

Section 1
NORMAL STRUCTURE AND FUNCTION

FPO

Chapter 6
Control of Ventilation and
Respiratory Muscles

Theodoros Vassilakopoulos

The respiratory muscles are the only muscles, along with the heart, that must work continuously, although intermittently, to sustain life. They have to repetitively move a rather complex elastic structure, the thorax, to achieve the entry of air into the lungs and thence effect gas exchange. The presence of multiple muscle groups in this system mandates that these muscles interact properly to perform their task despite their differences in anatomic location, geometric orientation, and motor innervation. They also should be able to adapt to a variety of working conditions and respond to many different chemical and neural stimuli.

This chapter describes some aspects of respiratory muscle function that are relevant to current understanding of the way these muscles accomplish the action of breathing and how their function is controlled by the respiratory centers located in the central nervous system.

THE RESPIRATORY CENTERS

Early studies of the neural control of breathing involved the section and ablation of various brain stem structures. From these studies emerged the classical description of the neural control of breathing that required centers in the medulla for the rhythmic generation of ventilatory drive plus additional areas in the pons (traditionally known as the pneumotaxic and apneustic centers) that modulated and regulated the basic rhythm. Nowadays, the very complex and inadequately explored and understood respiratory center structure and function can be summarized as follows (Figure 6-1):

- Primary centers responsible for the generation of respiratory rhythm are located in the medulla. Within the medulla, there are two bilateral aggregations of neurons having respiratory related activity.
 - The *dorsal respiratory group* (DRG) neurons are primarily inspiratory (firing on inspiration) and are located in the nucleus tractus solitarius (NTS). These neurons project contralaterally to the phrenic and intercostal motor neurons in the spinal cord and provide the primary stimulus for respiration. In addition, this region is the recipient of important afferent stimuli, most notably from peripheral and central chemoreceptors and from receptors in the lung. Many connections are present between the dorsal and ventral groups of neurons.
 - The *ventral respiratory group* (VRG) consists of a long column of respiratory neurons, some of which are

inspiratory (firing on inspiration) and some of which are expiratory (firing on expiration). It contains the nucleus ambiguus, which contains primarily inspiratory neurons that project to the larynx, pharynx, and tongue. Stimulation of these neurons causes dilation of the upper airways, which minimizes airway resistance during inspiration. The VRG connects polysynaptically, with inspiratory motor neurons in the thorax at T1 to T12 that transmit the drive to external intercostal muscles, and polysynaptically, with expiratory motor neurons in the thorax and abdomen that supply expiratory muscles such as the internal intercostal and abdominal muscles.

- An area of the ventrolateral medulla next to the nucleus ambiguus, the pre-Bötzinger complex, is hypothesized to be a critical site for respiratory rhythmogenesis. Current theory proposes that a group of pacemaker neurons depolarize, fire, and repolarize in a rhythmic fashion. This endogenous oscillatory activity can be modulated by afferent inputs, generating an efferent output that is translated into the respiratory drive. Apart from the pre-Bötzinger complex principally involved in controlling inspiratory motor activity, the retrotrapezoid-parafacial respiratory group (RTN/pFRG) appears to play at least a modulatory role and may be a conditional oscillator that controls active expiration.
- An additional mechanism is voluntary control of the respiratory muscles, signals for which originate in the motor cortex and pass directly to the spinal motor neurons by way of the corticospinal tracts. The medullary respiratory control center is bypassed. The voluntary control competes with automatic control at the level of the spinal motor neuron.

AFFERENT INPUTS TO THE RESPIRATORY CENTERS

The respiratory controller receives information from a variety of sources. Some of these involve the relatively straightforward chemoreceptor signals that provide closed-loop information on the gas exchange functions of the lung. These signals arise mainly from the central and peripheral chemoreceptors that mediate the response to hypoxia, hypercapnia, and acidemia. In addition, at any given time, many other inputs from the upper airways, the lung, the respiratory muscles, and the thoracic cage may be important in determining ventilatory drive (Figure 6-2). The states of cortical arousal, sleep, and emotion play important roles in the level of ventilation and the response to other stimuli.

6-2 Section 1 NORMAL STRUCTURE AND FUNCTION

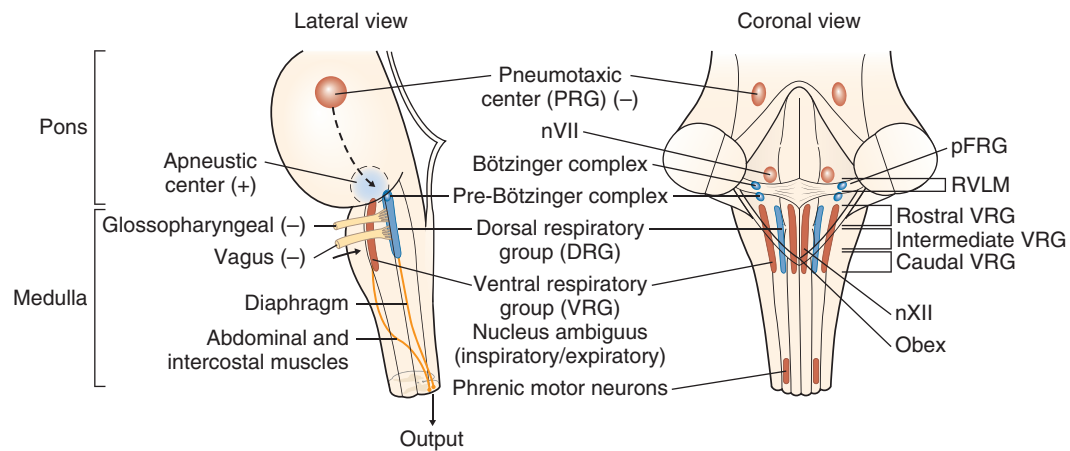


Figure 6-1 The respiratory centers. *nVII*, nucleus of cranial nerve VII; *pFRG*, retrotrapezoid-parafacial respiratory group; *RVLM*, rostral ventrolateral medulla.

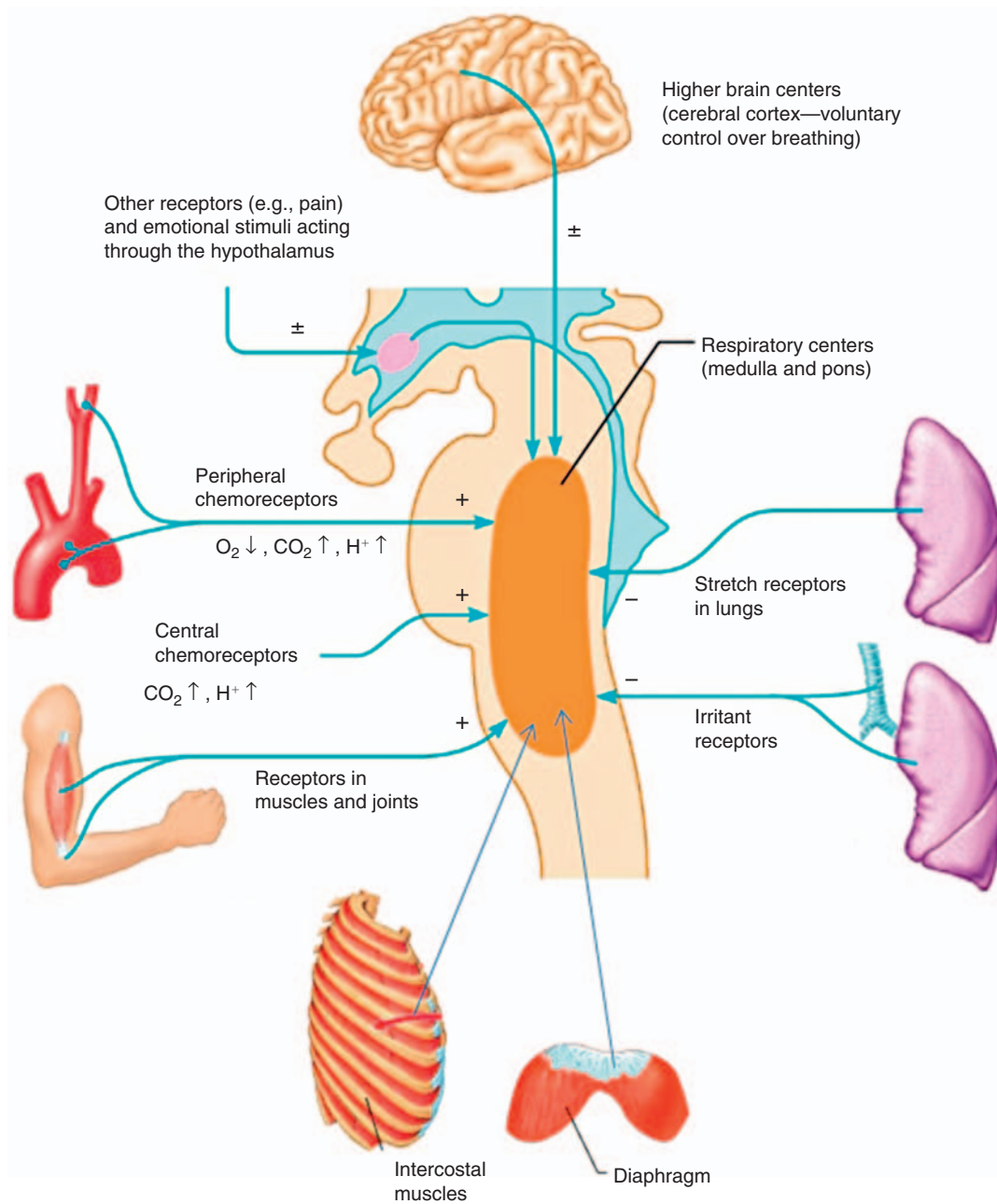


Figure 6-2 Input to the respiratory centers. The respiratory centers receive afferent information from the central and peripheral chemoreceptors, and from various receptors located in the respiratory system and other parts of the body, and input from higher brain centers.

