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 approximately at 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, because 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 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 patients who have bilateral diaphragmatic paralysis. In these patients, 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 8-1). This paradox 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 falls into two main components on the basis of 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 (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 8-2). The motor 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 that 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 8-2). The actions mediated by the changes in pleural and abdominal pressures are more complex: if one assumes that the diaphragm is the only muscle acting on the rib cage, it seems that it has two opposing effects when it contracts.
On the upper rib cage, it causes a decrease in the anteroposterior diameter, and this expiratory action is primarily because of the fall in pleural pressure (see Figure 8-2). 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 c. The Neck Muscles.

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 as 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 considered 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 causes the diaphragm to move cranially into the thoracic cavity, increasing the pleural pressure and decreasing lung volume. Thus, their action is expiratory.Expiration is usually 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 is also essential during cough.

Testing Respiratory Muscle Function

Muscles have two functions: to develop force and to shorten. In the respiratory system, force is usually estimated as pressure and shortening as lung volume change. Thus, quantitative characterization of the respiratory muscles usually relies on measurements of volumes and pressures.

Vital Capacity

Vital capacity (VC) is an easily obtained measurement with spirometry, which, when decreased, points to respiratory muscle weakness. The VC averages approximately 50 mL/kg in normal adults. However, VC is not specific and may be decreased because of both inspiratory and expiratory muscle weakness and restrictive lung and chest wall diseases. A marked fall (>30%) in VC in the supine compared with the erect posture (which in the normal individual is 5–10%) 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 muscle strength. These are measured at the side port of a
A small leak is incorporated to prevent glottic closure and buccal muscle use during inspiratory or expiratory maneuvers. The inspiratory and expiratory pressure must be maintained, ideally for at least 1.5 sec, so that the maximum pressure sustained for 1 sec can be recorded (Figure 8-3). The pressure measured during these maneuvers reflects the pressure developed by the respiratory muscles (Pmus), plus the passive elastic recoil pressure of the respiratory system including the lung and chest wall (Prs) (Figure 8-4). At FRC, Prs is 0 so that Pmo represents Pmus. However, at residual volume (RV), where P_{I,max} is usually measured, Prs may be as much as 30 cm H₂O, and thus makes a significant contribution P_{I,max} of up to 30% (or more if Pmus is decreased). Similarly, P_{I,max} is measured at total lung capacity (TLC), where Prs 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 the elderly. The tests are easy to perform and are well tolerated. However, the measurements exhibit significant between-subject and within-subject variability, as well as learning effect (values obtained improve as subjects become accustomed to the maneuvers). The normal ranges are wide, so that values in the lower quarter of the normal range are compatible both with normal strength and with mild or moderate weakness. However, a P_{I,max} of ~80 cm H₂O usually excludes clinically important inspiratory muscle weakness. Values less negative than this are difficult to interpret, and more detailed studies are required. A normal P_{E,max} with a low P_{I,max} suggests isolated diaphragmatic weakness.
When inspiratory muscle weakness is confirmed, the next diagnostic step is to unravel whether this is due to diaphragmatic weakness, because the diaphragm is the most important inspiratory muscle. This is accomplished by the measurement of maximum transdiaphragmatic pressure (Pdi,max). Pdi,max is the difference between gastric pressure (reflecting abdominal pressure) and esophageal pressure (reflecting intrapleural pressure) on a maximum inspiratory effort after the insertion of appropriate balloon catheters in the esophagus and the stomach, 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 that nasal flow is low and largely independent of the driving pressure that is the esophageal pressure. Pdi measured during a sniff (Pdi,sn,max) reflects diaphragm strength, and Pes reflects the integrated pressure of the inspiratory muscles on the lungs (Figure 8-5). Pressures measured in the mouth, nasopharynx, or one nostril give a clinically useful approximation to esophageal pressure during sniffs without the need to insert esophageal balloons, especially in the absence of significant obstructive airway disease. To be useful as a test of respiratory muscle strength, sniffs need to be maximal, which is relatively easy for most willing subjects, but may require some practice. 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 8-6). There is a wide range of normal values, reflecting the wide range of normal muscle strength in different individuals. In clinical practice, Pdi,sn,max values greater than 100 cm H\textsubscript{2}O in males and 80 cm H\textsubscript{2}O in females are unlikely to be associated with clinically significant diaphragm weakness. Values of maximal sniff esophageal or nasal pressure numerically greater than 70 cm H\textsubscript{2}O (males) or 60 cm H\textsubscript{2}O (females) are also unlikely to be associated with significant inspiratory muscle weakness. However, these reflect the integrated pressure of all the inspiratory muscles, and it is possible that there could be a degree of weakness of one or more of these muscle groups that would not be detected at this level. In chronic obstructive pulmonary disease, nasal sniff pressure tends to underestimate sniff esophageal pressure because of dampened pressure transmission from the alveoli to the upper airway but can complement \(F_{I,max}\) in excluding weakness clinically.

