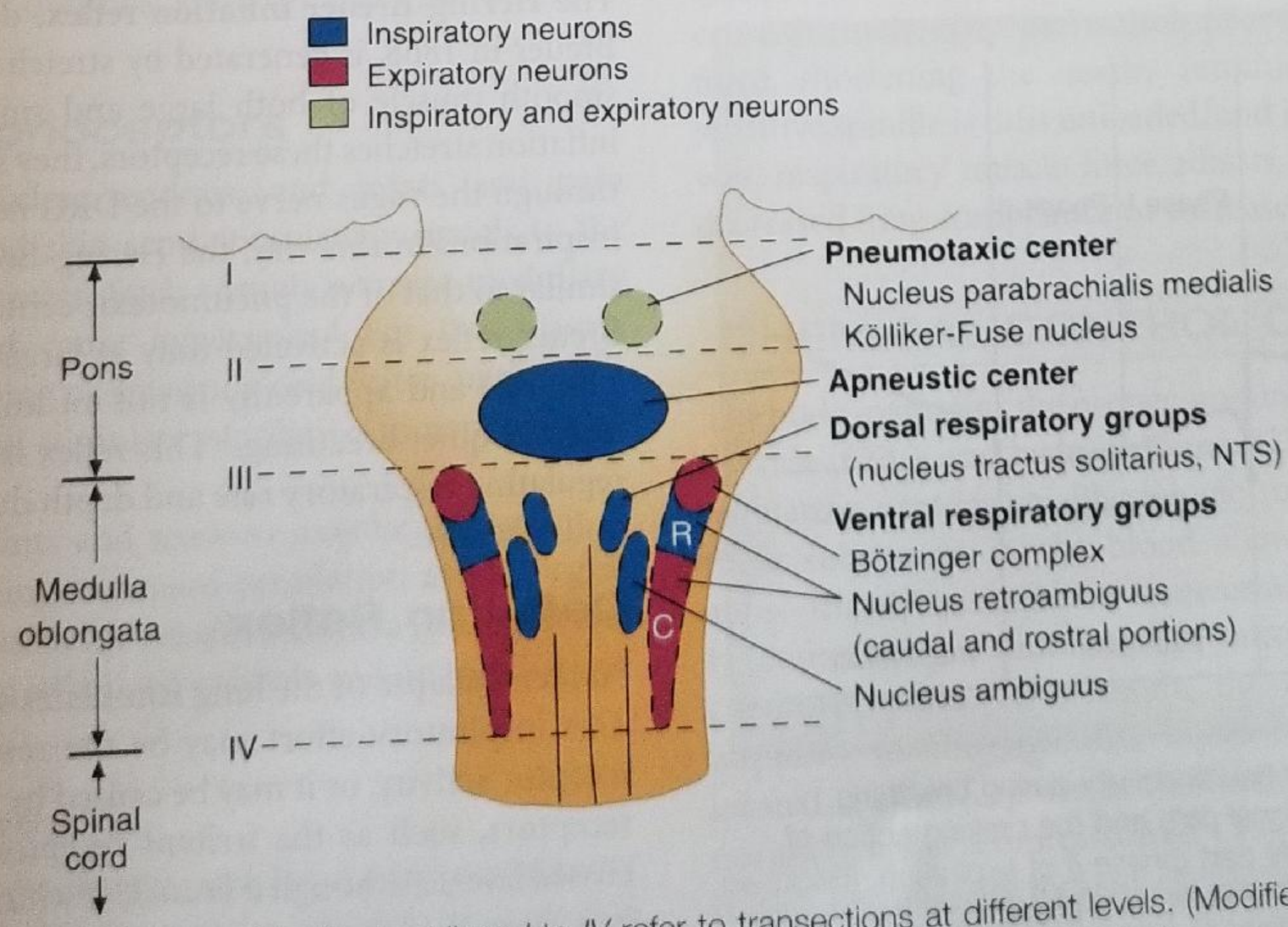

FIGURE 15-1 Dorsal view of the brainstem. Dashed lines *I* to *IV* refer to transections at different levels. (Modified from Beachey W: Respiratory care anatomy and physiology: foundations for clinical practice, ed 2, St Louis, 2007, Mosby.)

the *pacemaker hypothesis* and the *network hypothesis*.[2] The pacemaker hypothesis holds that certain medullary cells have intrinsic pacemaker properties (i.e., rhythmic self-exciting characteristics) and that these cells drive other medullary neurons. The network hypothesis suggests that rhythmic breathing is the result of a particular pattern of interconnections between neurons dispersed throughout the upper part of the VRG, the pre-Bötzinger complex, and the Bötzinger complex. This hypothesis assumes that certain populations of inspiratory and expiratory neurons inhibit one another and that one of the neuron types fires in a self-limiting way, such that it becomes less responsive the longer it fires. There is no definitive proof of either hypothesis; the precise origin of respiratory rhythm generation remains mysterious.[2]

Inspiratory Ramp Signal

The inspiratory muscles do not receive an instantaneous burst of signals from the dorsal and ventral inspiratory neurons. Rather, the firing rate of DRG and VRG inspiratory neurons increases gradually at the end of the expiratory phase, creating a ramp signal (Figure 15-2). The inspiratory muscles contract steadily and smoothly, gradually expanding the lungs rather than filling them in an abrupt inspiratory gasp. During exercise, various reflexes and receptors influence the medullary neurons, making the ramp signal much steeper, filling the lungs more rapidly.

During quiet breathing, inspiratory neurons fire with an increasing rate for approximately 2 seconds and then abruptly switch off, allowing expiration to proceed for approximately 3 seconds.[3] At the start of expiration, inspiratory neurons again fire briefly, holding back the early phase of expiration (see Figure 15-2). The inhibitory neurons that switch off the inspiratory ramp signal are controlled by the pneumotaxic center and pulmonary stretch receptors, which are discussed later in this chapter.