CENTRAL CHEMORECEPTORS

1 Central chemoreception involves neurons (and glia) at many sites within the hindbrain, including, but not limited to, the retrotrapezoid nucleus (glutamatergic neurons), the medullary raphe (serotonergic neurons), the locus ceruleus (noradrenergic neurons), the nucleus tractus solitarius, the lateral hypothalamus (orexin neurons), and the caudal ventrolateral medulla. Central chemoreception also has an important nonadditive interaction with afferent information arising at the peripheral chemoreceptors (carotid body). The exact role of each area and its relative importance may vary depending on the condition (e.g., sleep versus wakefulness) and is currently not definitely established. The central chemoreceptors respond to either local increases in CO_2 or decreases in pH. However, because the chemoreceptors are located on the brain side of the blood-brain barrier and H^+ ions do not readily cross this barrier, the central chemoreceptors are much more sensitive to increases in PaCO_2 than to decreases in blood pH. The central chemoreceptors are not sensitive to blood PO_2 .

PERIPHERAL CHEMORECEPTORS

The peripheral chemoreceptors include the carotid bodies and the aortic bodies. The carotid bodies are much more important than the aortic bodies in humans. The peripheral chemoreceptors are sensitive to both hypoxia and hypercapnia or acidosis. The site of chemoreception in the carotid body is the type I glomus cells; the type II cells play more of a supporting role, similar to that of glial cells. The hypoxic response causes a sharp increase in firing rate of the carotid sinus nerve when the PaO_2 is lowered below 60 mm Hg. Signal transduction involves the depolarization of the type I cells (by closing a potassium channel that normally is open at resting membrane potential). After the transduction in the type I cells, the signal is transmitted to the carotid sinus nerve endings. Rather than there being a single neurotransmitter, multiple inhibitory and excitatory neurochemicals function both as classical neurotransmitters and also as neuromodulators. Dopamine is abundant in type I cells but seems to be an inhibitory neurotransmitter. Adenosine triphosphate (ATP), by contrast, functions as the primary excitatory neurotransmitter, perhaps coreleased with acetylcholine.

The Hypercapnic Ventilatory Response

CO_2 is the most important factor in the control of ventilation under normal circumstances. The PaCO_2 is held very close to 40 mm Hg (6.5 kPa) during the course of daily activity with periods of rest and exercise. During sleep, it may vary a little more. Increasing PaCO_2 acts through a negative feedback loop to increase alveolar ventilation.

Both the central and peripheral chemoreceptors respond to hypercapnia. The carotid body provides about 20% to 30% of the total hypercapnic response. This response is fast, with a time constant of 10 and 30 seconds. The central chemoreceptor response accounts for about 70% to 80% of the total hypercapnic response but is slower, with a time constant in the range of 60 to 150 seconds. This slow central response requires 5 to 6 minutes of hypercapnia to reach steady-state ventilation. Steady-state ventilation has an apparently linear relationship to increasing PaCO_2 (normal values for the hypercapnic ventilatory response slope range between 1 and 2 L/minute/mm Hg). Hypoxia augments the hypercapnic response by shifting the CO_2 response curve to the left and increasing its slope. A

number of factors can influence the response to CO_2 (e.g., drugs, sleep-wakefulness).

The Hypoxic Ventilatory Response

The hypoxic ventilator response is due almost solely to the carotid bodies. Very little ventilatory response occurs until the arterial oxygen is lowered below 60 mm Hg (7.9 kPa), and then there is a sharp increase, just as in the firing rate of the carotid sinus nerve. Hypercapnia greatly augments the hypoxic response. Hypoxia and hypercapnia interact at the level of the carotid body, and their combination is an extremely powerful stimulus to ventilation.

UPPER AND LOWER RESPIRATORY TRACT RECEPTORS

Important receptors in the lung and the upper respiratory tract provide afferent information to the respiratory centers. This information is used in normal ventilation as well as to initiate maneuvers such as sneezing and coughing that need to override the gas exchanging role of the ventilatory system.

Reflexes from all along the respiratory tract provide information to the respiratory centers that will modify or sometimes even block the respiratory drive. Many of the reflexes of the airway are involved in protection, either through trying to clear the airway of foreign material through sneezing or coughing, or in preventing aspiration by closing the larynx during the swallowing of emesis. *Irritant receptors* are found in the nose and upper airways. They are triggered by nonspecific irritants, and their stimulation leads to reflex apnea. Pharyngeal reflexes are important in maintaining a patent airway. During inspiration, the pressure in the airway is negative, and because no intrinsic structures are present to hold the pharyngeal airway open (as with the tracheal cartilages), muscle tone must provide the counterforces to maintain an open airway. Receptors in the pharynx sense this negative pressure and signal the need for increased drive to the upper airway muscles during inspiration. In obstructive sleep apnea, this reflex may not be sufficient to overcome the forces that collapse the airway during inspiration.

Reflexes in the lower airway (tracheobronchial tree) also are involved in both shaping the ventilatory pattern and protecting the airway. *Rapidly adapting pulmonary stretch receptors* are so named because during constant stimulation they initially fire very rapidly but then soon decrease their firing rate. These receptors are located between airway epithelial cells and are found in abundance throughout the carina and at subsequent bronchial bifurcations. These locales are where contaminants in the inspired air (particles) are most likely to impact because of their mass. They are stimulated by irritant gases, histamine, and rapid or extreme lung inflation. They mediate reflex cough, bronchoconstriction, and hyperpnea. The *slowly adapting pulmonary stretch receptors* (PSRs) are located in airway smooth muscle and carry impulses in the vagus nerve by way of large myelinated fibers. They are activated by high lung volume or bronchoconstriction and mediate the Hering-Breuer reflex (early termination of inspiration, which in humans becomes active at an inspired volume of about 1 to 1.5 L). The *J receptors*, whose impulses are carried in small unmyelinated C fibers of the vagus nerve, have been so called because the nerve endings are found near (“juxta”) the alveolus in the walls of pulmonary capillaries or interstitium. They respond to mechanical deformation (e.g., pulmonary edema). Activation of these receptors causes rapid, shallow breathing and dyspnea.

RESPIRATORY MUSCLE-THORACIC CAGE RECEPTORS

Receptors in the respiratory muscles themselves also are very important: tendon organs that sense changes in tension, muscle spindles that sense changes in muscle length, and unmyelinated small afferent fibers that sense metabolic-inflammatory products. These somatic receptors provide information on the length-tension relationship of the respiratory muscles and make essential contributions to control of the work of breathing and respiratory loads. In addition to somatic receptors located in the intercostal muscles, rib joints, accessory muscles, and tendons, the output of receptors in other parts of the body, including skeletal muscles, can influence the respiratory pattern. At the onset of exercise, an increase in ventilation occurs that precedes the increase in PCO_2 that would be required for chemoreceptor signals. It is believed that the observed increase in ventilation is mediated by other mechanisms. For example, passively moving the limbs causes an increase in ventilation. The aforementioned somatic receptors presumably account for these observations. The control of ventilation during exercise and with changes in metabolic rate also involves afferent information from temperature and nociceptive receptors.

THE EFFERENT LIMB: THE RESPIRATORY MUSCLES

FUNCTIONAL ANATOMY

The Intercostal Muscles

The intercostal muscles are two thin layers of muscle fibers occupying each of the intercostal spaces. They are termed external and internal because of their surface relations, the external being superficial to the internal. The muscle fibers of the two layers run at approximately right angles to each other: The *external intercostals* extend from the tubercles of the ribs dorsally to the costochondral junctions ventrally, and their fibers are oriented obliquely, downward, and forward, from the rib above to the rib below. The *internal intercostals* begin posteriorly as the posterior intercostal membrane on the inner aspect of the external intercostal muscles. From approximately the angle of the rib, the internal intercostal muscles run obliquely, upward, and forward from the superior border of the rib and costal cartilage below to the floor of the subcostal groove of the rib and the edge of the costal cartilage above,

ending at the sternocostal junctions. All of the intercostal muscles are innervated by the intercostal nerves.

The external intercostal muscles have an inspiratory action on the rib cage, whereas the internal intercostal muscles are expiratory. An illustrative clinical example of the “isolated” inspiratory action of the intercostal muscles is offered by *bilateral diaphragmatic paralysis*. In patients with this deficit, inspiration is accomplished solely by the rib cage muscles. As a result, the rib cage expands during inspiration, and the pleural pressure falls. Because the diaphragm is flaccid and no transdiaphragmatic pressure can be developed, the fall in pleural pressure is transmitted to the abdomen, causing an equal fall in the abdominal pressure. Hence, the abdomen moves paradoxically inward during inspiration, opposing the inflation of the lung (Figure 6-3). This paradoxical motion is the cardinal sign of diaphragmatic paralysis on clinical examination and is invariably present in the supine posture, during which the abdominal muscles usually remain relaxed during the entire respiratory cycle. However, this sign may be absent in the erect posture.

The Diaphragm

The floor of the thoracic cavity is closed by a thin musculotendinous sheet, the diaphragm—the most important inspiratory muscle, accounting for approximately 70% of minute ventilation in normal subjects. The diaphragm is anatomically unique among the skeletal muscles in that its fibers radiate from a central tendinous structure (the central tendon) to insert peripherally into skeletal structures. The muscle of the diaphragm has two main components as defined at its point of origin: the *crural* (vertebral) part and the *costal* (sternocostal) part. The *crural* part arises from the crura (strong, tapering tendons attached vertically to the anterolateral aspects of the bodies and intervertebral disks of the first three lumbar vertebrae on the right and two on the left) and the three aponeurotic arcuate ligaments. The *costal* part of the diaphragm arises from the xiphoid process and the lower end of the sternum and the costal cartilages of the lower six ribs. These costal fibers run cranially so that they are directly apposed to the inner aspect of lower rib cage, creating a *zone of apposition*.

