CHAPTER 11

Muscle Function

Theodoros Vassilakopoulos, Ioanna Sigala, and Charis Roussos

The respiratory muscles are the only muscles, along with the heart, that have to work continuously, although intermittently, to sustain life. They have to move repetitively a complex elastic structure, the thorax, to achieve the entry of air into the lung and thence gas exchange. The great number of these muscles mandates that they should interact properly to perform their task despite their different anatomic locations, geometric orientations, and motor innervation. They should also be able to adapt to a variety of working conditions and respond to many different chemical and neural stimuli.

Describe the function of the respiratory muscles in a single chapter is extremely difficult. We therefore present certain aspects of respiratory muscle function that are relevant to an understanding of the role of these muscles in breathing. Accordingly, we first discuss the functional anatomy of the respiratory muscles. Next we describe the elastic properties of the thorax that the muscles must move to achieve ventilation in the section on the statics of breathing. The ability to take a breath depends on the balance between the inspiratory load and neuromuscular competence. However, the respiratory muscles must contract continuously to sustain life, and the ability to do this depends on the balance between energy supplies and demands. Consequently, we deal with the parameters of these balances and the way in which they interact in section on the ability to breathe. The factors that could impair the force-generating capacity of the respiratory muscles are then discussed. The respiratory muscles are plastic structures that adapt to changes in level of load. The impact of increased load and inactivity on the respiratory muscles is the topic of the last two sections of this chapter.

FUNCTIONAL ANATOMY

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 approximately at right angles to each other, and both layers are thicker behind than in front.[1]

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. Near the costochondral junctions, the external intercostals are replaced by a fibrous aponeurosis, the anterior intercostal membrane that extends to the anterior end of the intercostal space.

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.

Although the intercostal spaces have two layers of intercostal muscle fibers in their lateral portion, they contain a single muscle layer in their ventral and dorsal portion. Ventrally, between the sternum and the costochondral junctions, the only fibers are those of the internal intercostal muscles; these are particularly thick in

this region of the rib cage, where they are conventionally called the parasternal intercostals. Dorsally, from the angles of the ribs to the vertebrae, the only fibers come from the external intercostal muscles. These latter, however, are duplicated by a spindle-shaped muscle that runs in each interspace from the tip of the transverse process of the vertebra to the angle of the rib below; this muscle is the levator costae. All the intercostal muscles are innervated by the intercostal nerves.

The respiratory action of the intercostal muscles has been a matter of controversy throughout medical history. The most influential theory proposed to explain this action was that of Hamberger (1749), who based it on geometric considerations (Fig. 11.1): when an intercostal muscle contracts in one interspace, it pulls the upper rib downward and the lower rib upward. The actual movement of the ribs depends on the relative amount of torque around the center of rotation (the vertebral articulations) acting on the two points of attachment of the muscle to the respective ribs: the external intercostals run obliquely downward and forward, so their insertion to the lower rib is more distant from the center of rotation than their insertion to the upper rib. Hence when these muscles contract, the torque acting on the lower rib is greater than that acting on the upper rib, and its net effect is to raise the ribs. The reverse is true for the internal intercostals, which run upward and forward, so their action is to lower the ribs to which they are attached. The parasternal intercostals are part of the internal intercostal layer, but their action is referred to the sternum, rather than to the vertebral column (i.e., the center of rotation is the sternocostal junctions); therefore, by similar arguments, their contraction should raise the ribs.[2]

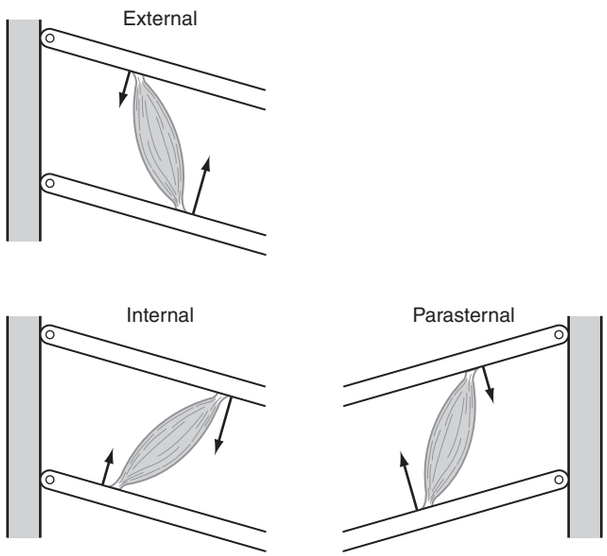

Figure 11.1 Diagram illustrating Hamberger's theory. In each panel, the *hatched area* represents the center of rotation (the spine for internal and external intercostal muscles and the sternum for parasternal muscles), and the *two bars oriented obliquely* represent two adjacent ribs. The intercostal muscles are depicted as single bundles, and the torques acting on the ribs during contraction of these muscles are represented by *arrows*. (From DeTroyer A, Loring SH: Actions of the respiratory muscles. In Roussos C [ed]: The Thorax. New York: Marcel Dekker, 1995.)

The Hamburger theory is incomplete, however, and cannot entirely explain the actions of the intercostal muscles on the ribs for two reasons.[3,4] First, the Hamburger model is planar, whereas in reality the ribs are curved. As a result, the changes in length of the intercostal muscles during a given rotation of the ribs (hence their mechanical advantage and action on the ribs) vary as a function of the position of the muscle fibers along the rib. Thus, during cranial rotation of the ribs, their curvature causes changes in muscle length that are greater in the dorsal region, decrease progressively as one moves around the rib cage, and are reversed as one approaches the sternum. This finding is in contrast to the Hamberger model, which predicts equal shortening of all external intercostals and equal lengthening of all internal intercostals during cranial rotation of two adjacent ribs. Second, the Hamburger model states that all the ribs rotate by equal amounts around parallel axes so the distance between adjacent ribs remains constant. In fact, the radii of curvature of different ribs are different, increasing from the top downward, so their rotations are similarly different. Consequently, there is a change in intercostal muscle length owing to the changes in the distance between the ribs from the top downward.

Despite the inaccuracies included in the Hamberger model, its predictions seem valid because experimental data suggest that the external intercostals, the parasternal intercostals, and the levatores costarum have an inspiratory action on the rib cage, whereas the internal intercostals are expiratory. During breathing at rest, normal humans have inspiratory activity in the parasternal intercostals.[5,6] This finding suggests that in humans the contribution of the parasternal intercostals to resting breathing is greater than that of the external intercostals. During loaded breathing, the activation of the external intercostals and levatores costarum increases, although the mechanical effectiveness of this reserve "load-compensating" system is relatively small.[7]

A clearly illustrative clinical example of the "isolated" inspiratory action of the intercostals is offered by patients who suffer from 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, thus causing an equal fall in abdominal pressure. Hence the abdomen moves paradoxically inward during inspiration, thus opposing the inflation of the lung. In fact, this paradoxic 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 whole respiratory cycle. On the contrary, this sign may be absent in the erect posture, in which some patients partially compensate for diaphragmatic paralysis by contracting the abdominal muscles during expiration, thus displacing the abdomen inward and the diaphragm cranially into the thorax. Relaxation of the abdominal muscles at the onset of inspiration may then cause outward motion of the abdominal wall and (passive) descent of the diaphragm that removes the characteristic paradoxic inspiratory inward abdominal motion.

Diaphragm

The floor of the thoracic cavity is closed by a thin musculotendinous sheet of complex structure and development, the diaphragm, which 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 central tendon of the diaphragm is thin, strong, and roughly trilobed. It has the shape of a boomerang, with its two ends pointing posterolaterally.[8] The central part is fused above with the fibrous pericardial sac, and both structures at this point are derived from the embryonic septum transversum.

The muscle of the diaphragm, all of which inserts into the central tendon, falls into two main components, according to its point of origin: the crural (vertebral) part and the costal (sternocostal) part. The crural (vertebral) part of the diaphragm arises from the crura and the three aponeurotic arcuate ligaments. The crura are 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. An ill-defined, fibrous thickening arch between the two crura forms the median arcuate ligament. A tendinous medial arcuate ligament passes from the crus on each side across the psoas major muscle to the tip of the transverse process of the first lumbar vertebra. From this point, a lateral arcuate ligament then runs to the 12th rib crossing the quadratus lumborum muscle. The medial and lateral arcuate ligaments are firmly adherent to the posterior body wall fused to the sheath and fascia of psoas and quadratus lumborum muscles, respectively. Muscle fibers arising from the crura and the arcuate ligaments pass upward to insert into the posterior border of the central tendon, overlapping to some extent and passing behind the fibers ascending from the 12th rib.

The costal (sternocostal) 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. From the back of the xiphoid process and the lower end of the sternum, muscle fibers pass almost horizontally backward into the anterior border of the central tendon. Separated from the sternal portion by a small gap, the sternocostal triangle, muscle fibers arise from the inner aspects of each costal cartilage from the 7th rib to the tip of the 12th rib. These costal fibers run cranially so they are directly apposed to the inner aspect of lower rib cage, thus creating a zone of apposition. Only at higher levels does an angle open up between them and the chest wall, and finally they converge horizontally onto the anterior, lateral, and, to some extent, posterior borders of the central tendon and increase progressively in length around the chest and from front to back. Frequently, a triangular gap remains between the fibers from the 12th rib and the most lateral fibers from the lateral arcuate ligament, thereby leaving a muscular deficiency, the vertebrocostal trigone.