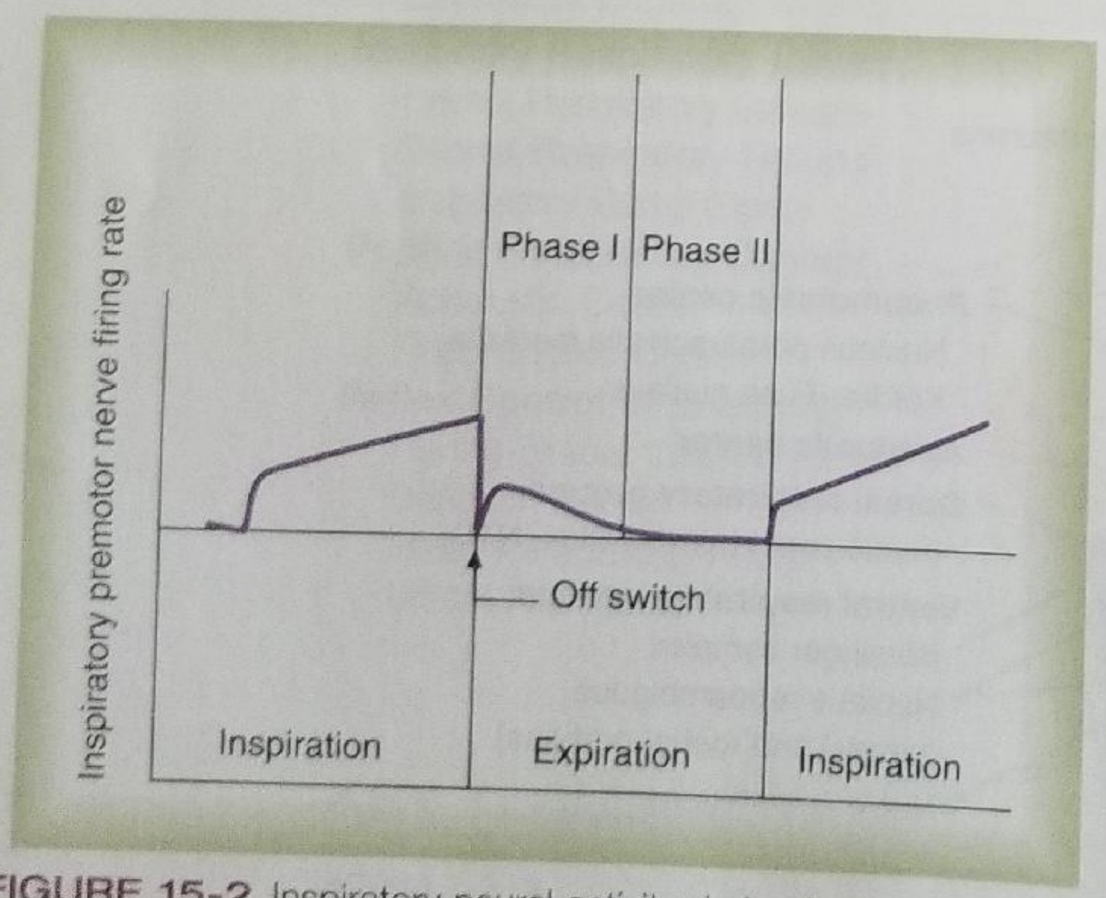

FIGURE 15-2 Inspiratory neural activity during breathing. Note the inspiratory ramp signal *(left)* and the braking action of inspiratory signals in the early part *(phase I)* of expiration. (Redrawn from Leff AR, Shumacher PT: Respiratory physiology: basics and applications, Philadelphia, 1993, Saunders.)

PONTINE RESPIRATORY CENTERS

If the brainstem is cut above the medulla (see Figure 15-1, *level III*), spontaneous respiration continues, although in an irregular pattern. The pons does not make breathing rhythmic; rather, it modifies the output of the medullary centers. Figure 15-1 shows two groups of neurons in the pons: (1) the apneustic center and (2) the pneumotaxic center.

Apneustic Center

The **apneustic center** does not occupy a well-defined anatomic location; its existence and function can be shown only if its connections to the higher pneumotaxic center and vagus nerves are severed. Under such circumstances, the DRG inspiratory neurons fail to switch off, causing prolonged inspiratory gasps interrupted by occasional expirations (**apneustic breathing**). Vagal and pneumotaxic center impulses hold the apneustic center's stimulatory effect on DRG neurons in check.

Pneumotaxic Center

The **pneumotaxic center** is a group of neurons located on both sides of the upper pons (see Figure 15-1). The pneumotaxic center controls the "off-switch" point of the inspiratory ramp, controlling inspiratory time. Strong pneumotaxic signals increase the respiratory rate, and weak signals prolong inspiration and increase tidal volumes. The exact nature of the interaction between the pneumotaxic and apneustic centers is poorly understood. They apparently work together to control the depth of inspiration.[3]

REFLEX CONTROL OF BREATHING

Hering-Breuer Inflation Reflex

The **Hering-Breuer inflation reflex,** described by Hering and Breuer in 1868, is generated by stretch receptors located in the smooth muscle of both large and small airways. When lung inflation stretches these receptors, they send inhibitory impulses through the vagus nerve to the DRG neurons, stopping further inspiration. In this way, the Hering-Breuer reflex has an effect similar to that of the pneumotaxic center. In adults, the Hering-Breuer reflex is activated only at large tidal volumes (≥800 to 1000 ml) and apparently is not an important control mechanism in quiet breathing.[2] This reflex is important, however, in regulating respiratory rate and depth during moderate to strenuous exercise.

Deflation Reflex

Sudden collapse of the lung stimulates strong inspiratory effort. This inspiratory effort may be the result of decreased stretch receptor activity, or it may be caused by the stimulation of other receptors, such as the irritant receptors and J-receptors (discussed later). Although it is unclear which receptors are involved, it is clear that the vagus nerve is the pathway (as it is for the Hering-Breuer reflex) and that the effect is hyperpnea.[1] The

deflation reflex is probably responsible for the hyperpnea observed with pneumothorax (air in the pleural space).

Head Paradoxical Reflex

In 1889, Head observed that if the Hering-Breuer reflex is blocked by cooling the vagus nerve, lung hyperinflation causes a further increase in inspiratory effort—the opposite of the Hering-Breuer reflex. The receptors for this reflex are called *rapidly adapting receptors* because they stop firing promptly after a volume change occurs. The Head reflex may help maintain large tidal volumes during exercise and may be involved in periodic deep sighs during quiet breathing. Periodic sighs help prevent alveolar collapse, or atelectasis. The Head reflex also may be responsible for the first breaths of a newborn.[1]

Irritant Receptors

Rapidly adapting irritant receptors in the epithelium of the larger conducting airways have vagal sensory nerve fibers. Their stimulation, whether by inhaled irritants or by mechanical factors, causes reflex bronchoconstriction, coughing, sneezing, tachypnea, and narrowing of the glottis. Some of these reflexes, called **vagovagal reflexes,** have both sensory and motor vagal components; they are responsible for laryngospasm, coughing, and slowing of the heartbeat. Endotracheal intubation, airway suctioning, and bronchoscopy readily elicit vagovagal reflexes. Physical stimulation of the conducting airways, as with suctioning or bronchoscopy, may cause a severe case of bronchospasm, coughing, and laryngospasm.

J-Receptors

C fibers in the lung parenchyma near the pulmonary capillaries are called *juxtacapillary receptors,* or **J-receptors.** Alveolar inflammatory processes (pneumonia), pulmonary vascular congestion (congestive heart failure), and pulmonary edema stimulate these receptors. This stimulation causes rapid, shallow breathing; a sensation of dyspnea; and expiratory narrowing of the glottis.

Peripheral Proprioceptors

Proprioceptors in muscles, tendons, and joints and pain receptors in muscles and skin send stimulatory signals to the medullary respiratory center. Such stimuli increase medullary inspiratory activity and cause hyperpnea.[4] For this reason, moving the limbs, slapping or splashing cold water on the skin, and other painful stimuli stimulate ventilation in patients with respiratory depression.