The shape of the relaxed diaphragm at the end of a normal expiration (at functional residual capacity [FRC]) is that of two domes joined by a “saddle” that runs from the sternum to the anterior surface of the spinal column (Figure 6-4). The motor

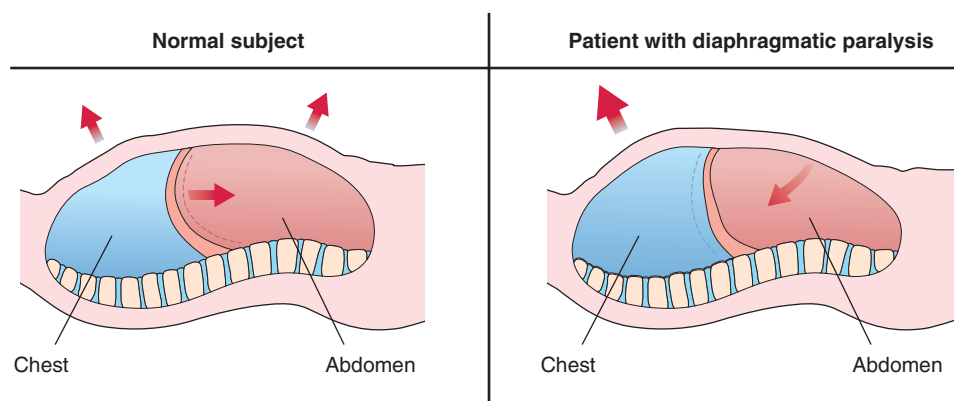
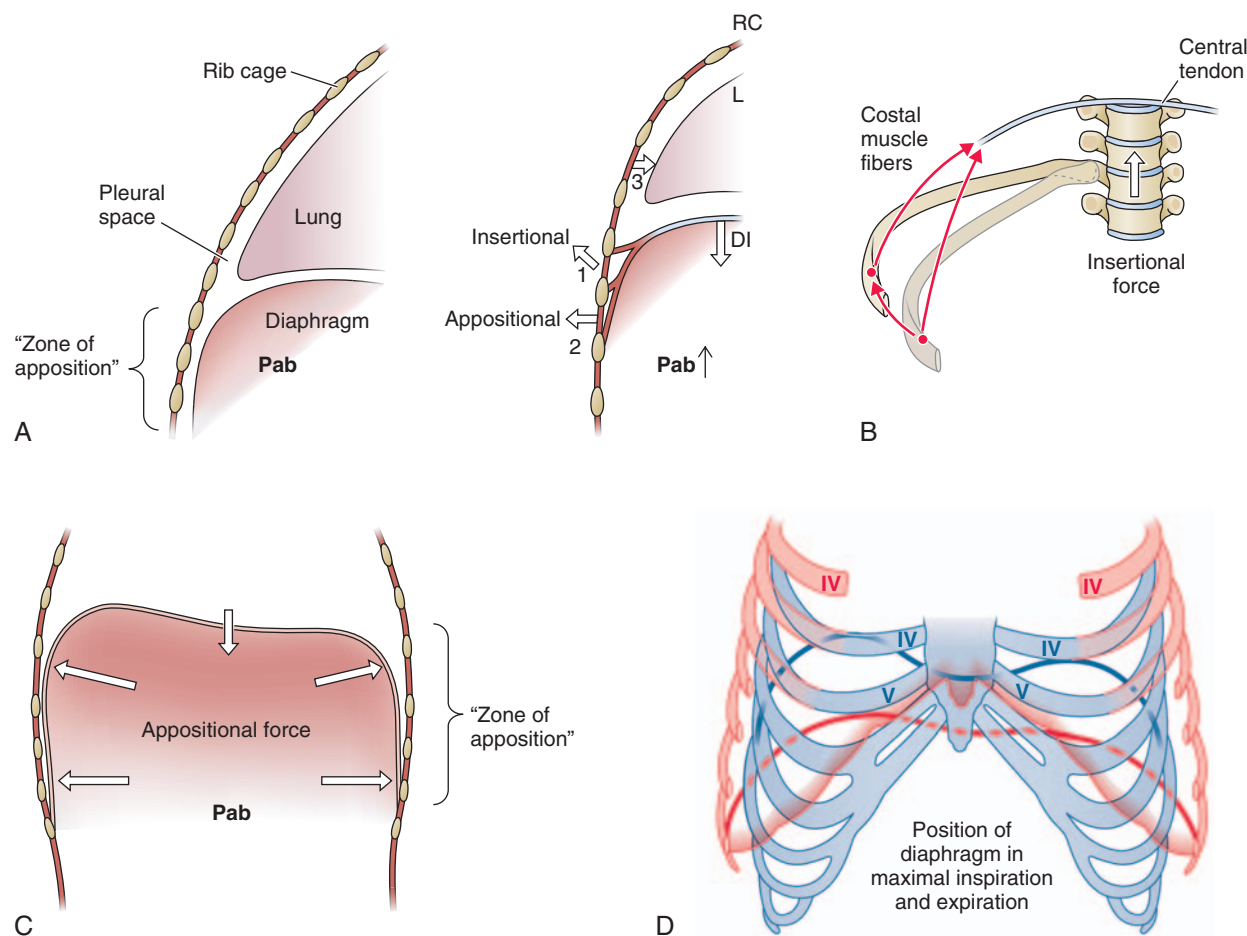


Figure 6-3 Schematic demonstration of normal abdominal and rib cage movement (*left panel*) and the paradoxical abdominal motion of isolated diaphragmatic paralysis (*right panel*). The diaphragm at resting end expiration is shown as a *solid line* and after inspiration as a *dashed line*. In the normal subject, the diaphragm moves caudally, and in the patient with diaphragmatic paralysis, the diaphragm moves in a cephalic direction. The anterior abdominal wall moves inward instead of outward.



9 Figure 6-4 Actions of the diaphragm. **A**, Zone of apposition and summary of diaphragmatic actions. When the diaphragm contracts, a caudally oriented force is being applied on the central tendon, and the dome of the diaphragm descends (DI). Furthermore, the costal diaphragmatic fibers apply a cranially oriented force to the upper margins of the lower six ribs that has the effect of lifting and rotating them outward (insertional force, *arrow 1*). The zone of apposition makes the lower rib cage part of the abdomen, and the changes in pressure in the pleural recess between the apposed diaphragm and the rib cage are almost equal to the changes in abdominal pressure (Pab). Pressure in this pleural recess rises rather than falls during inspiration because of diaphragmatic descent, and the rise in abdominal pressure is transmitted through the apposed diaphragm to expand the lower rib cage (*arrow 2*). All of these effects result in expansion of the lower rib cage. Within the upper rib cage, isolated contraction of the diaphragm causes a decrease in the anteroposterior diameter, and this expiratory action is caused primarily by the fall in pleural pressure (*arrow 3*). **B**, Insertional force; **C**, appositional force; **D**, shape of the diaphragm and the bony thorax at maximum inspiration and expiration.

innervation of the diaphragm is from the phrenic nerves, which also provide a proprioceptive supply to the muscle. When tension develops within the diaphragmatic muscle fibers, a caudally oriented force is applied on the central tendon, and the dome of the diaphragm descends; this descent has two effects. First, it expands the thoracic cavity along its craniocaudal axis, and consequently the pleural pressure falls. Second, it produces a caudal displacement of the abdominal visceral contents and an increase in the abdominal pressure, which in turn results in an outward motion of the ventral abdominal wall. Thus, when the diaphragm contracts, a cranially oriented force is being applied by the costal diaphragmatic fibers to the upper margins of the lower six ribs that has the effect of lifting and rotating them outward (insertional force) (see Figure 6-4). The actions mediated by the changes in pleural and abdominal pressures are more complex: Viewed as the only muscle acting on the rib cage, the diaphragm has two opposing effects when it contracts: On the upper rib cage, it causes a decrease in the anteroposterior diameter, and this expiratory action results primarily from the fall in pleural pressure (see Figure 6-4). On the lower rib cage, it causes an expansion. In fact, this is the

pattern of chest wall motion observed in *tetraplegic patients* with transection injury at the fifth cervical segment of the spinal cord or below, who have complete paralysis of the inspiratory muscles except for the diaphragm. This inspiratory action on the lower rib cage is caused by the concomitant action of two different forces, the “insertional” force already described and the “appositional” force.

The Sternocleidomastoids

The sternocleidomastoids arise from the mastoid process and descend to the ventral surface of the manubrium sterni and the medial third of the clavicle. Their neural supply is from the accessory nerve. The action of the sternocleidomastoids is to displace the sternum cranially during inspiration, to expand the upper rib cage more in its anteroposterior diameter than in its transverse one, and to decrease the transverse diameter of the lower rib cage. In normal subjects breathing at rest, however, the sternocleidomastoids are inactive, being recruited only when the inspiratory muscle pump is abnormally loaded or when ventilation increases substantially. Therefore, they should be considered to be accessory muscles of inspiration.

The Scalenes

The scalenes are composed of three muscle bundles that run from the transverse processes of the lower five cervical vertebrae to the upper surface of the first two ribs. They receive their neural supply mainly from the lower five cervical segments. Their action is to increase (slightly) the anteroposterior diameter of the upper rib cage. Although initially regarded as accessory muscles of inspiration, they are invariably active during inspiration. In fact, seated normal subjects cannot breathe without contracting the scalenes even when they reduce the required inspiratory effort by reducing tidal volume. Therefore, scalenes in humans are primary muscles of inspiration, and their contraction is an important determinant of the expansion of the upper rib cage during breathing.

The Abdominal Muscles

The abdominal muscles with respiratory activity are those constituting the ventrolateral wall of the abdomen (i.e., the rectus abdominis ventrally and the external oblique, internal oblique, and transversus abdominis laterally). They are innervated by the lower six thoracic nerves and the first lumbar nerve. As they contract, they pull the abdominal wall inward, thus increasing the intraabdominal pressure. This in turn causes the diaphragm to move cranially into the thoracic cavity, increasing the pleural pressure and decreasing lung volume. Thus, their action is expiratory. Expiration usually is a passive process but can become active when minute ventilation has to be increased (e.g., during exercise) or during respiratory distress. Expiratory muscle action also is essential during cough.

PHYSIOLOGY: THE ABILITY TO BREATHE: THE LOAD-CAPACITY BALANCE

For a person to take a spontaneous breath, the inspiratory muscles must generate sufficient force to overcome the elastance of the lungs and chest wall (lung and chest wall elastic loads), as well as the airway and tissue resistance (resistive load). This effort requires an adequate output of the centers controlling the muscles, anatomic and functional nerve integrity, unimpaired neuromuscular transmission, an intact chest wall, and adequate muscle strength. The mechanisms involved can be schematically represented by considering the ability to take a breath as a balance between inspiratory load and neuromuscular competence (Figure 6-5). Under normal conditions, this system is polarized in favor of neuromuscular competence (i.e., there are reserves that permit considerable increases in load). For spontaneous breathing, however, the inspiratory muscles should be able to sustain the aforementioned load over time as well as adjusting the minute ventilation to afford adequate gas exchange. The ability of the respiratory muscles to sustain this load without the onset of fatigue is called endurance and is determined by the balance between energy supply and energy demand (Figure 6-6).