The shape of the relaxed diaphragm 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.[9,10] The free surface curves to join the inside of the rib cage and then continues downward so the diaphragm becomes cylindric in the zone of apposition. The height of this zone in the standing human at rest is about 6 to 7 cm in the midaxillary line and occupies 25% to 30% of the total internal surface area of the rib cage. 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. Depending on whether the airways are open or closed, lung volume increases or alveolar pressure falls. Second, it produces 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. Furthermore, diaphragmatic contraction acts to displace the bony rib cage both directly through the insertions of the costal diaphragmatic fibers onto the ribs and indirectly through the effect of changing the pleural and abdominal pressures. Thus, when the diaphragm contracts, a cranially oriented force is 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). 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 appears that it has two opposing effects when it contracts. On the upper rib cage, it causes a decrease in the anteroposterior (AP) diameter, and this expiratory action is primarily the result of the fall in pleural pressure.[11] On the lower rib cage, it causes an expansion that is more pronounced along its transverse diameter than along its AP diameter. In fact, this is the pattern of chest wall motion observed in tetraplegic patients with transection injury at the C5 segment 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 zone of apposition makes the lower rib cage, in effect, part of the abdominal container, and measurements in dogs have established that, during breathing, 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.[12] Pressure in this pleural recess rises rather than falls during inspiration, a finding indicating that the rise in abdominal pressure is truly transmitted through the apposed diaphragm to expand the lower rib cage. This mechanism of diaphragmatic action has been termed the *appositional force*, and its magnitude depends directly on the size of the zone of apposition and on the rise in abdominal pressure and indirectly on the resistance provided by the abdominal contents to diaphragmatic descent. Clearly, for a given diaphragmatic contraction, the appositional force is greater when the rise in abdominal pressure and the zone of apposition are larger and when the resistance to diaphragmatic descent is higher because in this case the dome of the diaphragm descends less, the zone of apposition remains significant throughout inspiration, and the rise in abdominal pressure is larger. An illustrative clinical example of this latter effect is provided by tetraplegic patients: when the compliance of their abdomen decreases either by having them in the seated position or by means of a pneumatic cuff or an elastic binder around the abdomen, the expansion of the lower rib cage during inspiration is accentuated.[13] The greater area of apposed diaphragm at the sides of the rib cage, compared with that at the front, presumably accounts for the finding that the human diaphragm has a greater expanding action on the transverse than on the AP diameter of the lower rib cage.[11]

The balance between pleural pressure and the insertional and appositional forces of the diaphragm is also markedly affected by changes in lung volume. As lung volume decreases to less than FRC, the zone of apposition increases in size,[14] and the fraction of the rib cage exposed to pleural pressure decreases. As a result, the appositional force increases, whereas the effect of pleural pressure diminishes, so the inspiratory action of the diaphragm on the rib cage is enhanced. Conversely, as lung volume increases, the zone of apposition 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.[2,14–16] When lung volume approaches total lung capacity (TLC), the zone of apposition all but disappears,[14] and the diaphragmatic muscle fibers become oriented internally as well as cranially. As in the eviscerated animal, the insertional force of the diaphragm is then expiratory, rather than inspiratory, in direction. These two effects of increasing lung volume account for the inspiratory decrease in the transverse diameter of the lower rib cage in subjects with emphysema and severe hyperinflation (Hoover's sign).

The relationship between the lung volume and the mechanical effectiveness/advantage of the diaphragm is more pronounced whenever the lung volume changes acutely. When the lung volume increases chronically, some form of adaptation takes place to compensate partially for the mechanical disadvantage created for the diaphragm. In fact, it has been shown that in emphysematous hamsters the diaphragm drops out sarcomeres, resulting in a leftward shift of the whole length-tension curve so the muscle adapts to the shorter operating length.[17] The extent to which this adaption occurs in humans remains unclear as yet.

Although diaphragmatic contraction alone causes distortion of the rib cage at all lung volumes, normal humans breathing at rest expand the rib cage without distortion. Thus, during inspiration, the AP and transverse diameters of the lower rib cage increase proportionately and synchronously, and the AP diameter of the upper rib cage increases as well. This finding implies that, even during resting breathing, normal humans contract other muscles that expand the upper rib cage and increase the AP diameter of the lower rib cage.

Neck Muscles

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 AP diameter than in its transverse one, and to decrease the transverse diameter of the lower rib cage. This is inferred from the measurements of chest wall motion in subjects with transection of the upper cervical spinal cord,[18] in which the sternocleidomastoids are the only muscles spared. In essence, their isolated action counteracts the isolated action of the diaphragm on the upper rib cage.

In normal subjects breathing at rest, however, the sternocleidomastoids are inactive, recruited only when the inspiratory muscle pump is abnormally loaded or when ventilation increases substantially.[19,20] Therefore, they should be considered accessory muscles of inspiration.

Scalenes

The scalenes comprise 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 AP diameter of the upper rib cage.[21] Although earlier studies[22] had suggested that the scalenes function as accessory muscles of inspiration, more recent data[23] provide convincing evidence that these muscles 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 considerably.[23] Therefore, the 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.

STATICS OF BREATHING

The respiratory system is an elastic structure; that is, if a force is applied to it, it changes volume, and when the force is released, it returns to its resting configuration. Rohrer[23] proposed in 1916 that movement of the respiratory system is caused by pressure differences across the system to overcome the elastic resistance to volume change (elastic load), the frictional resistance to flow (resistive load), and the inertial resistance to mass acceleration (inertial load). The main function of the respiratory muscles is to provide the required pressure across the respiratory system to achieve its movement and thus the entry of air into the thorax. Although the act of breathing incorporates all the components initially described by Rohrer, it is really didactic to isolate each one and determine the pressure required to overcome each of the elastic, resistive, and inertial loads.

The term *statics of breathing* refers to the pressure-volume relationship of the respiratory system. As the origin of the word static implies (static is a Greek word meaning "with no movement"), this relationship has to be determined with no movement of air (no resistive pressure losses) and no acceleration of tissues (no inertial pressure losses) to reflect the elastic behavior of the respiratory system (elastic load).

One of the first experimental descriptions of the static properties of the respiratory system was that of Rahn and colleagues in 1946.[24] Normal subjects were asked to inspire a volume of air from a spirometer and then to relax against an occluded airway with an open glottis for a few seconds. This was repeated at various lung volumes. The pressure at the mouth was measured together with the lung volume and was recorded on an X-Y plot. Because under these conditions there is no flow of air within the airways, the pressure at the mouth equals the pressure in the airways and that of the alveoli. Consequently, the difference between the pressure in the mouth and the atmospheric pressure (i.e., body surface pressure) represents the distending pressure of the respiratory system. The volume at zero pressure is the resting volume of the respiratory system where mouth pressure equals zero and is the FRC. The horizontal distance from the solid line to the zero-pressure ordinate indicates total respiratory system distending (elastic) pressure ($P_{el,rs}$) and is negative (subatmospheric) below FRC and positive above FRC. Although Rahn and associates[24] reasoned that total pressure at the mouth is the sum of the pressures exerted by the elastic recoil properties of the chest wall ($P_{el,W}$) and the lung ($P_{el,L}$) (i.e., $P_{el,rs} = P_{el,L} + P_{el,W}$), these investigators were unable to measure these parameters directly. The best they could do was to use published values of the lung's in vitro pressure-volume relationship and to plot them on the pressure-volume diagram; then by subtracting $P_{el,L}$ from $P_{el,rs}$ at any volume, they calculated $P_{el,W}$ (Fig. 11.2). This diagram illustrates that lung recoil is positive at all lung volumes above residual volume (RV). On the contrary, the chest wall exhibits more complex behavior: from RV to approximately 60% of vital capacity (VC), the chest wall exerts outward elastic pressure (i.e., tends to expand). At FRC, which is approximately 40% of VC, there is an equilibrium between the inward pressure of the lungs and the outward pressure exerted by the rib cage; hence alveolar and mouth pressures are zero. From 60% of VC to TLC, the chest wall recoil is inward and is additive to that of the lungs.