Electrophysiologic Testing

The next diagnostic step consists of determining whether weakness is due to muscle, nerve, or neuromuscular transmission impairment. This requires the measurement of Pdi in response to bilateral supramaximal phrenic nerve electrical or magnetic stimulation, with concurrent recording of the elicited
electromyogram (EMG) of the diaphragm (called the compound muscle action potential, CMAP) with either surface or esophageal electrodes (Figure 8-7). If the phrenic nerve is stimulated, the diaphragm contracts. This 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 and thus changes in lung volume and initial length of the diaphragm), the isometric force-frequency curve of the diaphragm is obtained (Figure 8-8). (It should be noted that the usual rate of motor nerve discharge during voluntary muscle contraction in humans is between 5 and 15 Hz, and, because of the steep shape of the force-frequency curve in this range, small alterations in the discharge rate cause significant changes in the force produced. Maximum voluntary contractions, such as the $P_{1\text{max}}$ are achieved with discharge rates higher than 50 Hz, but cannot be sustained for long. 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 because of activation of the brachial plexus). Therefore, the transdiaphragmatic pressure developed in response to single supramaximal phrenic nerve stimulations at 1 Hz, called the twitch $P_{di}$, is commonly measured. Although technically demanding, this approach has the great advantage of being independent of patient effort/motivation. This 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 [Mwave] on the diaphragmatic EMG) (Figure 8-7, B). A prolonged conduction time suggests nerve involvement.

**FIGURE 8-5** 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 (Sn Pes) and sniff transdiaphragmatic pressures (Sn Pdi) are illustrated. The right panel shows an example 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 8-6** The sniff maneuver, which makes use of a nasal bung and an adapted pressure meter. A, Measurement setup. The meter returns a numerical value that is the amplitude of the pressure swing between atmospheric (0) pressure and the nadir. B, The trace produced. The meter returns a numerical value that is the amplitude of the pressure swing between atmospheric (0) pressure and the nadir.
However, electrophysiologic testing also has shortcomings. Although the conduction time or latency is prolonged in neuropathies that are predominantly demyelinating, it may be preserved in neuropathies that are predominantly axonal despite substantial diaphragm weakness. Moreover, when the preceding technique is used, it is important that costimulation of the brachial plexus be avoided, otherwise the action potential recorded from surface electrodes may originate from muscles other than the diaphragm. This problem is compounded if the phrenic nerve is stimulated by use of a magnetic technique. Classically, an axonal neuropathy is characterized by the finding of preserved latencies with diminished CMAP. Lack of CMAP after nerve stimulation is an indication of paralysis with the lesion located proximal to or at the neuromuscular junction. Decreased twitch Pdi in the face of normal CMAP is characteristic of contractile dysfunction that resides within the muscle.

**FIGURE 8-7 Electrophysiologic testing: The “twitch Pdi.”**

**A,** The twitch transdiaphragmatic pressure (Pdi) after magnetic/electrical stimulation. **B,** A detailed (enlarged) view of a compound muscle action potential (M wave), where 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. (Adapted from Vassilakopoulos T, Roussos C: Neuromuscular respiratory failure. In Clinical Critical Care Medicine, Slutsky A, Takala R, Torres R, eds. St. Louis: Mosby.)
breathe spontaneously, the inspiratory muscles should be able to sustain the aforementioned load over time as well as adjust the minute ventilation in such a way that there is adequate gas exchange. The ability of the respiratory muscles to sustain this load without the appearance of fatigue is called endurance and is determined by the balance between energy supplies and energy demands (Figure 8-10).

Energy supplies depend 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 supplies are adequate to meet the demands, and a large recruitable reserve exists (see Figure 8-10). Energy demands increase proportionally with the mean pressure developed by the inspiratory muscles per breath (PI) expressed as a fraction of maximum pressure that the respiratory muscles can voluntarily develop (PI/PI,max), the minute ventilation (V'E), the inspiratory duty cycle (T'I/T'TOT), and the mean inspiratory flow rate (VT/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).