Energy supply depends on the inspiratory muscle blood flow, the blood substrate (fuel) concentration and arterial oxygen content, the muscle's ability to extract and use energy sources, and the muscle's energy stores. Under normal circumstances, energy supply is adequate to meet the demand, and a large recruitable reserve exists (see Figure 6-6). Energy demand increases proportionally with the mean pressure developed by the inspiratory muscles per breath (P_i), expressed as a fraction of maximum pressure that the respiratory muscles can voluntarily develop ($P_i/P_{i,max}$), the minute ventilation (V_E), the inspiratory duty cycle (T_i/T_{tot}), and the mean inspiratory flow rate

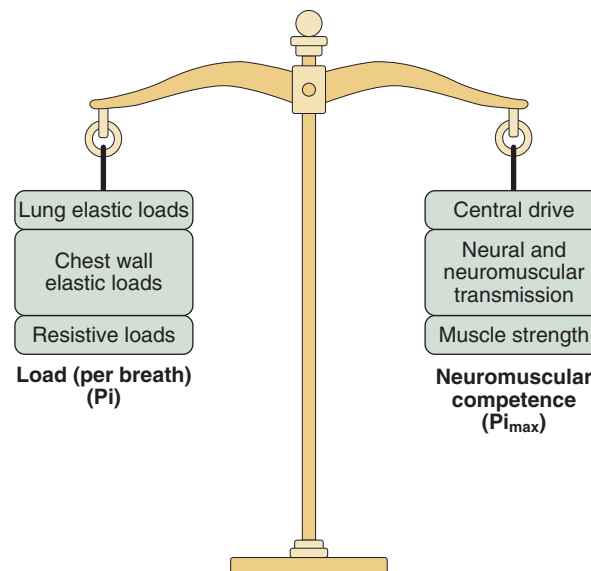


Figure 6-5 Balance between inspiratory load and neuromuscular competence. The ability to take a spontaneous breath is determined by the balance between the load imposed on the respiratory system (pressure developed by the inspiratory muscles, P_i) and the neuromuscular competence of the ventilatory pump (maximum inspiratory pressure; $P_{i,max}$). Normally, this balance weighs in favor of competence, permitting significant increases in load. However, if the competence is, for whatever reason, reduced below a critical point (e.g., drug overdose, myasthenia gravis), the balance may then weigh in favor of load, rendering the ventilatory pump insufficient to inflate the lungs and chest wall. (Modified from Vassilakopoulos T, Roussos C: *Neuromuscular respiratory failure*. In Slutsky A, Takala R, Torres, editors: *Clinical critical care medicine*, St. Louis, 2006, Mosby.)

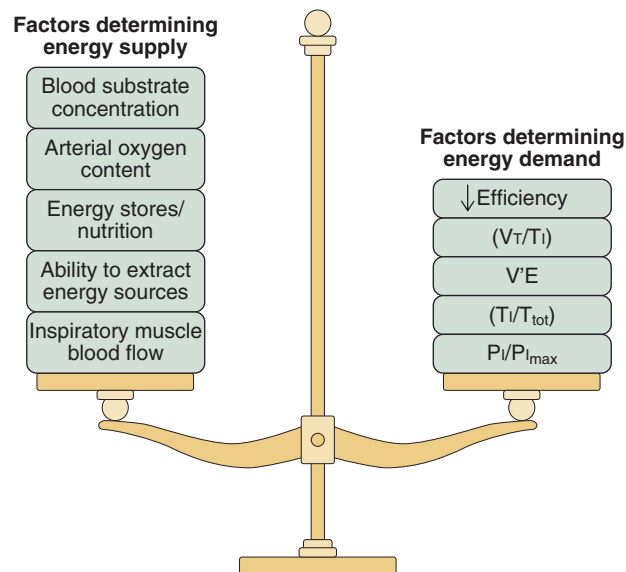


Figure 6-6 Factors determining the balance between energy supply and energy demand in maintaining neurorespiratory capacity. Respiratory muscle endurance is determined by the adequacy of energy for ventilatory needs. Normally, the supply is adequate to meet the demand, and a large reserve exists. Whenever this balance weighs in favor of demand, the respiratory muscles ultimately become fatigued, leading to inability to sustain spontaneous breathing. $P_i/P_{i,max}$, inspiratory pressure-maximum inspiratory pressure ratio; t_i/t_{tot} , duty cycle (ratio of fraction of inspiration to total breathing cycle duration); V_E , minute ventilation; V_T/t_i , mean inspiratory flow (tidal volume-inspiratory time ratio). (Modified from Vassilakopoulos T, Roussos C: *Neuromuscular respiratory failure*. In Slutsky A, Takala R, Torres, editors: *Clinical critical care medicine*, St. Louis, 2006, Mosby.)

4
5

(V_T/T_i) and are inversely related to the efficiency of the muscles. Fatigue develops when the mean rate of energy demands exceeds the mean rate of energy supply (i.e., when the balance is polarized in favor of demands).

6 The product of T_i/T_{tot} and the mean transdiaphragmatic pressure expressed as a fraction of maximal ($P_{di}/P_{di,max}$) defines a useful “tension-time index” (TTIdi) that is related to the endurance time (i.e., the time that the diaphragm can sustain the load imposed on it). Whenever TTIdi is smaller than the critical value of 0.15, the load can be sustained indefinitely, but when TTIdi exceeds the critical zone of 0.15 to 0.18, the load can be sustained for only a limited period—in other words, the endurance time. This variable was found to be inversely related to TTIdi. The TTI concept is assumed to be applicable not only to the diaphragm but also to the respiratory muscles as a whole:

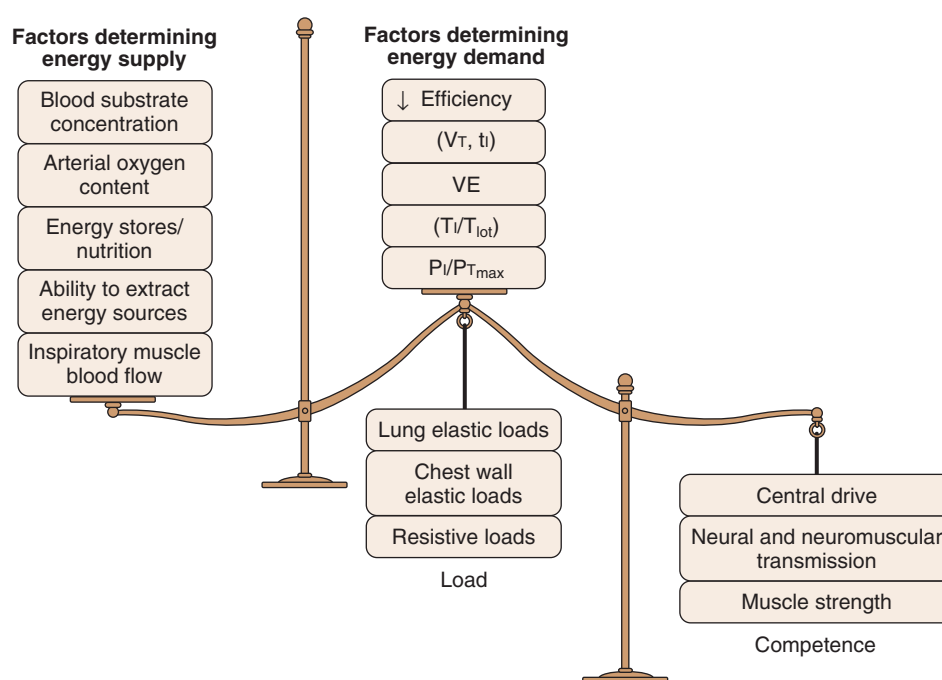
$$TTI = P_i/P_{i,max} \times T_i/T_{tot}$$

Because endurance is determined by the balance between energy supply and demand, TTI of the inspiratory muscles has to be in accordance with the energy balance view. In fact, as Figure 6-6 demonstrates, $P_i/P_{i,max}$ and T_i/T_{tot} , which constitute the TTI, are among the determinants of energy demand; an increase in either that will increase the TTI value also will increase the demand. But what determines the ratio $P_i/P_{i,max}$? The numerator, the mean inspiratory pressure developed per breath, is determined by the elastic and resistive loads imposed on the inspiratory muscles. The denominator, the maximum inspiratory pressure, is determined by the neuromuscular competence (i.e., the maximum inspiratory muscle activation that can be voluntarily achieved). It follows, then, that the value of $P_i/P_{i,max}$ is determined by the balance between load and competence (see Figure 6-5). But $P_i/P_{i,max}$ also is one of the determinants of energy demand (see Figure 6-6); therefore, the two balances (i.e., between load and competence and between energy supply and demand) are in essence linked, creating a single system (Figure 6-7). Schematically, when the central hinge of the system moves upward or is at least at the horizontal level, spontaneous ventilation can be sustained indefinitely (see Figure 6-7). The ability of a subject to breathe

spontaneously depends on the fine interplay of many different factors. Normally, this interplay moves the central hinge far upward and creates a great ventilatory reserve for the healthy person. When the central hinge of the system, for whatever reason, moves downward, spontaneous ventilation cannot be sustained, and ventilatory failure ensues.