The next major advance in the study of the statics of breathing came with the introduction of the esophageal balloon technique,[25] which allowed the measurement of esophageal pressure as an estimate of pleural pressure (P_{PL}) and consequently the partitioning of the respiratory system into its two components: lungs and chest wall. Because both share the same volume change, pressure partitioning is all that is necessary. Accordingly, Heaf and Prime[26] and Campbell[27] modified the Rahn diagram by plotting lung volume against P_{PL} under two conditions (Fig. 11.3): during breath-holding with the glottis open (which is achieved by the coordinated action of the inspiratory muscles) and during relaxation of the respiratory muscles with the airway occluded. Under the first condition, because there is no movement of air and the airway (glottis) remains open, the pressure in the

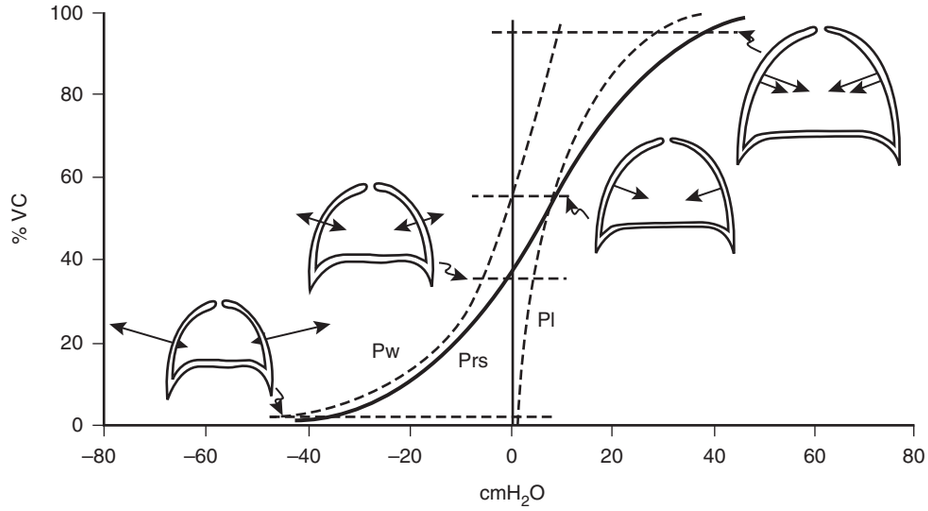

Figure 11.2 Static volume-pressure curves of the lung (Pl), chest wall (Pw), and total respiratory system (Prs) during relaxation in the sitting posture. The static forces of the lung and the chest wall are pictured by *arrows* in the side drawings. The dimensions of the arrows are not to scale; the volume corresponding to each drawing is indicated by *horizontal broken lines*. (From Rahn H, Otis AB, Chadwich LE, Fenn WO: The pressure-volume diagram of the thorax and lung. Am J Physiol 1946;146:161–178, as modified by Agostoni E, Mead J: Statics of the respiratory system. In Fenn WO [ed]: Handbook of Physiology. Section 3: Respiration, vol 1 Washington, DC:, American Physiological Society, 1964.)

mouth (i.e., the same with the atmospheric pressure) equals the pressure in the alveoli (i.e., Pm = Patm = PaLV). The difference between this pressure and the PPL (i.e., PaLV - PPL) represents the distending pressure of the lung (Pel,L). Because pressures are measured relative to Patm (i.e., Patm is considered to be zero), under this condition Pel,L = -PPL PPL = -Pel,L. Accordingly, if lung volume were plotted against PPL, the pressure-volume relationship of the lung would be obtained (*left curve* on Fig. 11.3). Under the second condition, the respiratory muscles are relaxed, and so the difference between PPL and body surface pressure (i.e., Patm) represents the distending pressure of the chest wall: Pel,W = PPL - Patm. Because Patm = 0, Pel,W = PPL, and if lung volume were plotted against PPL, the pressure-volume relationship of the chest wall would be obtained (*right curve* on Fig. 11.3). This is identical to the chest wall pressure-volume curve in the Rahn diagram. The two curves intersect at approximately -5 cm H_2O, the PPL value at resting FRC. The horizontal distance between the two curves gives the elastic pressure that must be developed (by either the respiratory muscles or the ventilator) to displace the system above or below its equilibrium volume (where the two curves intersect) and thus corresponds to the pressure-volume relationship of the entire respiratory system.

Neglecting dynamic considerations, the left-hand curve shows the pleural pressure-volume relationship during spontaneous breathing when airway pressure is near zero. The right-hand curve shows the pleural pressure-volume relationships during mechanical ventilation (when the respiratory muscles are relaxed), and the distance between the curves approximates alveolar pressure during mechanical ventilation.[28]

Note that this analysis considers the chest wall as a single compartment model (i.e., as having a single degree of freedom). This means that it is possible to measure the change in a single dimension of the chest wall and solve for changes in all other dimensions. Of course, the contribution of the abdomen, diaphragm, or rib cage to the volume displacements cannot be differentiated. Before this volume partitioning could be attempted, one had to know the pressures acting on these different compartments. This became possible after the work of Agostoni and Rahn,[29] who developed the method of measuring transdiaphragmatic pressure as the difference between gastric and esophageal pressure. By measuring gastric pressure as an index of abdominal pressure (Pab) and esophageal pressure as an index of pleural pressure, these investigators accomplished the pressure partitioning necessary to determine the pressures displacing the abdomen (Pab), as well as those acting on the inner surface of the rib cage (PPL). This set the stage for partitioning of the chest wall elastic properties into those of the abdomen and the rib cage. Although several techniques and models for this

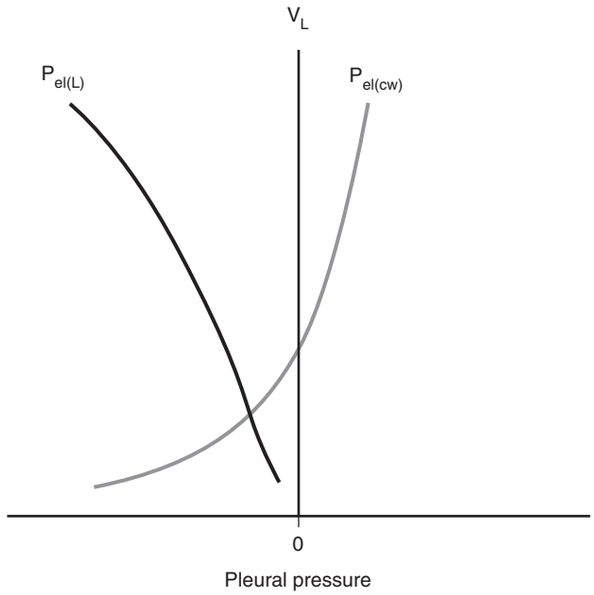

Figure 11.3 Pressure-volume curves of lung and chest wall. Esophageal pressure as estimate of pleural pressure (P_{PL}) on the horizontal axis is plotted against volume on the vertical axis. Data were obtained from normal young men under two conditions. *Left curve*, $Pel_{(L)}$ is the pressure-volume relationship when the lung is held inflated by the respiratory muscles with the glottis open and thus negative of transpulmonary pressure (alveolar minus pleural pressure). *Right curve*, $Pel_{(CW)}$ is the pressure-volume curve during muscular relaxation against an occluded airway. The curve defines the transthoracic pressure (pleural minus atmospheric pressure)–volume relationship. (From Rodarte JH: Lung and chest wall mechanics: Basic concepts. In Scharf SM [ed]: Heart-Lung Interactions in Health and Disease. New York: Marcel Dekker, 1989.)

partitioning have been proposed,[30–33] the one introduced by Konno and Mead[34] has gained wide acceptance and will be further analyzed. These investigators measured the surface motion displacements of the rib cage and abdomen and used them to represent the corresponding volume changes in both sitting and supine normal subjects keeping a fixed body position. These investigators hypothesized that the chest wall has two degrees of freedom (i.e., can accommodate lung volume by displacing the rib cage or diaphragm and abdomen independently, as parallel pathways). The sum of both displacements was monotonically related to changes in lung volume. AP displacements of the rib cage and abdominal wall were initially measured on many different chest wall surface points by means of linear differential transducers. Displacement of loci on the middle sternum and above the umbilicus were found to be those that best represent the volume displacement relationship of the rib cage and abdomen, respectively. The investigators recognized that in the boundary between the rib cage and the abdomen, there were more degrees of freedom. Even more degrees of freedom emerged by considering the cranial movement of rib cage[35] and by allowing flexion of the spine. Konno and Mead[34] expressed chest wall configuration by plotting rib cage versus abdominal AP wall dimensions (Fig. 11.4).[36] Each point in the diagram (i.e., each pair of AP dimensions) would represent a unique configuration of the chest wall at volumes from TLC to RV. The *dashed line* encircling the data points in Figure 11.4 represents the limits of possible configurations. The *continuous line* from RV to TLC represents the chest wall configurations (i.e., pairs of AP dimensions) obtained when the corresponding lung volumes were held by relaxing against a closed airway. This relaxation curve represents the minimum energy configuration at each lung volume, and distortion away from this configuration requires energy. If at any point along the relaxation line the subject closes the airway and shifts volume between the abdominal and rib cage compartments while lung volume remains constant (isovolume maneuver), the AP diameters of the rib cage and the abdomen will follow a line with a negative slope (i.e., the AP diameter of the

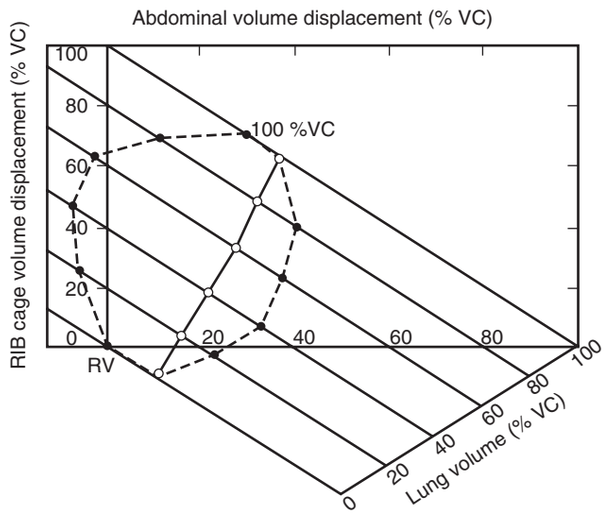

Figure 11.4 The Konno-Mead diagram. The rib cage anteroposterior dimensions are plotted against the abdominal anteroposterior dimensions. The displacements are expressed as a percentage of total over the vital capacity (VC) relative to values at active residual volume (RV). The *solid line with open points* indicates the configurations in relaxed states from total lung capacity (TLC) (100%) isovolume obtained by shifting volume from abdomen to chest and vice versa and by keeping a closed glottis (isovolume maneuvers). The area enclosed by the *dashed line* illustrates a range of possible configurations produced by submaximal contraction of rib cage and abdominal muscles. (From Smith J, Loring S: Passive mechanical properties of the chest wall. In Handbook of Physiology. Section 3: The Respiratory System, vol 3, part 2. Washington, DC: American Physiological Society, 1986.)

abdomen becomes smaller when the AP diameter of the rib cage becomes bigger and vice versa). In reality, these isovolume isopleths are flat loops showing hysteresis rather than lines. The AP diameter can be derived not only by linear pressure transducers, as originally described, but also with the use of magnetometers or Respitrace (respiratory inductive plethysmography bands), which, in fact, measures a cross-sectional area that is less susceptible to local distortion than with magnetometers.[37] Calibration of chest wall dimensions can be achieved by doing isovolume maneuvers at different lung volumes (e.g., at 20% intervals of the VC, as indicated in Fig. 11.4), thus providing a quantitative link between configuration and lung volume. The measurement of chest wall displacements has become a useful method to monitor ventilation noninvasively, and it has a precision to within approximately 10% of spirometric measurements.