Proprioceptors in joints and tendons may be important in initiating and maintaining increased ventilation at the beginning of exercise. Passive limb movement around a joint increases breathing rate in both anesthetized animals and unanesthetized humans.[4]

Muscle Spindles

Muscle spindles in the diaphragm and intercostal muscles are part of a reflex arc that helps the muscles adjust to an increased load. Muscle spindles are sensing elements located on intrafusal muscle fibers, arranged parallel to the main extrafusal muscle fibers (Figure 15-3). The extrafusal fibers that elevate the ribs are innervated by motor fibers (alpha fibers) different from the fibers that innervate the intrafusal spindle fibers (gamma fibers). When the main extrafusal muscle fiber and the intrafusal fibers contract simultaneously, the sensing element *(spindle)* of the intrafusal muscle fiber stretches and sends impulses over spindle afferent nerves directly to the spinal cord (see Figure 15-3). The spindle's afferent (sensory) nerve synapses directly with the alpha motor neuron in the spinal cord, sending impulses back to the main extrafusal muscle. A single synapse reflex arc is created. Alpha motor neuron impulses cause the main extrafusal muscle fibers to contract with greater force, shortening the nearby intrafusal fibers. The stretch-sensitive spindle is thus unloaded, and its impulses cease. In this way, inspiratory muscle force adjusts to the load imposed by decreased lung compliance or increased airway resistance.

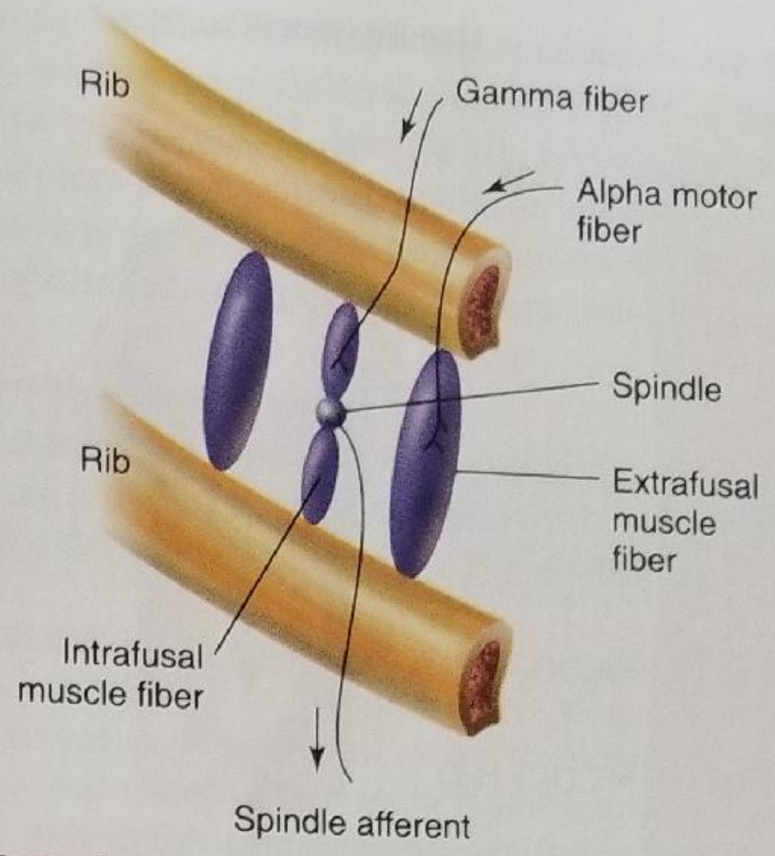

FIGURE 15-3 Stretch-sensitive muscle spindle located on the intrafusal fibers of intercostal muscles. Motor innervation for intrafusal fibers (gamma nerve fibers) is different than for extrafusal fibers (alpha nerve fibers). Spindle afferent nerve fibers synapse with alpha motor neurons in the spinal cord, creating a single synapse reflex arc.

CHEMICAL CONTROL OF BREATHING

The body maintains the proper amounts of oxygen (O_2), carbon dioxide (CO_2), and hydrogen ions (H^+) in the blood mainly by regulating ventilation. Physiologic mechanisms that monitor these substances in the blood allow ventilation to respond appropriately to maintain homeostasis. An increase in blood H^+ concentration stimulates specialized nerve structures called **chemoreceptors.** As a result, the chemoreceptors transmit impulses to the medulla, increasing ventilation. Centrally located chemoreceptors in the medulla respond to H^+, which normally arises from dissolved CO_2 in the cerebrospinal fluid (CSF). Peripherally located chemoreceptors in the fork of the common carotid arteries and the aortic arch are also sensitive

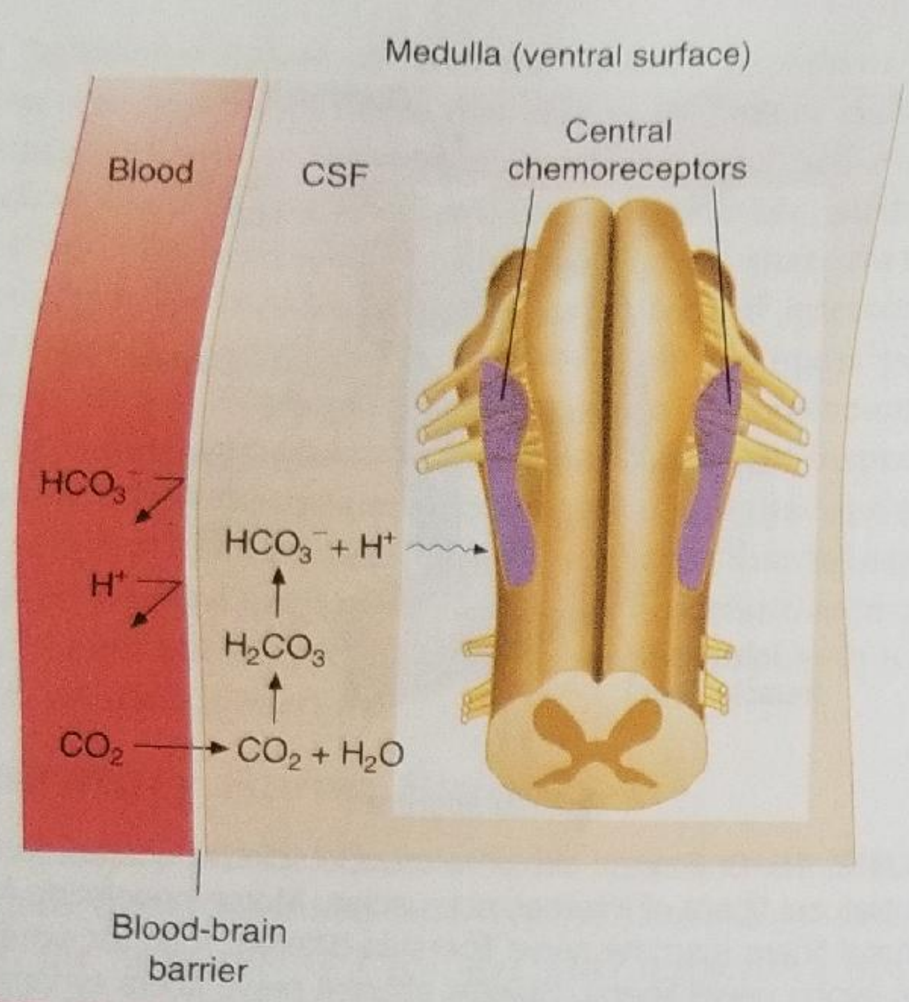

FIGURE 15-4 CO_2 stimulates the medullary chemoreceptors by forming H^+ in the cerebrospinal fluid (CSF). The blood-brain barrier is almost impermeable to H^+ and HCO_3^- but is freely permeable to CO_2. (Modified from Beachey W: Respiratory care anatomy and physiology: foundations for clinical practice, ed 2, St Louis, 2007, Mosby.)