HYPERINFLATION

Hyperinflation (frequently observed in obstructive airway diseases) compromises the force-generating capacity of the diaphragm for a variety of reasons: First, the respiratory muscles, like other skeletal muscles, obey the length-tension relationship. At any given level of activation, changes in muscle fiber length alter tension development. This is because the force-tension developed by a muscle depends on the interaction between actin and myosin fibrils (i.e., the number of myosin heads attaching and thus pulling the actin fibrils closer within each sarcomere). The optimal fiber length (L_o) for which tension is maximal is the length at which all myosin heads attach and pull the actin fibrils. Below this length (as with hyperinflation, which shortens the diaphragm), actin-myosin interaction becomes suboptimal, and tension development declines. Second, as lung volume increases, the zone of apposition of the diaphragm decreases in size, and a larger fraction of the rib cage becomes exposed to pleural pressure. Hence, the diaphragm’s inspiratory action on the rib cage diminishes. When lung volume approaches total lung capacity, the zone of apposition all but disappears (Figure 6-8), and the diaphragmatic muscle fibers become oriented horizontally internally (see Figure 6-8). The insertional force of the diaphragm is then expiratory, rather than inspiratory, in direction. This observation explains the inspiratory decrease in the transverse diameter of the lower rib cage in subjects with emphysema and severe hyperinflation (Hoover’s sign). Third, the resultant flattening of the diaphragm increases its radius of curvature (R_{di}) and, according to Laplace’s law, $P_{di} = 2T_{di}/R_{di}$, diminishes its pressure-generating capacity (P_{di}) for the same tension development (T_{di}).



12 **Figure 6-7** Factors determining the two aspects of balance in the system maintaining neurorespiratory capacity: (1) load and competence and (2) energy supply and demand. The relationship between these system components is depicted schematically. The $P_i/P_{i,max}$, one of the determinants of energy demand (see Figure 6-6), is replaced by its equivalent: the balance between load and neuromuscular competence (see Figure 6-5). In fact, this correlation is the reason the two balances are linked. When the central hinge of the system moves upward or is at least at the horizontal level, a balance exists between ventilatory needs and neurorespiratory capacity, and spontaneous ventilation can be sustained. In healthy persons, the hinge moves far upward, creating a large reserve. For abbreviations, see legends to Figures 6-5 and 6-6. (Modified from Vassilakopoulos T, Roussos C: *Neuromuscular respiratory failure*. In Slutsky A, Takala R, Torres R, editors: *Clinical critical care medicine*, St. Louis, 2006, Mosby.)

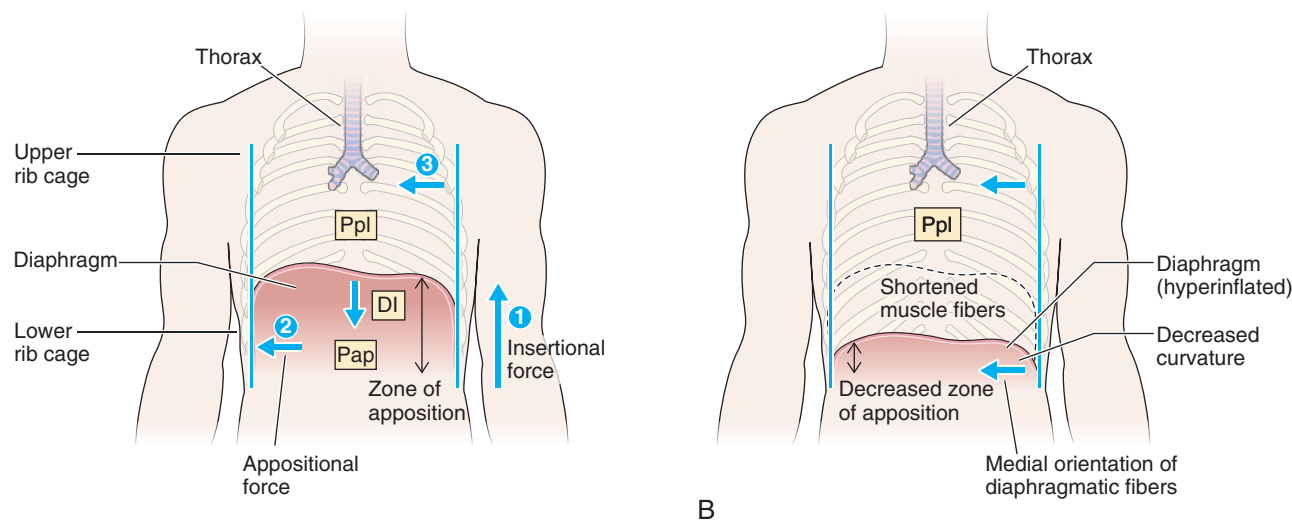


Figure 6-8 Consequences of hyperinflation on the diaphragm. **A**, Normal actions of the diaphragm, as in Figure 6-2. **B**, Deleterious effects of hyperinflation on the diaphragm. *DI*, diaphragmatic force; *Pap*, ••; *Ppl*, pleural pressure.

RESPIRATORY MUSCLE RESPONSES TO CHANGES IN LOAD

ACUTE RESPONSES TO INCREASED LOAD

Respiratory Muscle Fatigue

Fatigue is defined as the loss of capacity to develop force and/or velocity in response to a load that is reversible by rest. Fatigue should be distinguished from weakness, in which reduced force generation is fixed and not reversed by rest, although the presence of weakness may itself predispose a muscle to fatigue. The site and mechanisms of fatigue remain controversial. Theoretically, the site of fatigue may be located at any link in the long chain of events involved in voluntary muscle contraction leading from the brain to the contractile machinery. A widely used convention is to classify fatigue as central fatigue, peripheral high-frequency fatigue, or peripheral low-frequency fatigue.

Central fatigue is present when a maximal voluntary contraction generates less force than does maximal electrical stimulation. If maximal electrical stimulation superimposed on a maximal voluntary contraction can potentiate the force generated by a muscle, a component of central fatigue exists. This procedure applied to the diaphragm consists of the *twitch occlusion test*, which may separate central from peripheral fatigue. This test examines the transdiaphragmatic pressure (P_{di}) response to bilateral phrenic nerve stimulation superimposed on graded voluntary contractions of the diaphragm. Normally, the amplitude of the P_{di} twitches in response to phrenic nerve stimulation decreases as the voluntary P_{di} increases. During $P_{di_{max}}$, no superimposed twitches can be detected. When central diaphragmatic fatigue is present, superimposed twitches can be demonstrated. A number of experiments have suggested that a form of central diaphragmatic “fatigue” may develop during respiratory loading such that, at the limits of diaphragmatic endurance, a significant portion of the reduction in force production is due to failure of the central nervous system to completely activate the diaphragm. Central fatigue may be caused by a reduction in the number of motor units that can be recruited by the motor drive or by a decrease in motor unit discharge rates, or both. The observed decreased central firing rate during fatigue may in fact be a beneficial

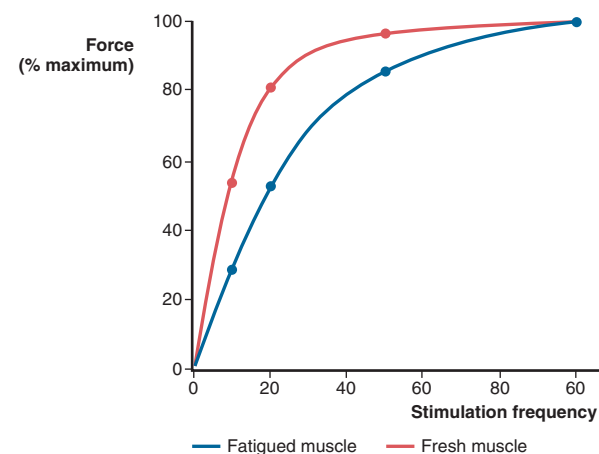


Figure 6-9 Force-frequency relationship of in vivo human respiratory muscles. The force-frequency curve for fresh muscle is shown in red, and that for muscle after a fatiguing task is shown in blue; a disproportionate force loss at low stimulation frequencies is evident. (Modified from Moxham J, Wiles CM, Newham D, Edwards RH: *Contractile function and fatigue of the respiratory muscles in man*, Ciba Found Symp 82:197-212, 1981.)

adaptive response preventing the muscle’s self-destruction by excessive activation.

Peripheral fatigue refers to failure at the neuromuscular junction or distal to this structure and is present when muscle force output falls in response to direct electrical stimulation. This type of fatigue may occur as a consequence of failure of impulse propagation across the neuromuscular junction, the sarcolemma or the T tubules (transmission fatigue), impaired excitation-contraction coupling, or failure of the contractile apparatus of the muscle fibers. Peripheral fatigue can be further classified into high- and low-frequency types on the basis of the shape of the muscle force-frequency curve (Figure 6-9). High-frequency fatigue results in depression of the forces generated by a muscle in response to high-frequency electrical stimulation (50 to 100 Hz), whereas low-frequency fatigue results in depression of force generation in response to low-frequency stimuli (1 to 20 Hz). *High-frequency fatigue* (see Figure 6-9) is attributed to transmission fatigue. Teleologically,

transmission block could be beneficial in some instances by protecting the muscle against excessive depletion of its ATP stores. Normal subjects breathing against high-intensity inspiratory resistive loads develop high-frequency fatigue, which resolves very quickly after cessation of the strenuous diaphragmatic contractions.

When the loss of force is not accompanied by a parallel decline in the electrical activity, impaired excitation-contraction coupling is thought to be responsible. This type of fatigue is characterized by a selective loss of force at low frequencies of stimulation (see Figure 6-9) despite maintenance of the force generated at high frequencies of stimulation, indicating that the contractile proteins continue to generate force so long as sufficient calcium is released by the sarcoplasmic reticulum. This *low-frequency fatigue* is characteristically long-lasting, with recovery occurring over several hours. Low-frequency fatigue occurs during high-force contractions and is less likely to develop when the forces generated are smaller, even if these are maintained for longer time periods, thereby achieving the same total work. As previously stated, fatigue develops when the mean rate of energy demands exceeds the mean rate of energy supply to the muscle (see Figure 6-6), resulting in depletion of muscle energy stores, acidosis from lactate accumulation, and excessive production of oxygen-derived free radicals. The exact interplay of all of these factors is not yet identified. Low-frequency fatigue occurs in the diaphragm of experimental animals during cardiogenic or septic shock, and in the diaphragm and sternocleidomastoid of normal subjects after breathing against very high inspiratory resistance or after sustaining maximum voluntary ventilation (for 2 minutes) (Figure 6-10). The clinical relevance of respiratory muscle fatigue is difficult to ascertain, because performing the measurements that are required for fatigue detection is problematic in situations in which fatigue is likely to be present (such as during acute hypercapnic respiratory failure).