By combining the pressure partitioning of Agostoni and Rahn with the volume partitioning already presented, one can measure the elastic properties of the rib cage and abdomen separately.[38] In the upright, standing position, the abdomen is considerably less compliant than the rib cage because the action of gravity causes the abdominal contents to stretch the anterior abdominal wall; in the supine position, however, abdominal compliance increases markedly.[39] As a result, abdominal motion during breathing is more prominent in the supine position than in the upright position.[40]

The Konno-Mead method does not measure displacement of the diaphragm. The actual lung volume displaced by the diaphragm is included in both rib cage expansion and abdominal displacement, and the exact contribution of the diaphragm to the two compartments remains a matter of controversy despite thorough investigation and ingenious theoretical analysis. This stems from the complex actions of the diaphragm and the finding that the rib cage and the diaphragm-abdomen complex, rather than being two independent pathways, seem to be mechanically coupled in ways that are not well understood. Detailed presentation of this challenging area of controversy is beyond the scope of this chapter, however, and the interested reader should consult several excellent reviews.[39–41]

ABILITY TO BREATHE: LOAD/CAPACITY BALANCE

For a human 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 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. This can be schematically represented by considering the ability to take a breath as a balance between inspiratory load and neuromuscular competence (Fig. 11.5). Under normal conditions, this system is polarized in favor of neuromuscular competence (i.e., there are reserves that permit considerable increases in load). However, for humans to breathe spontaneously, the inspiratory muscles should be able to sustain the previously mentioned load over time and also 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 (Fig. 11.6).

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 utilize energy sources, and the muscle's energy stores.[42,43] Under normal circumstances, energy supplies are adequate to meet the demands, and a large recruitable reserve exists (see Fig. 11.6).

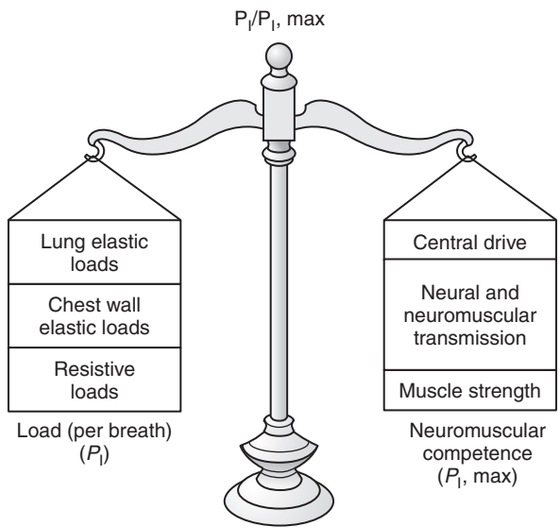

Figure 11.5 The ability to take a spontaneous breath is determined by the balance between the load imposed on the respiratory system (PI) and the neuromuscular competence of the ventilatory pump (PImax). Normally this balance weighs in favor of competence, thus permitting significant increases in load. However, if the competence is, for whatever reason, reduced to less than a critical point (e.g., drug overdose, myasthenia gravis), the balance may then weigh in favor of load, thus rendering the ventilatory pump insufficient to inflate the lungs and chest wall. (From Vassilakopoulos T, Zakynthinos S, Roussos C: Respiratory muscles and weaning failure. Eur Respir J 1996;9:2383–2400.)

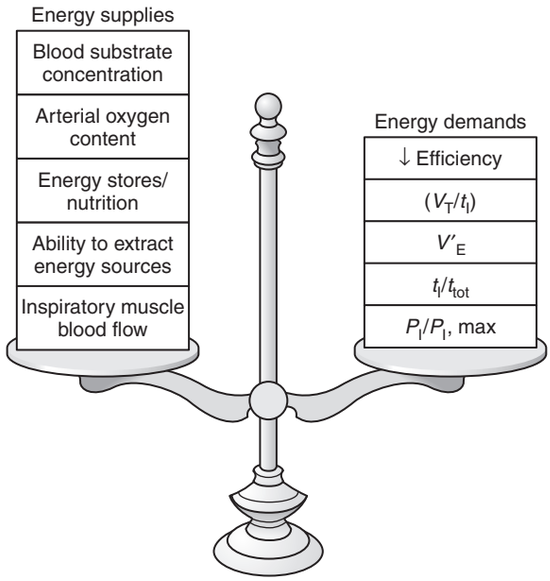

Figure 11.6 Respiratory muscle endurance is determined by the balance between energy supplies and demands. Normally, the supplies meet the demands, and a large reserve does exist. Whenever this balance weighs in favor of demands, the respiratory muscles ultimately become fatigued, leading to inability to sustain spontaneous breathing. (From Vassilakopoulos T, Zakynthinos S, Roussos C: Respiratory muscles and weaning failure. Eur Respir J 1996;9:2383–2400.)

Energy demands increase proportionally with the mean tidal pressure developed by the inspiratory muscles (PI) expressed as a fraction of maximum (PI/PImax), the minute ventilation, the inspiratory duty cycle (TI/TTOT), and the mean inspiratory flow rate (VT/TI) and are inversely related to the efficiency of the muscles.[42,43] Fatigue develops when the mean rate of energy demands exceeds the mean rate of energy supply[44] (i.e., when the balance is polarized in favor of demands)

$$Ud > Us\ W/E > Us \qquad (1)$$

where W is the mean muscle power, E is efficiency, Ud is energy demand, and Us is energy supply.

Bellemare and Grassino[45] suggested that the product of TI/TTOT and the mean transdiaphragmatic pressure expressed as a fraction of maximal (Pdi/Pdimax) 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 only for a limited time period (i.e., the endurance time). This was found to be inversely related to TTIdi. By analogy, a TTI was calculated for the rib cage muscles:

$$TTIrc = \text{mean value } P_{PL}/P_{PL}max\ TI/TT \qquad (2)$$

where P_{PL} is the pleural pressure, and the critical value was found to be 0.30.[46] The TTI concept is assumed to be applicable not only to the diaphragm, but also to the respiratory muscles as a whole[47]:

$$TTI = \frac{PI\ TI}{PImax\ TTOT} \qquad (3)$$

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where PI = mean inspiratory pressure per breath and PImax = maximal inspiratory pressure. Because we have stated that 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 11.6 demonstrates, PI/PImax and TI/TTOT, 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. The energy balance may then weigh in favor of demands leading to fatigue. Furthermore, Roussos and colleagues[48] directly related PI/PImax to the endurance time. The critical value of PI/PImax that could be generated indefinitely at FRC was approximately 0.60. Greater values of PI/PImax ratio were inversely related to the endurance time in a curvilinear fashion. When lung volume was increased from FRC to FRC + 1/2 inspiratory capacity, the critical values of PI/PImax and the endurance time were diminished greatly (20% to 25% of PImax).

What determines the PI/PImax ratio, however? The nominator, the mean inspiratory pressure, 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 achieved). It follows, then, that the value of PI/PImax is determined by the balance between load and competence (see Fig. 11.5). However, PI/PImax is also one of the determinants of energy demands (see Fig. 11.6); therefore, the two balances (i.e., between load and competence and energy supply and demand) are in essence linked, creating a system. Schematically, when the central hinge of the system moves upward, or is at least horizontal, spontaneous ventilation can be sustained indefinitely (Fig. 11.7). One can easily see that 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.