to H^+ and indirectly to CO_2. These receptors are also indirectly sensitive to hypoxemia because hypoxemia increases the sensitivity of the peripheral chemoreceptors to H^+.[2]

Central Chemoreceptors

H^+ ions, not CO_2 molecules, stimulate highly responsive chemosensitive nerve cells, located on both sides of the medulla. Nevertheless, these central chemoreceptors are extremely sensitive to CO_2 in an indirect fashion. These chemoreceptors are not in direct contact with arterial blood (Figure 15-4). Instead, they are bathed in the CSF, separated from the blood by a semipermeable membrane called the **blood-brain barrier.** This membrane is almost impermeable to H^+ and HCO_3^-, but it is freely permeable to CO_2. When $PaCO_2$ increases, CO_2 diffuses rapidly through the blood-brain barrier into the CSF. In the CSF, CO_2 reacts with water (H_2O) to form H^+ and HCO_3^- (see Figure 15-4). The H^+ ions generated in this fashion stimulate the central chemoreceptors, which stimulate the medullary inspiratory neurons. In this way, $PaCO_2$ is indirectly the primary minute-to-minute controller of ventilation. CO_2 diffusing from the blood into the CSF increases $[H^+]$ almost instantly, exciting the chemoreceptors within seconds. Alveolar ventilation increases by approximately 2 to 3 L/min for each 1-mm Hg increase in $PaCO_2$.[5]

The stimulatory effect of chronically high CO_2 on the central chemoreceptors gradually declines over 1 or 2 days because the kidneys reabsorb HCO_3^- ions in response to respiratory acidosis, bringing the blood pH level back toward normal. The increased number of HCO_3^- ions in the blood eventually diffuses across the blood-brain barrier into the CSF, where they buffer H^+ and bring the CSF pH level back to normal. This activity removes the stimulus to the chemoreceptors, and ventilation decreases. Thus an acute increase in $PaCO_2$ has a powerful effect on ventilation, which is greatly weakened after 1 or 2 days of adaptation.

Peripheral Chemoreceptors

The peripheral chemoreceptors are small, highly vascular structures known as the *carotid* and *aortic bodies*. The carotid bodies are located bilaterally in the bifurcations of the common carotid arteries. The aortic bodies are found in the arch of the aorta. These neural structures increase their firing rates in response to increased arterial $[H^+]$ regardless of its origin (i.e., whether from fixed acid accumulation or increased CO_2). The carotid bodies send their impulses to the respiratory centers in the medulla via the glossopharyngeal nerve, whereas the aortic bodies send their impulses over the vagus nerve. The carotid bodies exert much more influence over the respiratory centers than the aortic bodies do, especially with respect to arterial hypoxemia and acidemia.[1]

Because the carotid bodies receive an extremely high rate of blood flow, they have little time to remove O_2 from the blood. Therefore venous blood leaving the carotid bodies has almost the same O_2 content as the arterial blood entering them. The carotid bodies are exposed at all times to arterial blood, not venous blood, and they sense arterial (not venous) $[H^+]$.

Response to Decreased Arterial Oxygen

Traditionally, it was believed that the carotid bodies directly sense low PaO_2, implying that arterial hypoxemia is an independent stimulus to breathe—the so-called *hypoxic drive*. Although the peripheral chemoreceptors fire more frequently in the presence of arterial hypoxemia, they do so only because hypoxemia makes them more sensitive to H^+.[2] In other words, when PaO_2 is low, carotid body sensitivity to a given $[H^+]$ increases; in this way, hypoxia increases ventilation for any given pH. On the other hand, elevated PaO_2 (hyperoxia) decreases carotid body sensitivity to $[H^+]$. The carotid bodies respond to arterial hypoxemia only because hypoxia makes them more sensitive to $[H^+]$. This means that if the arterial $[H^+]$ is extremely low (high pH), as in severe alkalemia, hypoxemia has little effect on the carotid bodies.[2] Simply stated, the ultimate effect of hypoxemia is to increase the sensitivity of the peripheral chemoreceptors to the given blood $[H^+]$, which increases their firing rate and brings about increased ventilation.

Because of their extremely high blood flow rates, the carotid bodies respond to decreased arterial *partial pressure* of O_2 (in the indirect way just described) rather than to an actual decrease in arterial O_2 *content*. That is, the amount of O_2 the carotid bodies extract from each unit of rapidly flowing blood is so small that their O_2 needs are met entirely by dissolved O_2 in the plasma—which depends on the PaO_2. This is why conditions associated with low arterial O_2 content but normal PaO_2 (e.g., anemia and carbon monoxide poisoning) do not stimulate ventilation.[5]

When pH and $PaCO_2$ are normal (pH = 7.40 and $PaCO_2$ = 40 mm Hg), the nerve-impulse transmission rate of the carotid bodies does not increase significantly until the PaO_2 decreases to approximately 60 mm Hg.[5] If PaO_2 decreases further from 60 mm Hg to 30 mm Hg, the rate of impulse transmission increases sharply because hypoxemia makes the carotid bodies much more sensitive to a pH of 7.40. A decrease in PaO_2 from 60 mm Hg to 30 mm Hg corresponds to the sharpest decrease in O_2 content on the O_2-Hb equilibrium curve (i.e., the steepest part of the curve). Arterial hypoxemia does not stimulate ventilation greatly until the PaO_2 decreases to less than 60 mm Hg.

O_2 plays no role in the drive to breathe in healthy individuals at sea level. High altitude causes a healthy person's ventilation to increase because low barometric pressure decreases the inspired PO_2 and the arterial PO_2, which increases the sensitivity of peripheral chemoreceptors to their H^+ environment. The resulting increase in ventilation is less than expected, however, because hyperventilation decreases $PaCO_2$ and increases arterial pH. The increased pH depresses the medullary respiratory center, counteracting the excitatory effect of a low PaO_2 on peripheral chemoreceptors. Hypoxemia-induced hyperventilation may be impossible in certain conditions, such as severe chronic obstructive pulmonary disease (COPD), in which lung mechanics are so deranged that the stimulatory effect of hypoxemia on ventilation fails to decrease $PaCO_2$ regardless of the patient's effort. In such instances, there is no alkalosis to counteract the stimulatory effects of hypoxemia on ventilation.