The product of T'I/T'TOT and the mean transdiaphragmatic pressure expressed as a fraction of maximal (Pdi/Pdi,max) defines a useful “tension-time index” (TTI evade) that is related to the endurance time (i.e., the time that the diaphragm can...
Whenever $TTI_{di}$ is smaller than the critical value of 0.15, the load can be sustained indefinitely; but when $TTI_{di}$ exceeds the critical zone of 0.15–0.18, the load can be sustained only for a limited time period, in other words, the endurance time. This was found to be inversely related to $TTI_{di}$. The $TTI$ concept is assumed to be applicable not only to the diaphragm but also to the respiratory muscles as a whole: 

$$TTI = \frac{P_I}{P_{I,\text{max}}} \frac{T_I}{T_{TOT}}$$

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 8-4 demonstrates, $P_I/P_{I,\text{max}}$ and $T_I/T_{TOT}$. which constitute the $TTI$, are among the determinants of energy demands; an increase in either that will increase the $TTI$ value will also increase the demands. But what determines the ratio $P_I/P_{I,\text{max}}$? The nominator, 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 neuro-muscular competence (i.e., the maximum inspiratory muscle activation that can be voluntarily achieved). It follows, then, that the value of $P_I/P_{I,\text{max}}$ is determined by the balance between load and competence (see Figure 8-9). But $P_I/P_{I,\text{max}}$ is also one of the determinants of energy demands (see Figure 8-10); therefore, the two balances (i.e., between load and competence and energy supply and demand) are in essence linked, creating a system (Figure 8-11). 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 8-11). 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 individual. 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 ($L_o$) where 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
Fatigue is defined as the loss of beneficial effects. It should be distinguished from weakness in which the presence of weakness may itself predispose a muscle to fatigue. 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, peripheral high-frequency fatigue, or peripheral low-frequency fatigue.

**Central 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 that may separate central from peripheral fatigue. This test examines the transdiaphragmatic pressure (Pdi) response to bilateral phrenic nerve stimulation superimposed on graded voluntary contractions of the diaphragm. Normally, the amplitude of the Pdi twitches in response to phrenic nerve stimulation decreases as the voluntary Pdi increases. During Pdi,max, no superimposed twitches can be detected. When 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 so 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 adaptive response preventing the muscle’s self-destruction by excessive activation.

**Peripheral Fatigue.** 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 because of failure of impulse propagation across the neuromuscular junction, the muscle surface membrane or the t tubules (transmission fatigue), impaired excitation—contraction coupling, or failure of the contractile apparatus of the muscle fibers (because of alterations in metabolism or changes in contractile proteins).
Peripheral fatigue can be further classified into high-frequency and low-frequency fatigue on the basis of the shape of the muscle force-frequency curve (Figure 8-8). High-frequency fatigue results in depression of the forces generated by a muscle in response to high-frequency electrical stimulation (50–100 Hz), whereas low-frequency fatigue results in depression of force generation in response to low-frequency stimuli (1–20 Hz). Low-frequency fatigue can occur in isolation, but high-frequency fatigue is invariably associated with some alterations in muscle force generation at lower frequencies.

High-Frequency Fatigue. During artificial stimulation of a motor neuron, especially at high frequencies, muscle force declines rapidly in association with the decline in CMAP amplitude. This response, known as “high-frequency fatigue” (see Figure 8-8), is attributed to transmission fatigue. The site of this type of fatigue may be located postsynaptically (from a decrease in sarcolemmal membrane endplate excitability or a reduction in action potential propagation into the t tubular system) or presynaptically (probably in fine terminal filaments of the motor nerve or less frequently from depletion of synaptic transmitter substance). Teleologically, transmission block could be beneficial in some instances by protecting the muscle against excessive depletion of its ATP stores, which would lead to rigor mortis. Normal subjects breathing against high-intensity inspiratory resistive loads develop high-frequency fatigue, which resolves very quickly after cessation of the strenuous diaphragmatic contractions.