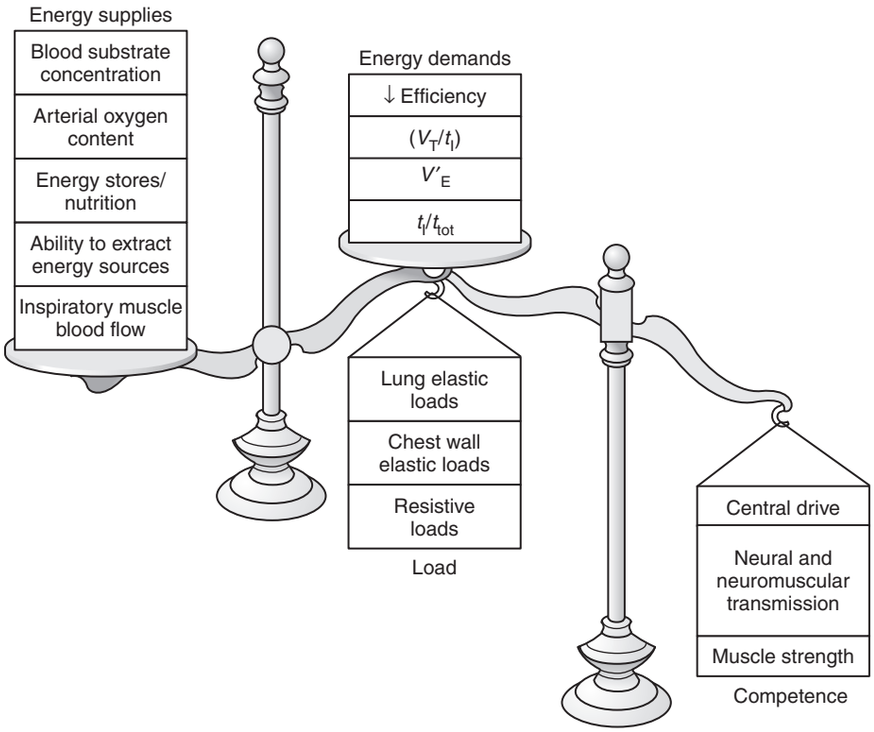

Figure 11.7 The system of two balances incorporating the various determinants of load, competence, energy supplies, and demands is represented schematically. The PI/PImax that was one of the determinants of energy demands (see Fig. 11.6) is replaced by its equivalent: the balance between load and neuromuscular competence (see Fig. 11.5). In fact, this is the reason that the two balances are linked. When the central hinge of the system moves upward or is at least at a horizontal level, an appropriate relationship between ventilatory needs and neurorespiratory capacity exists, and spontaneous ventilation can be sustained. In healthy persons, the hinge moves far upward to create a large reserve. (From Vassilakopoulos T, Zakynthinos S, Roussos C: Respiratory muscles and weaning failure. Eur Respir J 1996;9:2383–2400.)

When the central hinge of the system, for whatever reason, moves downward, spontaneous ventilation cannot be sustained, and ventilatory failure ensues, ultimately necessitating mechanical ventilation.

FACTORS IMPAIRING MUSCLES' FORCE-GENERATING CAPACITY

Decreased Neuromuscular Competence

Proper function of the respiratory muscles requires an adequate output of the centers controlling them, anatomic and functional integrity of the nerves supplying them, unimpaired neuromuscular transmission, and adequate muscle strength. A defect at any of these levels would obviously decrease neuromuscular competence and thus the muscles' force-generating capacity.

Decreased Respiratory Drive

Central nervous system (CNS) depression caused by neurologic damage, toxic-metabolic encephalopathy, or drug overdose (sedatives, narcotics) is commonly the cause of decreased drive to the respiratory muscles. Metabolic alkalosis is another potential factor. Furthermore, occult hypothyroidism, sleep deprivation, and starvation are recognized as potential causes of decreased respiratory drive.[49] Dysfunction of the respiratory center may be caused by bulbar poliomyelitis, myotonic dystrophy, or acid maltase deficiency.[50] Alterations in central respiratory control may also develop in patients with neuromuscular disorders that do not produce specific dysfunction of the respiratory center. These alterations may be related to sleep-induced hypoventilation.[51]

Decreased Neural and Neuromuscular Transmission

Neural transmission to the respiratory muscles may be interrupted in phrenic nerve or spinal cord transection. Transmission may also be impaired in phrenic nerve injury (thermal, hypoxic, or traction injury during cardiac surgery[52]), demyelinating diseases, immunologic conditions (e.g., Guillain-Barré syndrome,[50,53] multiple sclerosis) or toxin-induced disorders (e.g., diphtheria), or in diseases affecting the lower motoneurons, whether infectious (e.g., poliomyelitis) or degenerative (e.g., amyotrophic lateral sclerosis). Various other neuropathies could also be included, but are rare enough to merit special mention in this context.

AU: Rare enough not to merit…?

Neuromuscular transmission, in turn, may be impaired by toxins (e.g., botulism that inhibits presynaptic acetylcholine release), an episode of myasthenia gravis, and drugs (organophosphate poisoning, aminoglycosides, and, especially, neuromuscular blockers).[50,54] Critical illness polyneuropathy is a syndrome of prolonged muscle weakness or paralysis typically manifesting

as failure to wean from mechanical ventilation.[50,55] The cause is unknown, although sepsis, multiple organ failure, shock, hypoxia, medications, and prolonged use of neuromuscular blocking agents have been implicated.[56] Electrophysiologic studies reveal abnormalities primarily characterized by axonal degeneration.[50,56,57] Although critical illness polyneuropathy is usually improved in parallel with the underlying disease, weaning is difficult, and the mortality rate is high in these patients.[50,56]

Muscle Weakness

Muscle weakness, a condition in which the capacity of a rested muscle to generate force is impaired, can be caused by a variety of reasons: (1) inflammatory, alcohol, and thyroid myopathies; (2) muscular dystrophies; (3) myopathies induced by drugs, especially corticosteroids,[58,59] antibiotics (aminoglycosides), and relaxants; (4) malnutrition[60–62] and muscle atrophy (especially important in the critically ill patient); (5) obesity[63]; (6) electrolyte imbalances, including hypocalcemia,[64] hypokalemia,[65] hypophosphatemia,[66,67] and both hypomagnesemia[68] and hypermagnesemia[65]; (7) hypercapnia (acute)[69] and acidosis,[70,71] which are important factors in the development of muscular weakness because most patients who increase their carbon dioxide tension (P_{CO_2}) enter a vicious cycle in which the increased P_{CO_2} reduces muscle strength,[69] ventilatory failure is thus worsened, and P_{CO_2} is further increased; (8) mechanical disadvantage; (9) sepsis and endotoxic shock; and (10) disuse atrophy.

With regard to mechanical disadvantage, hyperinflation is a factor. Respiratory muscles, like other skeletal muscles, obey the length-tension relationship. At any given level of activation, changes in muscle fiber length alter active and passive tension and thus modify actin-myosin interaction. At a concrete fiber length, active tension is maximal, whereas below or above this, it declines. Respiratory muscle length depends largely on lung volume and, to a lesser extent, on thoracoabdominal configuration.[35,72,73] The exact in vivo relationships have not been defined in detail. However, it is believed, based on animal experiments,[74,75] that fiber length for inspiratory muscles (diaphragm and intercostals) is near RV. In addition, a relationship between lung volume and diaphragmatic fiber length in humans has been confirmed[76] that could entirely explain the decreases in pressure with increasing lung volume by corresponding decreases in contractility. Hyperinflation, then, causes a decrease in the respiratory muscle's length and a change in their geometry that clearly decreases PImax. However, an important distinction should be made between the chronic, slowly developing static hyperinflation resulting from loss of lung elastic recoil and the acute, rapidly developing dynamic hyperinflation caused by bronchoconstriction, respiratory tract infection, or abnormally increased frequency of breathing (see the earlier discussion of the diaphragm). In fact, it has been shown that changes in inspiratory muscle characteristics can compensate for the decrease in the operating length caused by hyperinflation. In emphysematous hamsters, the diaphragm drops out sarcomeres, thus resulting in a leftward shift of the whole length-tension curve so the muscle adapts to the shorter operating length.[17] These alterations in muscle fiber length-tension characteristics may help to restore the mechanical advantage of the diaphragm in chronically hyperinflated states, although the extent to which this adaptation occurs in humans remains unclear.

Indirect evidence for the existence of such an adaptation in humans comes from the work of Similowski and co-workers,[77] who studied the contractile properties of the human diaphragm of well-nourished, stable, chronically hyperinflated patients with chronic obstructive pulmonary disease (COPD). These investigators showed that, at comparable lung volumes, the twitch transdiaphragmatic pressure (i.e., the Pdi developed in response to supramaximal bilateral phrenic nerve stimulation) was higher in the patients than in the normal controls, whereas the reverse was true when Pdi twitch was measured at the corresponding FRCs. Thus, in chronically hyperinflated patients with COPD, some form of adaptation (length adaptation being the most probable) must have accounted for the better contractile performance of the diaphragm at the same lung volumes compared with physiologically normal persons. This adaptation may partially counterbalance the deleterious effects of hyperinflation on the contractility and inspiratory action of the diaphragm in patients with COPD. Furthermore, changes in thoracoabdominal configuration also alter the fiber length and the pressure generated independently of changes in lung volume. In fact, Grassino and colleagues[35] found that Pdi at the same lung (isolung) volume and a given level of excitation depended on thoracoabdominal configuration. Pdi decreased when rib cage volume decreased. Thus, it can be assumed that, at any given lung volume, an inward paradoxic rib cage movement would decrease PImax because it would lower rib cage volume. This is observed in patients with neuromyopathies (e.g., tetraplegia) or COPD (Hoover's sign). Changes in thoracoabdominal configuration can also explain the decrease in PImax observed in patients with kyphoscoliosis.[78]

As noted earlier and as convincingly evident from animal models, sepsis and endotoxic shock pose a potentially great threat to respiratory muscle contractility.[79–84] This is especially important for mechanically ventilated patients because mechanical ventilation, per se, greatly increases the risk of infection and sepsis, thus potentially initiating a vicious cycle.

Another factor mentioned earlier is disuse atrophy. Artificial ventilation may be followed by respiratory muscle

weakness resulting from atrophy (secondary to disuse). This is likely because muscles that are used most often, such as the inspiratory muscles (particularly the diaphragm), atrophy the fastest,[85] as discussed at the end of this chapter.