RULE OF THUMB

Hypoxemia is not associated with an increased drive to breathe until PaO_2 is less than 60 mm Hg, after which the drive to breathe increases proportionally with the decrease in PaO_2.

Response to Increased $PaCO_2$ and Hydrogen Ions

For a given increase in $PaCO_2$ or $[H^+]$, the carotid bodies are less responsive than the central chemoreceptors. The peripheral chemoreceptors account for only 20% to 30% of the ventilatory response to hypercapnia.[5] However, they respond to increased arterial $[H^+]$ more rapidly than the central chemoreceptors. The explanation is that, in contrast to the central chemoreceptors, the carotid bodies are exposed directly to arterial blood. The body's initial ventilatory response to metabolic acidosis is fairly quick, even though H^+ crosses the blood-brain barrier with difficulty.

As stated earlier, hypoxemia increases the sensitivity of the peripheral chemoreceptors to H^+ and indirectly to $PaCO_2$. Conversely, high PaO_2 (hyperoxia) *decreases* the peripheral chemoreceptors' PCO_2 sensitivity to almost zero.[2] This means that when the PaO_2 is high, the ventilatory response to $PaCO_2$ is mainly due to the central chemoreceptors, which are unaffected by hypoxemia.

Because the only effect of hypoxia on the peripheral chemoreceptors is to increase their sensitivity to arterial $[H^{++}]$—and indirectly to $PaCO_2$—the following statements are true: (1) High PO_2 renders the peripheral chemoreceptors almost unresponsive to PCO_2, and (2) low $PaCO_2$ renders the peripheral chemoreceptors almost unresponsive to hypoxemia.[2] Coexisting arterial hypoxemia, acidemia, and high $PaCO_2$ (i.e., asphyxia) maximally stimulate the peripheral chemoreceptors.

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Delayed Hyperventilation at High Altitude

PROBLEM: If a person ascends to an elevation of 10,000 feet above sea level, his or her inspired PO_2 decreases because of low barometric pressure; this excites the peripheral chemoreceptors and causes an increase in ventilation. Why must a day or so pass at this altitude before ventilation increases to its maximal level?

SOLUTION: Hypoxia-induced hyperventilation reduces $PaCO_2$ and creates alkalemia. This condition produces an alkalotic CSF because the blood-brain barrier is nearly impermeable to HCO_3^- ions; that is, as CO_2 diffuses out of the CSF in response to the low arterial blood PCO_2, HCO_3^- remains behind in the CSF. The central chemoreceptors are exposed to an alkalotic environment, diminishing the effect of the hypoxic ventilatory stimulus on peripheral chemoreceptors. In other words, the development of respiratory alkalosis limits the degree of hypoxia-induced hyperventilation. Over the first 24 hours or so of hyperventilation, HCO_3^- gradually diffuses out of the CSF across the blood-brain barrier, restoring the CSF pH level to normal. In addition, the kidneys excrete HCO_3^- to compensate for the respiratory alkalemia. Consequently, the blood pH level decreases toward normal, and the hypoxic ventilatory stimulus keeps the $PaCO_2$ low. As the CSF pH level returns to normal, the progressively unrestrained hypoxic stimulus increases ventilation further. It takes approximately 24 hours of high-altitude exposure before ventilation increases to its maximal level.

Individuals with chronic hypercapnia secondary to advanced COPD have depressed ventilatory responses to acute increases in arterial CO_2, partly because of their altered acid-base status and partly because their deranged lung mechanics prevents them from increasing their ventilation adequately.[1] The altered acid-base status arises from the preexisting high levels of blood buffer base, a compensatory response to chronic respiratory acidosis (see Chapter 14).

RULE OF THUMB

The ventilatory response to hypoxemia is greatly enhanced by hypercapnia and acidemia.

Control of Breathing in Chronic Hypercapnia

A sudden increase in arterial PCO_2 causes an immediate increase in ventilation because CO_2 rapidly diffuses from the blood into