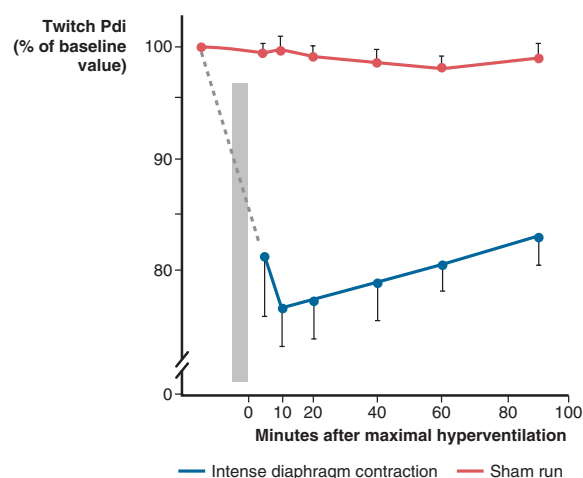


Figure 6-10 Low-frequency fatigue of the diaphragm in normal subjects. The mean twitch tension (i.e., twitch transdiaphragmatic pressure Pdi) is shown before and at intervals up to 90 minutes after intense diaphragmatic contraction (in this case, a 2-minute period of maximal normocapnic hyperventilation) in nine healthy adults (blue symbols). Data after a sham (“normal breathing”) run in the same subjects are shown in red. A significant decline in twitch Pdi is observed that has only partially recovered at 90 minutes, which confirms the presence of low-frequency diaphragmatic fatigue. (Data from Hamnegård CH, Wragg SD, Kyroussis D, et al: Diaphragm fatigue following maximal ventilation in man, Eur Respir J 9:241-247, 1996.)

INFLAMMATION AND INJURY

Strenuous diaphragmatic contractions (induced by resistive breathing, which accompanies many disease states such as chronic obstructive pulmonary disease [COPD] and asthma) initiate an inflammatory response consisting of elevation of plasma cytokines and recruitment and activation of white blood cell subpopulations. These cytokines are produced within the diaphragm secondary to the increased muscle activation. Strenuous resistive breathing results in diaphragmatic ultrastructural injury (such as sarcomere disruption, necrotic fibers, flocculent degeneration, and influx of inflammatory cells) in both animals and humans. The mechanisms involved are not definitively established but may involve intradiaphragmatic cytokine induction, adhesion molecule upregulation, calpain activation, and reactive oxygen species formation. Cytokines also are essential in orchestrating muscle recovery after injury by enhancing proteolytic removal of damaged proteins and cells (through recruitment and activation of phagocytes) and by activating satellite cells. Satellite cells are quiescent cells of embryonic origin that reside in the muscle and are transformed into myocytes when the muscle becomes injured, to replace damaged myocytes.

CHRONIC RESPONSES TO INCREASED LOAD

Plasticity and Adaptation

The respiratory muscles are plastic organs that respond with structural and functional changes or adaptations to chronic changes in the load they are facing and thus in their activity.

COPD is the paradigm of a disease characterized by chronically increased respiratory muscle load. A major adaptation of the respiratory muscles is fiber type transformation. The myosin heavy chain component of the myosin molecule constitutes the basis for the classification of muscle fibers as either (type I) or (type II) (Figure 6-11). Myosin heavy chain exists in various isoforms, which in increasing order of maximum shortening velocity are myosin heavy chain (MHC) I, IIa, and IIb, the last type being the fastest (see Figure 6-11). The diaphragm in healthy humans is composed of approximately 50% type I fatigue-resistant fibers, 25% type IIa, and 25% type IIb. Muscles can modify their overall MHC phenotype in two ways: (1) preferential atrophy or hypertrophy of fibers containing a specific MHC isoform and (2) actual transformation from one fiber type to another. In COPD, a transformation of type II to type I fibers occurs, resulting in a great predominance of type I fatigue-resistant fibers. This altered makeup increases the resistance of the diaphragm to fatigue development but at the same time compromises the force-generating capacity, because type I fibers can generate less force than type II fibers can.

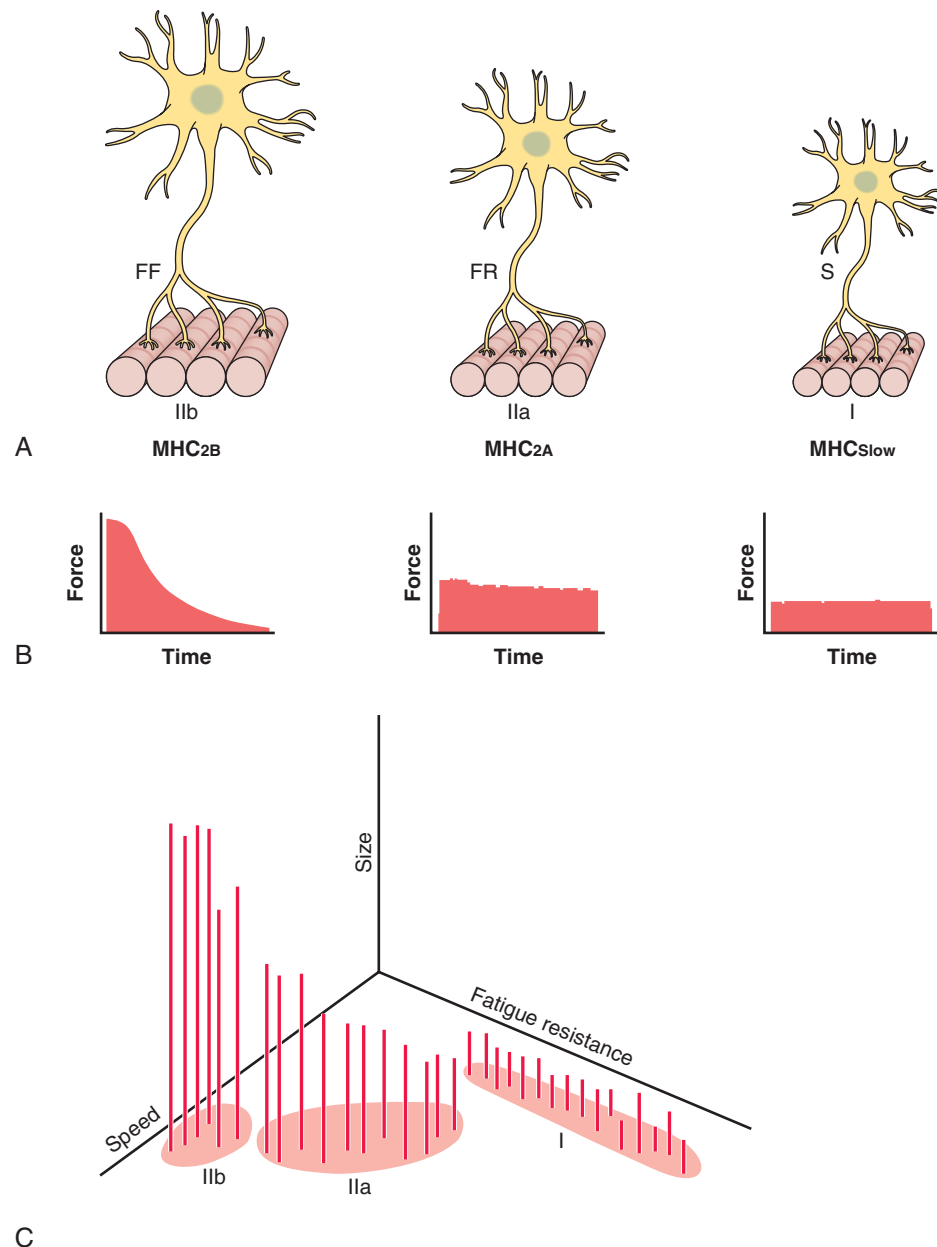
Adaptation is not restricted to only fiber type transformation. In an animal model of COPD (in emphysematous hamsters), the number and the length of sarcomeres decrease, resulting in a leftward shift of the length-tension curve, so that the muscle adapts to the shorter operating length induced by hyperinflation. These alterations may help restore the mechanical advantage of the diaphragm in chronically hyperinflated states. In humans, this adaptation seems to occur by sarcomere length shortening.

Respiratory Muscle Response to Inactivity: Unloading

Respiratory muscles adapt not only when they function against increased load but also when they become inactive, as happens

6-10 Section 1 NORMAL STRUCTURE AND FUNCTION

Figure 6-11 Properties of skeletal muscle fiber types. Different fiber types in the diaphragm muscle are distinguished by size, myosin heavy chain content, contractile characteristics (force and speed of contraction), and fatigue resistance (type S, slow; type FR, fast-twitch, fatigue-resistant; and type FF motor units, fast-twitch, fatigable—types I, Ila, and IIb, respectively), as well as myosin heavy chain (MHC) isoform expression (MHC_{slow}, MHC_{2A}, and MHC_{2B}). **A**, Size; **B**, force; **C**, size-speed of contraction-fatigue resistance. (Modified from Mantilla CB, Sieck GS: Mechanisms underlying motor unit plasticity in the respiratory system, *J Appl Physiol* 94:1230-1241, 2003; and Jones DA: Skeletal muscle physiology. In Roussos C, editor: *The thorax*, ed 2, New York, 1995, Marcel Dekker, pp 3-32.)



during denervation or when a mechanical ventilator takes over their role as force generator to create the driving pressure permitting airflow into the lungs. Inactivity and unloading of the diaphragm associated with mechanical ventilation are harmful, resulting in decreased diaphragmatic force-generating capacity, diaphragmatic atrophy, and diaphragmatic injury this combination of effects has been designated *ventilator-induced diaphragmatic dysfunction* (VIDD). The mechanisms are not fully explained, but muscle atrophy, oxidative stress, structural injury, and muscle fiber remodeling contribute to a variable extent in the development of VIDD.

TESTING RESPIRATORY MUSCLE FUNCTION

Muscles have two functions: to develop force and to shorten. In the respiratory system, *force* usually is estimated as pressure and *shortening* as lung volume change.

VITAL CAPACITY

Vital capacity (VC) is easily measured with spirometry; decreases in VC point to respiratory muscle weakness. The VC averages approximately 50 mL/kg in normal adults. VC changes are not specific, however, and decreases may result from both inspiratory and expiratory muscle weakness and may be associated with restrictive lung and chest wall diseases. A marked fall (of greater than 30%) in VC in the supine compared with that in the erect posture (which in the normal person is 5% to 10%) is associated with severe bilateral diaphragmatic weakness.