ADAPTATION OF THE RESPIRATORY MUSCLES TO INCREASED LOAD

Immune Response to Loaded Breathing

The respiratory muscles are plastic organs that respond to either acute or chronic increases of their activity with structural and functional changes- adaptation. Strenuous resistive breathing, such as accompanies many disease states as COPD and asthma, represents a form of "exercise" for the respiratory muscles that initiates an inflammatory response consisting of elevation of plasma cytokines and recruitment and activation of lymphocyte subpopulations.[86] These cytokines do not originate from monocytes, but are instead produced within the diaphragm secondary to the increased muscle activation. More specifically, levels of interleukin-6 (IL-6) and, to a lesser extent, IL-1β, tumor necrosis factor-α (TNF-α), IL-10, IL-4, and interferon-γ (IFN-γ) increase in the diaphragm of rats undergoing inspiratory resistive loading in a time-dependent manner (Fig. 11.8).[87] Oxidative stress is a major stimulus for the cytokine induction secondary to loaded breathing. The administration of antioxidants and reactive oxygen species scavengers in healthy subjects undergoing resisting breathing reverses the observed increase of IL-1β and TNF-α in plasma, whereas it greatly limits the increase of IL-6.[88] In addition, in vitro experiments have proven that reactive oxygen species can stimulate the induction of IL-6 from myoskeletal cells in a manner that involves the transcriptional activation of the IL-6 gene through an NF-κB– dependent pathway.[89] Consequently, the diaphragm is the only proven source of cytokine induction secondary to loaded breathing, and oxidative stress is the only proven stimulus. More studies are needed to elucidate other potential sources and stimuli.

Loaded breathing–induced cytokine up-regulation may have many implications in respiratory muscle function that could be both adaptive and maladaptive. The production of cytokines within the diaphragm may be mediating the diaphragm muscle fiber injury that occurs with strenuous contractions or may contribute to the expected repair process. These cytokines may also compromise diaphragmatic contractility or contribute to the development of muscle cachexia.

Muscle Injury

Strenuous resistive breathing results in diaphragmatic injury in both animals and humans.[90–92] The mechanisms involved are not definitely established, and it is tempting to speculate that intradiaphragmatic cytokine induction could be involved in mediating the injurious process,[87] by recruiting initially neutrophils and later monocytes within the muscle, and augmenting oxidative stress in a paracrine fashion,[93] which could contribute to muscle injury.[90] Cytokines and cytokine receptors are up-regulated in the muscles in various forms of muscle injury,[94] as well as in muscle diseases such as critical illness polyneuropathy and myopathy.[95] However, the cytokine response is not only maladaptive. In fact, not only are proinflammatory cytokines such as IL-1β, TNF-α, and IFN-γ induced, but also anti-inflammatory cytokines such as IL-4, IL-10, and IL-6 (which has some proinflammatory but mainly anti-inflammatory properties[96]) are up-regulated,[87] a finding suggesting that some of these cytokines may serve to control local inflammation.[96]

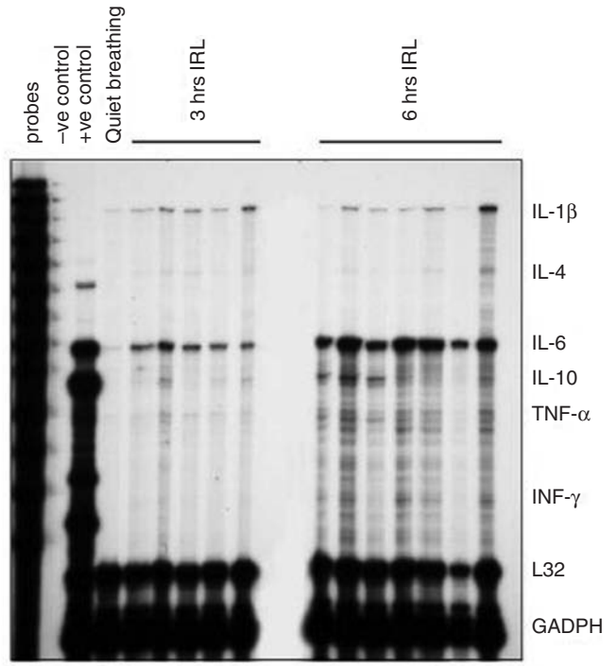

Figure 11.8 Resistive loading and intradiaphragmatic cytokine expression. Representative autoradiograph of ribonuclease protection assay performed on diaphragm muscle samples obtained after 3 hours *(lanes 5 to 9)* and 6 hours *(lanes 10 to 16)* of inspiratory resistive loading (IRL). *Lanes 1 to 3*, Probe, negative (–ve) control and positive (+ve) control, respectively. *Lane 4*, Diaphragm of a quietly breathing rat. A total of 10 μg RNA was used in each lane. (From Vassilakopoulos T, Divangahi M, Rallis G, et al: Differential cytokine gene expression in the diaphragm in response to strenuous resistive breathing. Am J Respir Crit Care Med 2004;170:154–161.)

Muscle Regeneration

Cytokines are also essential in orchestrating muscle recovery after injury. Cytokines such as TNF-α, IL-6,

LIF (leukemia inhibitory factor), and IL-1β and their cognate receptors are up-regulated in skeletal muscle after injury.[94,97–100] These cytokines enhance proteolytic removal of damaged proteins and damaged cells (through recruitment and activation of phagocytes) and activate satellite cells.[101,102] Satellite cells are quiescent cells of embryonic origin that reside in the muscle and are transformed into myocytes either during the normal muscle remodeling or when the muscle becomes injured, to replace damaged myocytes.[103]

Muscle Contractility

Cytokines may affect contractility of the diaphragm. TNF-α impairs contractility of the diaphragm.[104,105] The intradiaphragmatic expression of cytokines and especially TNF-α with the attendant contractility-depressing effect may contribute to the development of peripheral muscle fatigue (i.e., decreased force production on constant electrical stimulation of the muscle) observed after resistive loading.[106] The intradiaphragmatic expression of cytokines and especially TNF-α may also explain the observation that force decline after resistive loading is proportionally greater than the observed muscle injury.[107] Whereas force declines by as much as 30%, the degree of injury is only 9%, a finding suggesting that other factors in addition to injury depress the contractility of the diaphragm.[107]

Respiratory Muscle Fatigue

In daily life, the word *fatigue* is usually used to express tiredness or weakness. A National Heart, Lung and Blood Institute workshop defined fatigue as the loss of capacity to develop force or velocity in response to a load that is reversible by rest.[108] According to this definition, fatigue may be present before the point at which a muscle is unable to continue to perform a particular task (task failure). In applying this concept to the inspiratory muscles, one could conclude that they may be fatigued before there is hypercapnia because of their inability to continue to generate sufficient pressure to maintain alveolar ventilation.[109] 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 mechanism 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. It is not certain whether failure to generate force results from reduced central motor output (central fatigue) or from failure at the neuromuscular junction or within the muscle machinery (peripheral fatigue). For the respiratory system, the following question arises: Do the respiratory controllers become too tired to drive the muscles to maintain adequate ventilation when the respiratory system is presented with a fatiguing load, or do the muscles become unable to generate the required force despite an adequate neural drive? Although no definite answer can be given, at least for the diaphragm when fatigue is induced by an intermittent contraction breathing protocol, approximately 50% of the force decline can be attributed to reduced central motor drive, and the remainder can be attributed to peripheral muscle contractile failure.[108] However, it is not yet clear whether such a CNS depression is the result of primary central failure or of an adaptation of the CNS to the changes in the contracting muscles that reflects a protective mechanism to prevent an undue reduction of intrinsic muscle fiber strength.

Central Fatigue

Central fatigue is considered present when a maximal voluntary contraction generates less force than does maximal electrical stimulation.[110,111] If maximal electrical stimulation superimposed on a maximal voluntary contraction can potentiate the force generated by a muscle, a component of central fatigue is said to exist. This procedure applied to the diaphragm consists of the twitch occlusion test, which may separate central from peripheral fatigue.[112,113] 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 Pdi twitches in response to phrenic nerve stimulation decreases as the voluntary Pdi increases.[112] During maximal voluntary contractions of the diaphragm (Pdimax), no superimposed twitches can be detected. When diaphragmatic fatigue was induced either by resistive loads or by expulsive contractions against a bounded abdominal wall,[113] superimposed twitches could be demonstrated at the limits of diaphragmatic endurance, but not at the start of the experiment. At these limits, voluntary Pdimax had decreased by 50%, whereas the Pdimax estimated from the twitch occlusion had decreased by only 25%. Consequently, at the limits of diaphragmatic endurance, although peripheral fatigue was present, a significant portion of the reduction in the force was the result of failure of the CNS to activate the diaphragm completely. Similar results were also reported by McKenzie and associates in 1992 for fatigue induced by diaphragmatic expulsive maneuvers.[114]

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. However, central fatigue should not be confused with the progressive decrease in firing rate during maximum contraction because, in this case, as opposed to fatigue, superimposed supramaximal electric tetanic stimulation does not increase muscle force.[115]

The observed decreased central firing rate during fatigue[116] may, in fact, be a beneficial adaptive response: fatigue is characterized by slowing of the muscle contractile speed. In addition, for any muscle or motor unit, the minimum excitation frequency required to generate force and tetanic fusion (i.e., maximum force) is proportional to its contractile speed. Thus, if during fatigue the degree of contractile slowing matches the decline in motoneuron firing rate, the latter does not result in any additional reduction in muscle force. On the contrary, it would avoid the failure of impulse propagation associated with high-frequency fatigue as well as the complete depletion of vital chemicals within the muscle cell that could otherwise occur if high-frequency excitation were maintained. This brings up the question of how such an adaptation is initiated. It seems likely that activation of muscle afferents by some fatigue-induced change within the muscle inhibits motoneuron activity by reducing its firing rate. Although unequivocal proof is lacking, it has been shown that afferent information through large (type I and II) and especially small (type III and IV) fibers affects the central respiratory controller's discharge in terms of firing rate, firing time, and frequency of breathing[117]; the latter is observed in states of diaphragmatic fatigue in both animals and humans.[118] These sensory fibers are activated primarily by extracellular metabolic changes (e.g., low pH, ischemia, increased osmolarity) and some substances.[81] It is therefore tempting to hypothesize that, as the contractile properties and the diaphragmatic chemistry change during fatigue, respiratory muscle afferents through the phrenic nerve may affect the output of respiratory centers in terms of firing rate or timing.