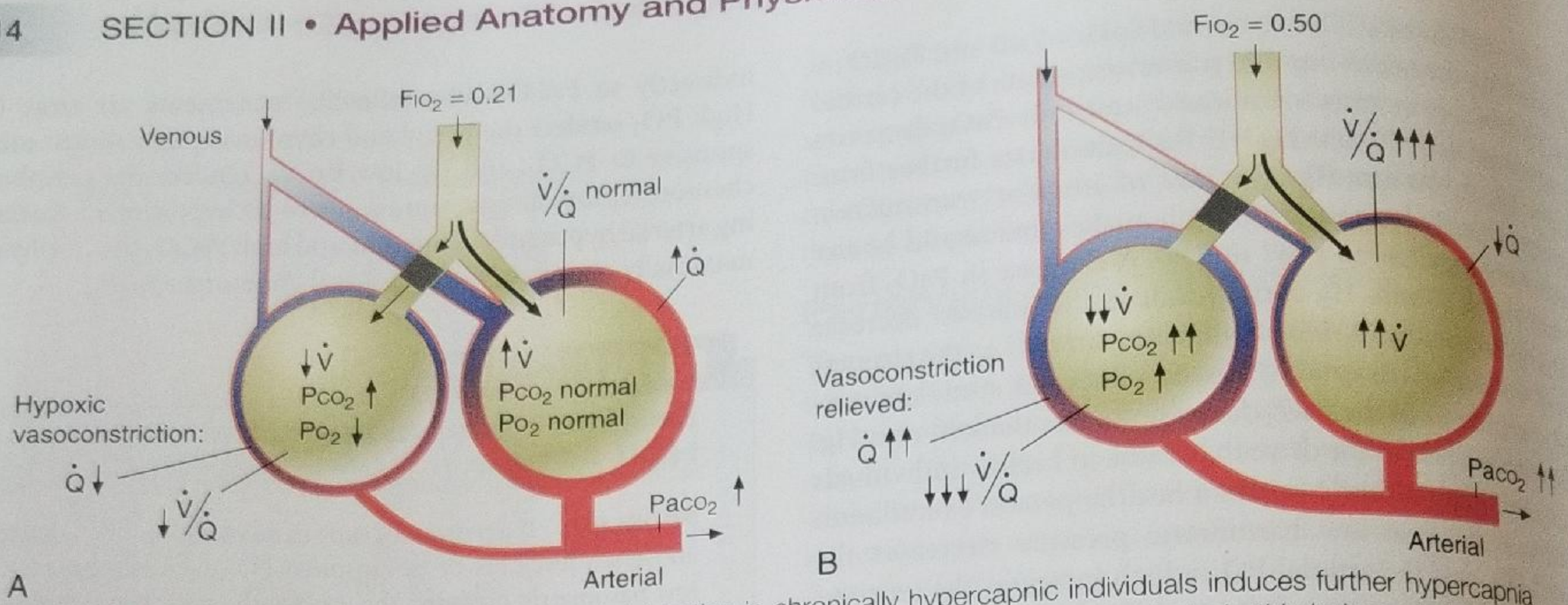

FIGURE 15-5 Proposed mechanism whereby O_2 administration in chronically hypercapnic individuals induces further hypercapnia by creating $\dot{V}/\dot{Q}$ mismatches. **A,** Low $\dot{V}/\dot{Q}$ unit *(left)* is hypoxic and hypercapnic while breathing ambient air; this induces pulmonary vasoconstriction. **B,** Breathing 50% O_2 predisposes the poorly ventilated unit to absorption atelectasis, further decreasing its ventilation, and simultaneously relieves hypoxic vasoconstriction, increasing its blood flow. These events (1) lower the poorly ventilated unit's $\dot{V}/\dot{Q}$ ratio further and (2) divert blood flow away from and ventilation toward already well-ventilated units. The latter increases alveolar dead space (high $\dot{V}/\dot{Q}$). (Modified from Beachey W: Respiratory care anatomy and physiology: foundations for clinical practice, ed 2, St Louis, 2007, Mosby.)

the CSF, increasing the $[H^+]$ surrounding central chemoreceptors. If $PaCO_2$ increases gradually over many years, as might occur in the development of severe COPD and worsening lung mechanics, the kidneys compensate by increasing the plasma $[HCO_3^-]$, which keeps arterial pH within normal limits. As plasma HCO_3^- levels increase, HCO_3^- ions slowly diffuse across the blood-brain barrier, keeping CSF pH within its normal range. Because the central chemoreceptors respond to $[H^+]$, not the CO_2 molecule, they sense a normal pH environment, even though the $PaCO_2$ is abnormally high.

This adaptation explains why the chronically high $PaCO_2$ of people with severe COPD does not overly stimulate their ventilation. Instead, the hypoxemia that accompanies chronic hypercapnia becomes a major part of the minute-to-minute breathing stimulus in the roundabout way discussed previously; hypoxemia increases the sensitivity of the peripheral chemoreceptors to $[H^+]$, increasing the nerve impulses they transmit to the medulla, which stimulates ventilation. Patients with severe COPD are invariably hypoxemic when breathing room air because their lungs have ventilation and blood flow mismatches. It stands to reason that breathing supplemental O_2 would increase the PaO_2 and make the carotid bodies less sensitive to $[H^+]$, which would decrease ventilation further and increase the $PaCO_2$.

Oxygen-Associated Hypercapnia

The $PaCO_2$ of chronically hypercapnic patients with COPD sometimes increases acutely after these patients are given supplemental O_2. The reason for this phenomenon has been a subject of much debate and misunderstanding. The traditional explanation for this phenomenon has been that O_2 breathing removes the hypoxic ventilatory stimulus and induces hypoventilation, but this explanation is probably overly simplified. The reduction in minute ventilation after O_2 breathing in patients with advanced COPD is generally severe enough to account for the increased $PaCO_2$. The most significant reason for hypercapnia following O_2 breathing in severe COPD is that it worsens the ventilation-perfusion ($\dot{V}/\dot{Q}$) relationships in the lungs.

When patients with severe COPD breathe supplemental O_2 it abolishes the hypoxic pulmonary vasoconstriction present in poorly ventilated lung regions. As a result, vascular resistance of underventilated regions decreases, and these areas receive more blood flow, drawing blood away from well-ventilated regions (Figure 15-5). At the same time that poorly ventilated regions receive more blood flow, they become even less ventilated as O_2-rich inspired gas washes out resident nitrogen gas, making these alveoli more subject to absorption atelectasis (i.e., O_2 may be absorbed by the pulmonary circulation more rapidly than the slowed ventilation can replenish it—notice the further decreased $\dot{V}$ in Figure 15-5, *B*). As a result, inspired gas flows preferentially to the compliant, already well-ventilated alveoli (see Figure 15-5, *B*), increasing their $\dot{V}/\dot{Q}$. The increased $\dot{V}/\dot{Q}$ in these alveoli is exaggerated further as a greater proportion of the cardiac output than before is redirected to poorly ventilated alveoli, because their vascular resistance was reduced by O_2 breathing.

To summarize, O_2 breathing causes more blood flow to be directed to poorly ventilated alveoli, which takes blood flow away from well-ventilated alveoli. The key point is that already underventilated alveoli receive additional blood flow, which causes blood PCO_2 to increase further. These events can occur without a decrease in overall minute ventilation.

It is important to keep in mind that the diagnosis of COPD on a patient's medical record does not mean the patient has chronically high $PaCO_2$ or that O_2 administration may be associated with hypercapnia. These characteristics are present only in severe end-stage disease, which includes only a small percentage of patients with a COPD diagnosis. Concern ab

(Unassociated hypercapnia and acidemia is not justifiable in most patients with a diagnosis of COPD. O_2 should never be withheld from acutely hypoxemic patients with COPD for fear of inducing hypoventilation and hypercapnia. Tissue oxygenation is the overriding priority; O_2 must never be withheld from exacerbated, hypoxemic patients with COPD for any reason. The clinician must be prepared to support ventilation mechanically if O_2 administration is accompanied by severe hypoventilation.

Central Chemoreceptor Response to Acute Carbon Dioxide Increase in Chronic Hypercapnia

As discussed earlier, the kidneys compensate for the acidic effects of chronic hypercapnia by increasing the plasma HCO_3^- level, keeping the medullary chemoreceptor pH environment in the normal range. This does not mean that the medullary chemoreceptors cannot respond to further *acute* increases in $PaCO_2$. A sudden elevation in $PaCO_2$ immediately crosses the blood-brain barrier into the CSF, generating H^+ that then stimulates the medullary chemoreceptors. The resulting ventilatory response is depressed, however, for chemical and mechanical reasons: (1) The blood's increased buffering capacity (high HCO_3^- level) in chronic hypercapnia prevents arterial pH from decreasing as sharply as it would in normal conditions, and (2) abnormal breathing mechanics hamper the lung's ability to increase ventilation appropriately. To illustrate the blood's changed buffering capacity, compare a healthy person (pH = 7.40, $PaCO_2$ = 40 mm Hg, HCO_3^- = 24 mEq/L) with a chronically hypercapnic person (pH = 7.38, $PaCO_2$ = 60 mm Hg, HCO_3^- = 34 mEq/L). A sudden increase of 30 mm Hg in $PaCO_2$ of both individuals causes the healthy person's arterial pH to decrease to 7.21 and the hypercapnic person's pH to decrease to only 7.24. (These values are calculated using the Henderson-Hasselbalch equation, assuming a 1-mEq/L increase in plasma HCO_3^- concentration for each acute increase of 10 mm Hg in $PaCO_2$.) The central chemoreceptors of a chronically hypercapnic patient experience less stimulation than the central chemoreceptors of normal individuals for the same increase in $PaCO_2$.