MAXIMAL STATIC MOUTH PRESSURES

Measurement of the maximum static inspiratory ($P_{I_{max}}$) or expiratory ($P_{E_{max}}$) pressure that a subject can generate at the mouth is a simple way to estimate inspiratory and expiratory

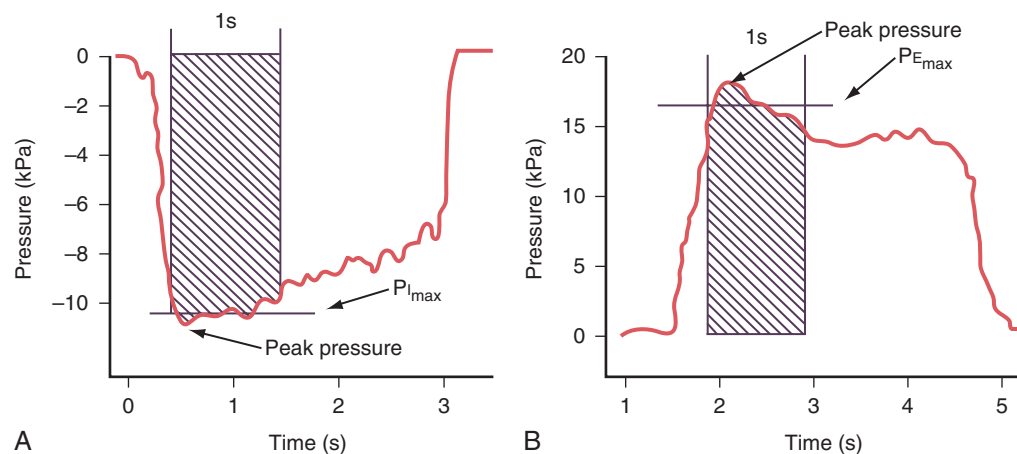


Figure 6-12 Maximum inspiratory-expiratory pressures. **A**, Pressure tracing from a subject performing a maximal inspiratory maneuver ($P_{I_{max}}$). A peak pressure is seen, and the 1-second average is determined by calculating the shaded area. **B**, Typical pressure tracing from a subject performing a maximal expiratory maneuver ($P_{E_{max}}$). (Modified from American Thoracic Society/European Respiratory Society: ATS/ERS statement on respiratory muscle testing, *Am J Respir Crit Care Med* 166:518–624, 2002.)

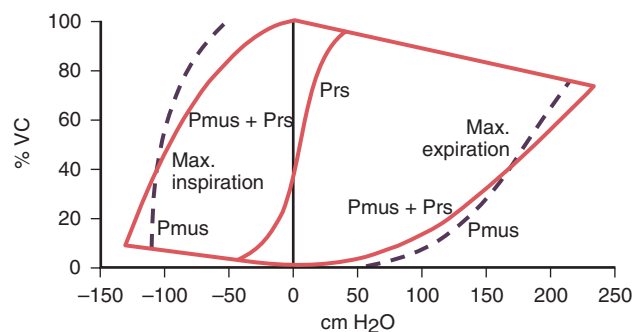


Figure 6-13 Relationship of muscle and respiratory pressures at different lung volumes. Vertical axis represents lung volume as a percentage of vital capacity (% VC). Horizontal axis represents alveolar pressure in cm H₂O. The broken lines indicate the pressure contributed by the muscles. P_{mus} , pressure developed by the respiratory muscles; P_{rs} , pressure of the respiratory system. (Modified from Agostoni E, Mead J: *Statics of the respiratory system*. In Fenn WO, Rahn H, editors: *Handbook of physiology: respiration*, vol 1, section 3, Washington, DC, 1964, American Physiological Society, pp 387–409.)

muscle strength. These pressures are measured at the side port of a mouthpiece that is occluded at the distal end. A small leak is incorporated to prevent glottic closure and buccal muscle use during inspiratory or expiratory maneuvers. The pressure must be maintained for at least 1.5 seconds, so that the maximum pressure sustained for 1 second can be recorded (Figure 6-12). The pressure measured during these maneuvers (P_{mo}) reflects the pressure developed by the respiratory muscles (P_{mus}), plus the passive elastic recoil pressure of the respiratory system including the lung and chest wall (P_{rs}) (Figure 6-13). At FRC, P_{rs} is 0, so P_{mo} represents P_{mus} . However, at residual volume (RV), where $P_{I_{max}}$ usually is measured, P_{rs} may be as much as 30 cm H₂O and thus makes a significant contribution $P_{I_{max}}$ of up to 30% (or more if P_{mus} is decreased). Similarly, $P_{E_{max}}$ is measured at total lung capacity (TLC), where P_{rs} can be up to 40 cm H₂O. Clinical measures and normal values of $P_{I_{max}}$ and $P_{E_{max}}$ do not conventionally subtract the elastic recoil of the respiratory system. Normal values are available for adults, children, and elderly persons. The tests are easy to perform and well tolerated, yet they are associated with significant between- and within-subject variability, as well as learning effect.

Nevertheless, a $P_{I_{max}}$ of -80 cm H₂O usually excludes clinically important inspiratory muscle weakness.

TRANSDIAPHRAGMATIC PRESSURE

When inspiratory muscle weakness is confirmed, the next diagnostic step is to unravel whether the underlying problem is diaphragmatic weakness, because the diaphragm is the most important inspiratory muscle. This determination is accomplished by the measurement of maximum transdiaphragmatic pressure ($P_{di_{max}}$). $P_{di_{max}}$ is the difference between gastric pressure (reflecting abdominal pressure) and esophageal pressure (reflecting intrapleural pressure) on a maximal inspiratory effort after the insertion of appropriate balloon catheters in the stomach and the esophagus, respectively.

SNIFF PRESSURES

A sniff is a short, sharp voluntary inspiratory maneuver performed through one or both unoccluded nostrils. It achieves rapid, fully coordinated recruitment of the diaphragm and other inspiratory muscles. The nose acts as a Starling resistor, so nasal flow is low and largely independent of the driving pressure that is the esophageal pressure. P_{di} measured during a sniff ($P_{di,sn_{max}}$) reflects diaphragm strength, and P_{es} reflects the integrated pressure of the inspiratory muscles on the lungs (Figure 6-14). Pressures measured in the mouth, nasopharynx, or one nostril give a clinically useful approximation of esophageal pressure during sniffs without the need to insert esophageal balloons, especially in the absence of significant obstructive airway disease.

The nasal sniff pressure is the easiest measurement for the subject. Pressure is measured by wedging a catheter in one nostril by use of foam, rubber bungs, or dental impression molding (Figure 6-15). The subject sniffs through the contralateral unobstructed nostril. A wide range of normal values has been documented, reflecting the variability in normal muscle strength from person to person. In clinical practice, $P_{di,sn_{max}}$ values greater than 100 cm H₂O in males and 80 cm H₂O in females are unlikely to be associated with clinically significant diaphragm weakness. Values of maximal sniff esophageal or nasal pressure greater than 70 cm H₂O (in males) or 60 cm

6-12 Section 1 NORMAL STRUCTURE AND FUNCTION

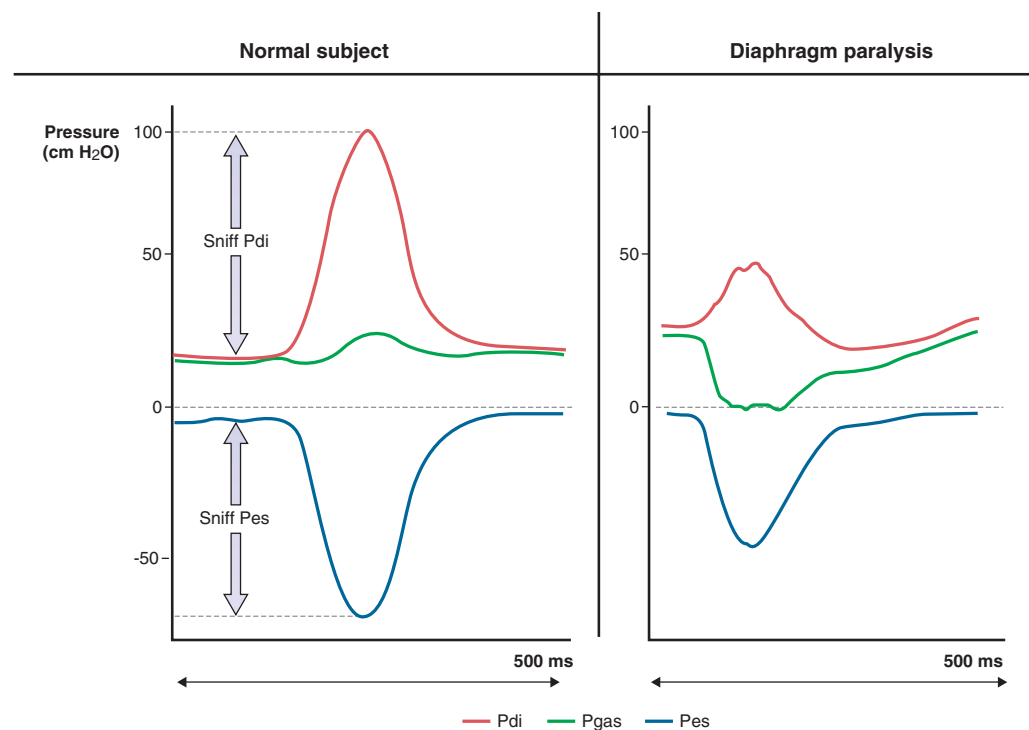
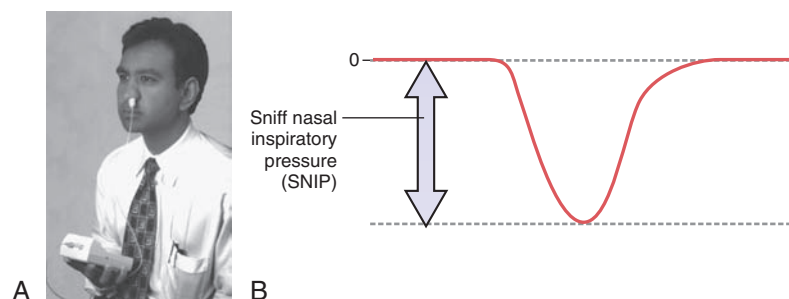


Figure 6-14 Examples of the sniff maneuver. *Left panel* shows a recording from a healthy subject. Note that the esophageal (pleural) pressure change is subatmospheric, whereas the intraabdominal pressure becomes more positive. Measurement conventions for the sniff esophageal (Sniff Pes) and sniff transdiaphragmatic (Sniff Pdi) pressures are illustrated. *The right panel* shows a recording from a patient with bilateral diaphragmatic paralysis. Note that there is now a negative pressure change in the abdominal compartment, because the diaphragm fails to prevent pressure transmission from the thorax.