This hypothesis is further supported by animal experiments in which endogenous opioid pathways are activated in response to acute, intense flow-resistive loading, thus reducing overall ventilatory output[119–121] (Fig. 11.9); this reduction, secondary to increased endorphin activity, is signaled by small fiber afferents stimulated by lactate accumulation and pH fall in the respiratory muscles.[119] Thus, it is possible that afferents, through the small fibers during loaded breathing in various clinical states, modulate endogenous opioids[122,123] as an adaptive response, thereby minimizing breathlessness and avoiding or delaying the onset of respiratory muscle fatigue.

In summary, as fatigue ensues, central discharge rate decreases, either as primary central failure (central fatigue) or as an adaptive response preventing the muscle's self-destruction by excessive activation. The importance of central fatigue in clinical ventilatory failure remains uncertain.

Peripheral Fatigue

This type of fatigue may occur because of failure of impulse propagation across the neuromuscular junction or over the muscle surface membrane (transmission fatigue) or because of failure of the contractile apparatus of the muscle fibers (impaired excitation-contraction coupling). During artificial stimulation of a motoneuron, especially at high frequencies, muscle force declines

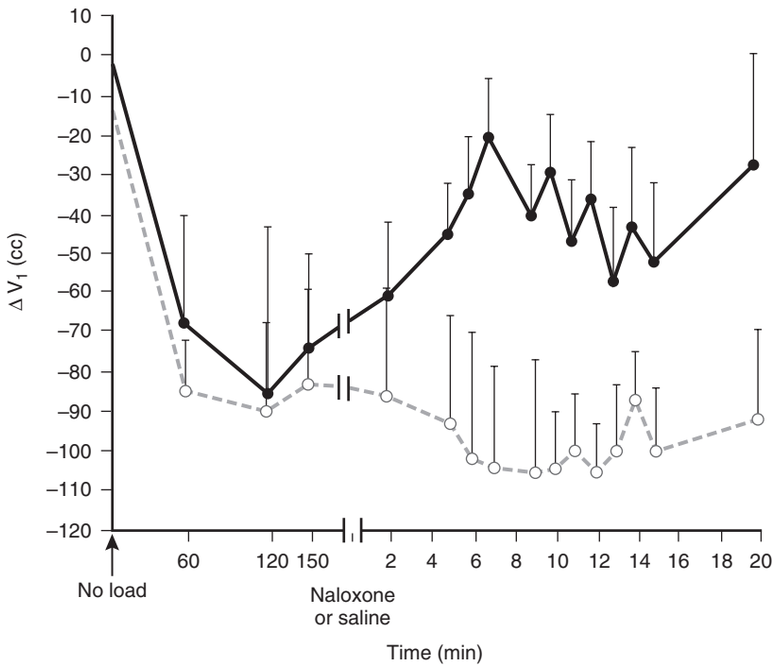

Figure 11.9 Tidal volume response of unanesthetized goats to 2.5 hours of high-inspiratory, flow-resistive loading before and following the administration of naloxone *(filled circles)* or saline *(open circles)*. Tidal volume, which fell considerably during loading, increased significantly but transiently after naloxone administration, whereas saline had no effect. (Note the change in time scale on the X-axis.) The data indicate that an increase in airway resistance can activate the endogenous opioid system. Furthermore, the increase in tidal volume immediately following naloxone suggests that these potentially fatiguing loads reduce tidal volume before the onset of overt muscle fatigue by a mechanism that, in addition to the direct mechanical effect of the load, involves the endogenous opioid system. Data are presented as mean ±SEM. (From Scardella AT, Parisi RA, Phair DK, et al: The role of endogenous opioids in the ventilatory response to acute flow-resistive loads. Am Rev Respir Dis 1986;133:26–31.)

rapidly in association with the decline in action potential amplitude. This response, known as high-frequency fatigue (Fig. 11.10), is attributed to transmission fatigue. The site of this type of fatigue may be located postsynaptically (from a decrease in end-plate excitability) or presynaptically (probably in fine terminal filaments of the motor nerve or less frequently from depletion of synaptic transmitter substance).[124]

The development of this type of failure during voluntary contraction is questionable because each motor unit is excited at a rate matched to its particular contractive properties. In fact, evoked muscle compound action potential (M-wave) amplitudes are generally found to remain unimpaired, and, in addition, no unique relationship between muscle force and activity on electromyography (EMG) has been observed.[108] Evidence that neuromuscular transmission and cell membrane excitation are adequate during fatigue produced by voluntary contractions was found in experiments in dogs in cardiogenic and septic shock.[83,125] As the diaphragm became fatigued, the relationship of integrated phrenic nerve activity (Ephr) and diaphragmatic EMG increased proportionally so their relationship remained unaltered. However, these experiments may not be specific in testing this question; for example, changes in the wave form of action potential through the run may have compensated for discrepancies between Ephr and EMG. Teleologically, transmission block could be beneficial in some instances. As suggested by some authors,[126] if failure occurs at the neuromuscular junction or in the excitation of the cell membrane, it may protect the muscle against excessive depletion of its adenosine triphosphate (ATP) stores, which would lead to rigor mortis. If high-frequency fatigue is the result of failure of the neuromuscular junction, it may be speculated that such a failure can exist in the human diaphragm. In fact, it has been clearly shown that normal subjects breathing against inspiratory loads develop high-frequency fatigue,[127] which may reflect neuromuscular junction failure.

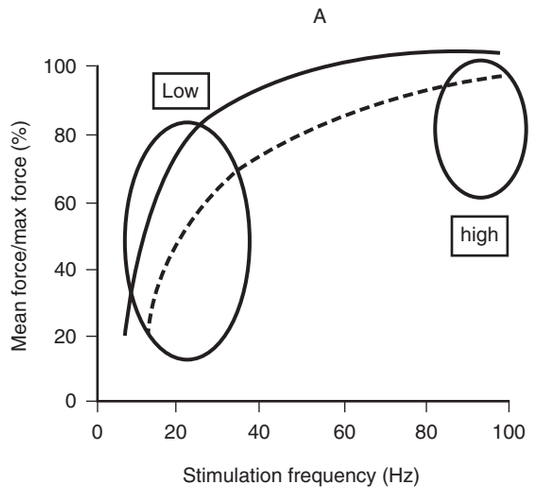

Figure 11.10 Frequency-force curve of skeletal muscles illustrating the curve for fresh muscle *(solid line)* and a shift to the right with fatigue *(dashed line)*. (From Moxham J, Edwards RH, Aubier M, et al: Changes in EMG power spectrum (high-to-low ratio) with force fatigue in humans. J Appl Physiol 1982;53:1094–1099.)

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.[128] This type of fatigue is characterized by a selective loss of force at low frequencies of stimulation (low-frequency fatigue) (see Fig. 11.10), despite maintenance of the force generated at high frequencies of stimulation, a finding indicating that the contractile proteins continue to generate force. This type of fatigue is not related to depletion of ATP or phosphocreatine (PCr) and is characteristically long lasting, taking several hours to recover. The mechanism of this type of fatigue is not well known. It may occur because of a reduced supply of calcium (Ca^{2+}) or a change in the affinity of the troponin binding site for Ca^{2+}. These defects would reduce the twitch and hence would reduce the force developed at low stimulation. In contrast, at higher stimulation frequencies, a relatively normal force can be generated when the interior of the fiber is saturated with Ca^{2+}.[129] Other possibilities include structural damage[129] or an alteration in the compliance of the series elastic component of the muscle.[130]

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 periods, thereby achieving the same total work. It thus appears likely that muscle ischemia and reliance on anaerobic metabolism are important factors in the generation of low-frequency fatigue.