Low-Frequency Fatigue. All processes that link the electrical activation of the muscle fiber and the various metabolic and enzymatic processes providing energy to the contractile machinery are called excitation-contraction coupling processes. Impaired excitation contraction coupling is thought to be responsible when the loss of force is not accompanied by a parallel decline in the electrical activity. This type of fatigue is characterized by a selective loss of force at low frequencies of stimulation (low-frequency fatigue) (see Figure 8-8) despite maintenance of the force generated at high frequencies of stimulation, indicating that the contractile proteins continue to generate force provided that sufficient calcium is released by the sarcoplasmic reticulum. The mechanism of this type of fatigue is not understood. It may occur because of a reduced level of calcium availability caused by alterations in sarcoplasmic reticulum function or a reduction in the calcium sensitivity of the myofilaments (troponin binding site) at submaximal calcium concentrations (because of high hydrogen and phosphate ion concentration). These defects would reduce the force developed at low-frequency stimulation. In contrast, at higher stimulation frequencies, a relatively normal force can be generated when the interior of the fiber is saturated with calcium. This type of fatigue is characteristically long lasting, taking several hours to recover. 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 8-10), resulting in depletion of muscle energy stores, pH changes from lactate accumulation, and excessive production of oxygen-derived free radicals. However, the exact interplay of all these factors is not yet identified in either the diaphragm or other skeletal muscles. Accordingly, low-frequency fatigue occurs in the diaphragm of experimental animals during cardiogenic or septic shock. Low-frequency fatigue has also been found in the diaphragm and sternocleidomastoid of normal subjects after they breathed against very high inspiratory resistance or after sustaining maximum voluntary ventilation (for 2 min) (Figure 8-13).

The clinical relevance of respiratory muscle fatigue is difficult to figure out, because the measurements that are required for fatigue detection are hard to apply in situations where fatigue is likely present (such as during acute hypercapnic respiratory failure).

Inflammation and Injury. Strenuous diaphragmatic contractions (induced by resistive breathing, which accompanies many disease states such as 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 definitely established but may involve intradiaphragmatic cytokine induction, adhesion molecule upregulation, calpain activation, and reactive oxygen species formation. Cytokines are also 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

**FIGURE 8-13** Demonstration of low-frequency fatigue of the diaphragm in normal subjects. The mean twitch tension (twitch trans-diaphragmatic pressure; Tw Pdi) is shown before and at intervals up to 90 min after intense diaphragmatic contraction (in this case, a 2-min period of maximal normocapnic hyperventilation) in nine healthy adults (blue symbols). Data in the same subjects after a sham (“normal breathing”) run are shown in red. A significant decline in Tw Pdi is observed that has only partially recovered at 90 min, which confirms the presence of low-frequency diaphragmatic fatigue. (Data from Hamnegård C-H, Wragg SD, Kyroussis D, et al: Diaphragm fatigue following maximal ventilation in man. Eur Respir J 1996; 9:241–247.)
transformed into myocytes, when the muscle becomes injured, to replace damaged myocytes.

**Chronic Responses**

**Increased Load**

**Plasticity and Adaptation.** The respiratory muscles are plastic organs that respond to chronic changes of the load they are facing and thus of their activity with structural and functional changes/adaptations.

COPD is the paradigm of a disease with 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 8-14, A). 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 latter being the faster (Figure 8-14, C). The

**FIGURE 8-14** 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), 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. (Adapted from Mantilla CB, Sieck GS: Mechanisms underlying motor unit plasticity in the respiratory system. J Appl Physiol 2003; 94:1230–1241, and Jones DA: Skeletal muscle physiology. In Roussos C, ed: The Thorax, 2nd ed. New York: Marcel Dekker; 3–32).
Diaphragm in healthy humans is composed of approximately 50% type I fatigue-resistant fibers, 25% type IIA, and 25% type IIB. There are two ways in which muscles can modify their overall MHC phenotype: preferential atrophy/hypertrophy of fibers containing a specific MHC isoform and actual transformation from one fiber type to another. In COPD, there is a transformation of type II to type I fibers, resulting in a great predominance of type I fatigue-resistant fibers. This 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.

Adaptation is not only restricted to fiber type transformation. In an animal model of COPD (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.

**Inactivity-Unloading**

Respiratory muscles do not only adapt when they function against increased load but also when they become inactive, as happens during denervation or when a mechanical ventilator undertakes their role as force generator to create the driving pressure permitting airflow into the lungs. Inactivity and unloading of the diaphragm caused by mechanical ventilation is harmful, resulting in decreased diaphragmatic force-generating capacity, diaphragmatic atrophy, and diaphragmatic injury, which are described by the term *ventilator-induced diaphragmatic dysfunction* (VIDD). The mechanisms are not fully explained, but muscle atrophy, oxidative stress, structural injury, and muscle fiber remodeling contribute to various extents in the development of VIDD.

**SUGGESTED READINGS**