RULE OF THUMB

Tissue oxygenation is of overriding importance and must not be sacrificed because of concern about hypercapnia and acidemia in a patient with exacerbated COPD.

VENTILATORY RESPONSE TO EXERCISE

Strenuous exercise can increase CO_2 production and O_2 consumption by 20-fold.[3] Ventilation normally keeps pace with CO_2 production, keeping $PaCO_2$, PaO_2, and arterial pH constant. Because arterial blood gases do not change during normal exercise, some other mechanism must be responsible for the increased ventilation in healthy individuals during exertion.

The exact mechanism responsible for this increase in ventilation is not well understood. Especially mysterious is the abrupt increase in ventilation at the onset of exercise, long before any chemical or humoral changes can occur in the body. Two predominating theories for this phenomenon are: (1) When the cerebral motor cortex sends impulses to exercising muscles, it apparently sends collateral excitatory impulses to the medullary respiratory centers; (2) exercising limbs moving around their joints stimulate proprioceptors, which transmit excitatory impulses to the medullary centers.[1,3] Evidence also suggests that the sudden increase in ventilation at the onset of exercise is a learned response.[1,3] With repeated experience, the brain may learn to anticipate the proper amount of ventilation required to maintain normal blood gases during exercise.

ABNORMAL BREATHING PATTERNS

Commonly described abnormal breathing patterns include Cheyne-Stokes respiration, Biot respiration, apneustic breathing, and central neurogenic hypoventilation and hyperventilation. In **Cheyne-Stokes respiration,** respiratory rate and tidal volume gradually increase and then gradually decrease to complete **apnea** (absence of ventilation), which may last several seconds. Tidal volume and breathing frequency gradually increase again, repeating the cycle. This pattern occurs when cardiac output is low, as in congestive heart failure, delaying the blood transit time between the lungs and the brain.[4] In this instance, changes in respiratory center PCO_2 lag behind changes in arterial PCO_2.

For example, when an increased $PaCO_2$ from the lungs reaches the respiratory neurons, ventilation is stimulated; this lowers the $PaCO_2$ level. By the time the reduced $PaCO_2$ reaches the medulla to inhibit ventilation, hyperventilation has been in progress for an inappropriately long time. When blood from the lung finally does reach the medullary centers, the low $PaCO_2$ greatly depresses ventilation to the point of apnea. $PaCO_2$ increases, but an increase in respiratory center PCO_2 is delayed because of low blood flow rate. The brain eventually does receive the high $PaCO_2$ signal, and the cycle is repeated. Cheyne-Stokes respiration may also be caused by brain injuries in which the respiratory centers over-respond to changes in the PCO_2 level.

Biot respiration is similar to Cheyne-Stokes respiration except that tidal volumes are of identical depth. It occurs in patients with increased intracranial pressure (ICP), but the mechanism for this pattern is unclear.[4]

Apneustic breathing indicates damage to the pons. Central neurogenic hyperventilation is characterized by persistent hyperventilation driven by abnormal neural stimuli. It is related to midbrain and upper pons damage associated with head trauma, severe brain hypoxia, or lack of blood flow to the brain.[6] Conversely, central neurogenic hypoventilation means the respiratory centers do not respond appropriately to ventilatory stimuli, such as CO_2. It also is associated with head trauma and brain hypoxia as well as narcotic suppression of the respiratory center.[6]

CARBON DIOXIDE AND CEREBRAL BLOOD FLOW

CO_2 plays an important role in regulating cerebral blood flow. Its effect is mediated through the formation of H^+ by CO_2.[7] Increased PCO_2 dilates cerebral vessels, increasing cerebral blood flow, whereas decreased PCO_2 constricts cerebral vessels and reduces cerebral blood flow. In patients with traumatic brain injury (TBI), the brain swells acutely; this increases the ICP in the rigid skull to such high levels that blood supply to the brain might be cut off, causing cerebral hypoxia *(ischemia)*. That is, high ICP may exceed cerebral arterial pressure and stop blood flow to the brain.

Although controversial, mechanical hyperventilation has been used for many years in selected patients with TBI to decrease $PaCO_2$ and reduce the cerebral blood flow and ICP. In patients with TBI, a cerebral blood volume reduction of only 0.5 to 0.7 ml reduces the ICP by 1 mm Hg; for every 1-mm Hg acute reduction in $PaCO_2$ (between 20 mm Hg and 60 mm Hg), there is a 3% reduction in cerebral blood flow. Although an acute reduction in $PaCO_2$ reduces ICP, it also reduces cerebral blood flow and potentially causes cerebral ischemia. For this reason, the practice of inducing mechanical hyperventilation in patients with TBI is debatable primarily because it may well reduce blood flow and O_2 to an injured organ. On the other end of the spectrum; however, *hypoventilation* in a head trauma patient with an already high ICP is especially dangerous because hypercapnia dilates cerebral vessels and elevates the ICP even more.

The debate centers around the question of whether a hyperventilation-induced decrease in cerebral blood flow creates an additional hypoxic insult to the already ischemic brain and whether patients managed in this way have better clinical outcomes than patients in whom hyperventilation is not instituted. A comprehensive review of the subject published in 2005 concluded that hyperventilation produced no advantage in long-term clinical outcome of TBI compared with ventilation that maintained $PaCO_2$ in the normal range.[7] The authors concluded that in TBI, hyperventilation therapy should be considered only for patients with high ICPs; no benefit can be expected if ICP is normal. They further concluded that hyperventilation is most appropriate in the second or third day after injury because cerebral blood flow is lowest in the first 24 hours after injury, and the risk for inducing ischemia through hyperventilation is greatest during this time. The authors advise against the hyperventilation of patients with TBI to $PaCO_2$ less than 30 mm Hg because of the increased danger of cerebral ischemia. Finally, hyperventilation is effective for only approximately 24 to 48 hours because compensatory renal elimination of HCO_3^- in the face of alkalemia restores the acid-base balance, negating the vasoconstrictive effect of hypocapnia. In any case, *hypoventilation* in patients with head trauma and increased ICP is especially dangerous because hypercapnia dilates cerebral vessels and increases ICP further. Even opponents of hyperventilation generally maintain $PaCO_2$ of patients with TBI in the low to normal range at approximately 35 mm Hg.[8]

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Mechanical Hyperventilation of a Patient With Traumatic Brain Injury

PROBLEM: An automobile accident victim, previously healthy, sustained a closed head injury with accompanying high ICP. Mechanical ventilation in the intensive care unit is required, and the physician asks the RT for input regarding ventilator strategies and what $PaCO_2$ should be targeted?