Figure 6-15 The sniff maneuver. A nasal bung and an adapted pressure meter are used for this test. **A**, Measurement setup. The meter returns a numerical value that represents the amplitude of the pressure swing between atmospheric (0) pressure and the nadir. **B**, The tracing produced. The meter returns a numerical value that is the amplitude of the pressure swing between atmospheric (0) pressure and the nadir.



H₂O (in females) also are unlikely to be associated with significant inspiratory muscle weakness.

ELECTROPHYSIOLOGIC TESTING

Electrophysiologic testing helps in determining whether weakness is due to muscle, nerve, or neuromuscular transmission impairment. This determination requires the measurement of Pdi in response to bilateral supramaximal phrenic nerve electrical or magnetic stimulation, with concurrent recording of the elicited electromyogram (EMG) at the diaphragm—the compound muscle action potential (CMAP)—with either surface or esophageal electrodes (**Figure 6-16**).

If the phrenic nerve is stimulated, the diaphragm contracts. Each contraction is called a twitch. If the stimulus is intense enough, all phrenic fibers are activated synchronously, giving reproducible results. The intensity of the twitch increases with the frequency of stimulation. If multiple impulses stimulate the phrenic nerve, the contractions summate to cause a tetanic contraction. Thus, if both phrenic nerves are

stimulated with various frequencies (1, 10, 20, 50, and 100 Hz) at the same lung volume with closed airway (to prevent entry of air with consequent changes in lung volume and initial length of the diaphragm), the isometric *force-frequency curve* of the diaphragm is obtained (see **Figure 6-16**). Stimulation of the phrenic nerve with high frequencies is technically difficult to achieve (because of displacement of the stimulating electrode by local contraction of the scalene muscles and movement of the arm and shoulder due to activation of the brachial plexus). Therefore, the transdiaphragmatic pressure developed in response to single supramaximal phrenic nerve stimulation at 1 Hz, called the *twitch Pdi*, is commonly measured. Although technically demanding, this approach has the great advantage of being independent of patient effort or motivation. The twitch Pdi also allows for the measurement of *phrenic nerve conduction time*, or *phrenic latency* (i.e., the time between the onset of the stimulus and the onset of CMAP [M wave] on the diaphragmatic EMG tracing) (see **Figure 6-16, B**). A prolonged conduction time suggests nerve involvement.

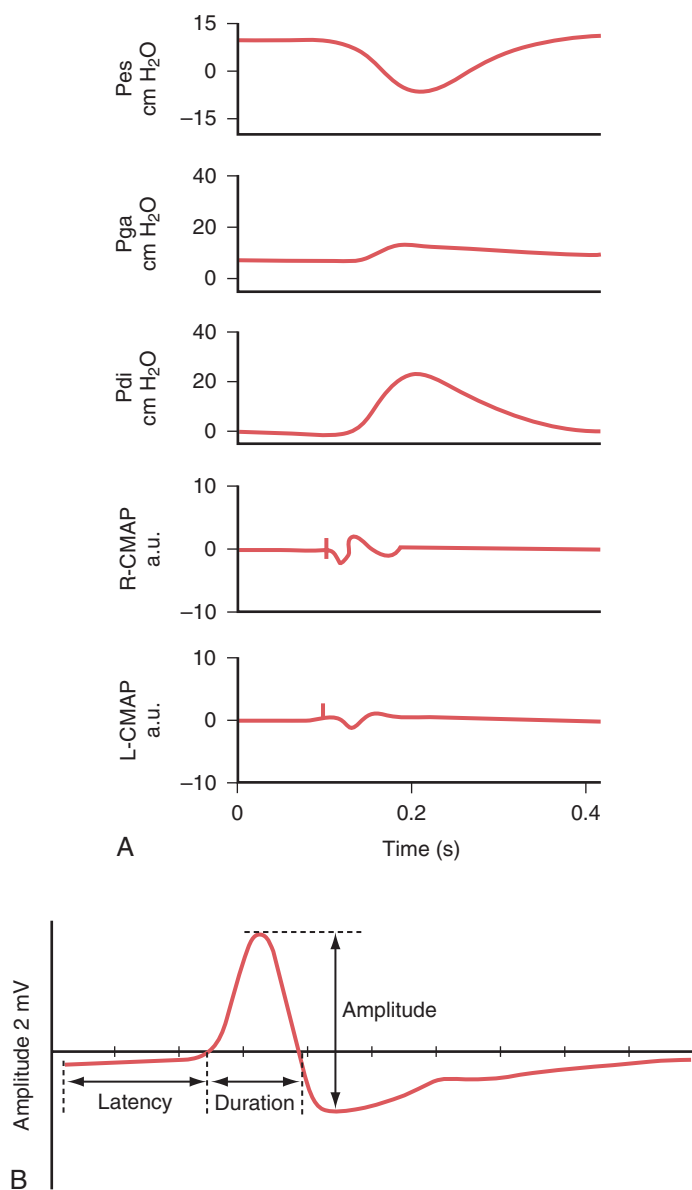


Figure 6-16 Electrophysiologic testing: The “twitch Pdi.” **A**, The twitch transdiaphragmatic pressure (Pdi) after magnetic or electrical stimulation. **B**, A detailed (enlarged) view of a compound muscle action potential (M wave), in which the latency (time from stimulus to muscle depolarization), the duration, and the amplitude of the electromyogram are evident. *a.u.*, arbitrary units; *L-CMAP*, left compound motor action potential; *Pes*, esophageal pressure; *Pga*, gastric pressure; *R-CMAP*, right compound motor action potential. (Modified from Vassilakopoulos T, Roussos C: *Neuromuscular respiratory failure*. In Slutsky A, Takala R, Torres R, editors: *Clinical critical care medicine*, St. Louis, 2006, Mosby.)

15

CONTROVERSIES AND PITFALLS

- The actual mechanisms of respiratory rhythmogenesis have not been definitively established. When the pre-Bötzinger complex was discovered, it was hypothesized to be the sole generator of respiratory rhythm. Subsequent work suggested the presence of a second respiratory rhythm generator, located rostral to the pre-Bötzinger complex in the region of the retrotrapezoid nucleus–parafacial respiratory group (RTN/pFRG) and functioning primarily as a conditional oscillator for generating expiratory motor output; this model is the core of the “two-oscillator” hypothesis. The existence

of a second respiratory oscillator is still controversial, and whether it persists into adulthood also is still debated (although with waning intensity).

- Still to be determined within the framework of respiratory rhythm generation is whether single pacemaker neurons in the pre-Bötzinger complex generate the respiratory rhythm or whether the pre-Bötzinger complex network functions as a self-organized group pacemaker, wherein individual pacemaker neurons can be embedded but are not essential for emergent network rhythms that depend on connectivity and synaptically activated burst-generating currents. So-called emergent systems are widespread in biology. They consist of autonomous agents that interact according to simple rules and produce meaningful population-level behaviors. When these behaviors are rhythmic, the underlying network always incorporates two essential features: positive feedback, which serves to coordinate individual elements and promote the formation of a collective temporal pattern, and negative feedback, which can temporarily halt or reverse the assembly process fueled by positive feedback. These processes, by their nature, alternate. The rhythms are called *emergent* because individual agents interact in accordance with simple rules, but none possesses a blueprint for the collective behavior that results.
- The clinical relevance of respiratory muscle fatigue is controversial. Physicians usually institute noninvasive or invasive mechanical ventilation in patients presenting with conditions in which the load the respiratory muscles are facing is fatiguing, because clinical signs of severe respiratory distress (such as tachypnea, accessory muscle use, and diaphoresis) develop before respiratory muscle fatigue is established. Furthermore, the objective diagnosis of respiratory muscle fatigue is impractical in the clinical arena (such as the emergency department), because the required electrophysiologic testing is time-consuming and technically demanding, which makes it hard to implement in acutely dyspneic patients with respiratory distress.
- With most volitional tests of respiratory muscle function, a significant learning effect is characteristic. Thus, repeat testing is required before the diagnosis of respiratory muscle weakness is established, especially in elderly persons or in patients for whom cooperation may be difficult.

SUGGESTED READINGS

- American Thoracic Society/European Respiratory Society: ATS/ERS statement on respiratory muscle testing, *Am J Respir Crit Care Med* 166:518–624, 2002.
- Mantilla CB, Sieck GS: Invited review: mechanisms underlying motor unit plasticity in the respiratory system, *J Appl Physiol* 94:1230–1241, 2003.
- Roussos C, Zakyntinos S: Fatigue of the respiratory muscles. *Intensive Care Med* 22:134–155, 1996.
- Vassilakopoulos T: Ventilator-induced diaphragmatic dysfunction: the clinical relevance of animal models, *Intensive Care Med* 34:7–16, 2008.
- Vassilakopoulos T, Roussos C: Neuromuscular respiratory failure. In Slutsky A, Takala R, Torres R, editors: *Clinical critical care medicine*, St. Louis, 2006, Mosby, pp 275–282.
- Vassilakopoulos T, Roussos C, Zakyntinos S: The immune response to resistive breathing, *Eur Respir J* 24:1033–1043, 2004.
- Vassilakopoulos T, Zakyntinos S, Roussos C: Respiratory muscles and weaning failure, *Eur Respir J* 9:2383–2400, 1996.
- Vassilakopoulos T, Zakyntinos S, Roussos C: Muscle function: basic concepts. In Marini JJ, Slutsky A, editors: *Physiologic basis of ventilator support*, New York, 1998, Marcel Dekker, pp 103–152.