DISCUSSION: More than 40 years ago, clinical investigation showed that the volume of the swollen brain could be reduced by decreasing the $PaCO_2$. Since then, mechanical hyperventilation has been a cornerstone in managing increased ICP associated with TBI.[7] Hyperventilation decreases ICP by causing cerebral vasoconstriction, ultimately reducing cerebral blood volume. This subject is not without controversy because hyperventilation-induced cerebral vasoconstriction has the potential to reduce cerebral blood flow to levels that cause cerebral hypoxia *(ischemia)*. This concern has dampened enthusiasm for hyperventilation in TBI. Both the proponents and the opponents of hyperventilation recognize that TBI poses an ischemic threat to the brain; proponents believe that the reduction of cerebral blood flow ultimately improves cerebral oxygenation by reducing the ICP, which helps sustain the cerebral perfusion pressure. Opponents point out that no other hypoxic organ in the body is treated by reducing its blood flow and O_2 supply. (Hyperventilation in this context is generally defined as $PaCO_2 < 35$ mm Hg.[7])

SUMMARY CHECKLIST

- The DRGs and VRGs of neurons in the medulla generate the basic cyclic breathing pattern.
- Apneustic center impulses prevent medullary inspiratory neurons from switching off, creating a prolonged, gasping inspiration.
- Impulses from the pneumotaxic center inhibit the apneustic center and inspiratory neurons of the DRGs, shortening inspiratory time and increasing respiratory rate.
- Various reflexes from peripheral sources affect the breathing pattern by altering the output of the medullary center.
- Central chemoreceptors in the medulla are bathed in the CSF, separated from arterial blood by a semipermeable membrane called the *blood-brain barrier*.
- The blood-brain barrier is almost impermeable to arterial H^+ and HCO_3^- ions, but it is freely permeable to arterial CO_2.
- Central chemoreceptors stimulate increased ventilation in response to the H^+ formed in the CSF by the reaction between arterial CO_2 and H_2O.
- Peripheral chemoreceptors, located mainly in the carotid bodies, respond to arterial $[H^+]$; hypoxemia increases the sensitivity of chemoreceptors to a given arterial pH.
- The peripheral chemoreceptors are indirectly stimulated by arterial CO_2 to the extent that CO_2 reacts with H_2O to form H^+.

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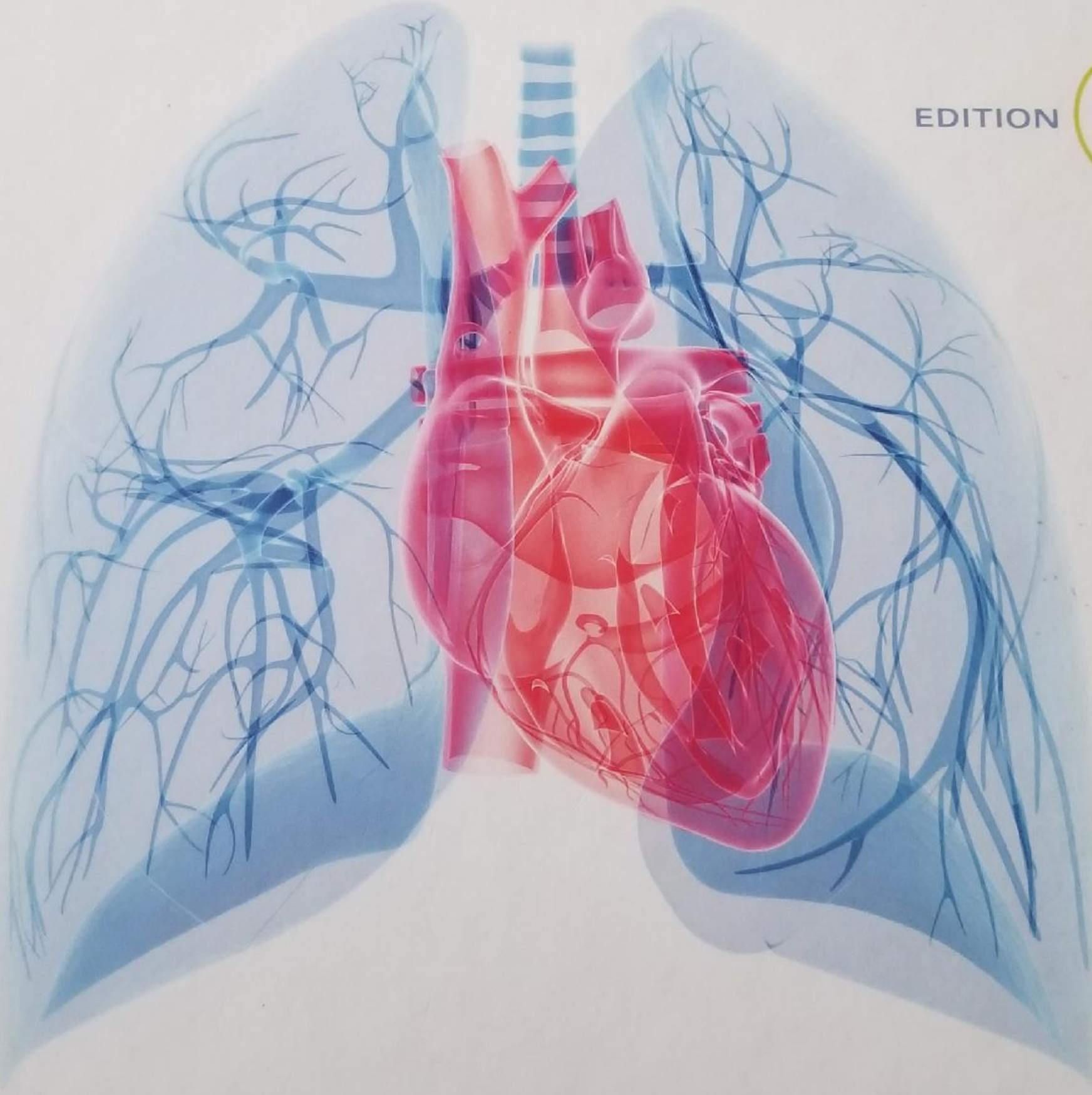

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EGAN'S FUNDAMENTALS OF RESPIRATORY CARE, ELEVENTH EDITION ISBN: 978-0-323-34136-3

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Library of Congress Cataloging-in-Publication Data

Egan's fundamentals of respiratory care / [edited by] Robert M. Kacmarek, James K. Stoller, Albert J. Heuer ; consulting editors, Robert L. Chatburn, Richard H. Kallet.—Eleventh edition.
p. ; cm.
Fundamentals of respiratory care
Includes bibliographical references and index.
ISBN 978-0-323-34136-3 (hardcover : alk. paper)
I. Kacmarek, Robert M., editor. II. Stoller, James K., editor. III. Heuer, Albert J., editor. IV. Chatburn, Robert L., editor. V. Kallet, Richard H., editor. VI. Title: Fundamentals of respiratory care.
[DNLM: 1. Respiratory Therapy–methods. 2. Respiratory Tract Diseases–therapy. WF 145]
RM161
615.8′36–dc23

2015036692

Content Strategist: Sonya Seigafuse
Content Development Manager: Billie Sharp
Content Development Specialist: Heather Yocum
Publishing Services Manager: Catherine Jackson
Senior Project Manager: Rachel E. McMullen
Design Direction: Renee Duenow

Printed in Canada

Last digit is the print number: 9 8 7 6 5 4 3 2 1

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