In this regard, impaired excitation-contraction coupling occurred in the diaphragm of the dog during cardiogenic or septic shock[83,125]; despite a threefold increase of the integrated EMG, Pdi decreased (Fig. 11.11). Low-frequency fatigue and, by inference, impaired excitation-contraction coupling has also been found in the diaphragm and sternomastoid of normal subjects after they breathed against very high inspiratory resistance.[127,131]

Because low- frequency fatigue impairs force generation at physiologic firing frequencies, ventilation may be reduced. To compensate for low-frequency fatigue, motoneuron firing frequency must be increased, or

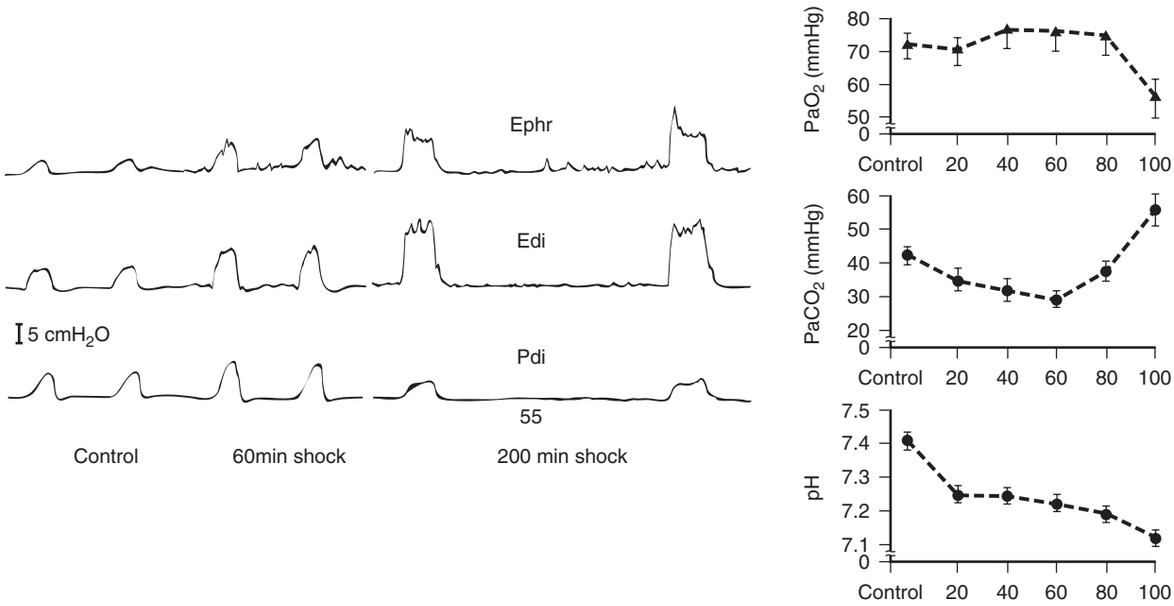

Figure 11.11 *Left*, Representative tracing of one dog during endotoxic shock showing changes in integrated phrenic neurogram (Ephr) *(top)*, integrated diaphragmatic electromyogram (Edi) *(middle)*, and transdiaphragmatic pressure (Pdi) *(bottom)*. *Left*, During control; *middle*, 60 minutes after the onset of endotoxic shock; *right*, 200 minutes after the onset of endotoxic shock and before the death of the animal. *Right*, Time course of mean arterial oxygen tension (Pao2) *(top)*, carbon dioxide tension (Paco2) *(middle)*, and mean arterial pH *(bottom)* for 10 dogs breathing spontaneously. *Points*, means; *bars*, ±SE. Note the significant fall of Pao2 and the rise of Paco2 before the death of these animals. (From Hussain SN, Simkus G, Roussos C: Respiratory muscle fatigue: A cause of ventilatory failure in septic shock. J Appl Physiol 1985;58:2033–2040.)

additional contractile units must be recruited, by an increase in central respiratory drive. This can be demonstrated by recording the smoothed and rectified EMG (SREMG) from the sternomastoid during the production of standard forces when the muscle has low-frequency fatigue compared with the response obtained for fresh muscle.[131] Depression of respiratory drive by hypoxia or drugs could therefore impair compensatory responses, and ventilation would then become inadequate.

Metabolic Considerations in Muscle Fatigue

Most studies conclude that the major factors underlying neuromuscular fatigue occur within the muscle fibers and mainly result from depletion of muscle energy stores or pH changes from lactate accumulation.[108] The substances directly involved in the transformation of chemical energy into mechanical work in skeletal muscles are ATP, adenosine diphosphate (ADP), inorganic phosphate (Pi), hydrogen ions (H^+), magnesium ions (Mg^{2+}), and PCr. ATP leaves the mitochondria and diffuses in the contractile machinery of the cell, where ATPase enzymes hydrolyze one of the pyrophosphate bonds and liberate large quantities of energy in the process:

$$\text{MgATP} + \text{H}_2\text{O} \xrightarrow{\text{ATPases}} \text{MgADP} + \text{Pi} + \text{H}^+ + \text{Energy} \quad (4)$$

PCr is used to regenerate ATP:

$$\text{MgADP} + \text{PCr} \rightarrow \text{MgATP} + \text{Cr} \quad (5)$$

Metabolic changes may cause fatigue either through a reduction of high-energy compounds (e.g., PCr and ATP) or through an accumulation of breakdown products (e.g., Pi, H^+, lactate).

ATP is the immediate energy source for energy-requiring processes such as cross-bridge cycling and ion pumping, and a significant reduction of the myoplasmic ATP concentration would affect cell function. Generally reported reductions of ATP in fatigue are small (from approximately 6 to 5 mM) and would, if representative, be unlikely to affect cell function. However, several studies have found considerably larger reductions (up to

approximately 50%).[132] Furthermore, local concentrations at sites where ATP turnover is particularly high may well be lower than the cell average (e.g., in the narrow space between the t-tubules and the terminal cisternae of the sarcoplasmic reticulation, called the triad).[133] Historically, lactic acid accumulation has received great attention as the cause of fatigue in the skeletal muscles. Similarly, blood lactate elevation has been found in subjects breathing through high inspiratory loads to exhaustion,[134] but there is no direct evidence that the lactic acid produced by the respiratory muscles is the culprit in fatigue. However, animals in cardiogenic shock develop substantially less lactic acidosis if they are mechanically ventilated than if they are breathing spontaneously,[135] a finding indicating that the respiratory muscles produce great amounts of lactic acid if they are working under fatiguing conditions.

The effects of lactic acid on force generation are believed to be mediated by lowering the pH. H^+ and Pi are among the breakdown products of energy metabolism that have the greatest effect on the contractile apparatus.[136] An increased concentration of these ions results in both reduced maximum tension production (i.e., tension at saturating Ca^{2+} concentration) and reduced myofibrillar Ca^{2+} sensitivity.[137] In addition, H^+ exerts a direct negative effect on the contractile process itself, which is not related to pH.[137]

The increase in energy demands in the working skeletal muscles, including the respiratory muscles, is provided mainly by the combustion of fat, blood glucose, and glycogen of the muscle. During submaximal prolonged heavy exercise, exhaustion coincides with the depletion of muscle glycogen, whereas exercise capacity is enhanced when the storage of muscle glycogen is increased.[138] Similar observations have been made in the diaphragm of dogs with low cardiac output.[135] However, why glycogen depletion coincides with fatigue is not clear. During prolonged intermittent heavy exercise that depends on aerobic metabolism, the rate of utilization of fatty acids and glucose is high; although these substances circulate in large amounts in the bloodstream, they cannot provide sufficient energy to the muscle to meet the demands. Hence muscle glycogen must be used to supplement the bloodborne fuels, and fatigue will occur when it is depleted.

Oxygen-derived free radicals have been implicated as mediators of respiratory muscle dysfunction,[139] particularly diaphragm fatigue, because pretreatment with free radical scavengers (e.g., N-acetylcysteine,[140] dimethylsulfoxide, lazaroid agents) resulted in a reduction in the rate at which diaphragm fatigue developed in response to oxidative stress. However, the precise source of free radicals, the particular physiologic conditions under which they can be generated, and the protective mechanism of different free radical scavengers in the respiratory muscles remain unclear.[139]

To summarize, glycogen depletion, lactic acid accumulation, acidosis of every kind, inability to utilize bloodborne substances, decrease in the rate of ATP hydrolysis, and increased oxygen-derived free radical production affect loss of force. However, the exact interplay of all these factors is not yet identified in either the diaphragm or the other skeletal muscles.

Integrated View of Respiratory Muscle Fatigue

Fatigue is likely to be the result of a dynamic process in which compensatory mechanisms are overwhelmed in a closed-loop system consisting of central motor drive, peripheral impulse propagation, excitation-contraction coupling, depletion of energy substrates, or metabolite accumulation and feedback-modulating reflexes.[108] The site of fatigue may be placed at any level from the CNS to the contractile machinery depending on the experimental setting. For an individual muscle, a close relationship exists between excitation and energy metabolism. It has been shown that a protective mechanism may exist at the site of the action potential or beyond, so when fuel is depleted, failure of the activation system occurs and in extreme fatigue prevents the muscle from destroying itself, which would happen if the ATP level fell to zero. A decrease in excitation may result from failure of the neuromuscular junction,[126] or it may stem from a reduced rate of firing by the CNS,[115] or both. In the respiratory system, in addition to the reduction in firing frequency, the CNS may respond by altering the frequency and the duty cycle. Although it has not yet been proved, such an alteration in the responses of central controllers could be brought about by afferents from the fatiguing inspiratory muscles and the chest wall. These small (types III and IV) fibers possibly reduce central respiratory output by modulating endorphins as an adaptive response to avoid or delay respiratory muscle fatigue.

An alternate, not mutually exclusive mechanism reducing central respiratory output (see earlier) is the production of cytokines by the strenuously contracting diaphragm secondary to resistive loading. Cytokines, especially IL-1β and IL-6, are very strong stimulants of the hypothalamic-pituitary-adrenal (HPA) axis,[141–143] and they exhibit significant synergism.[144] Both these cytokines stimulate concomitant adrenocorticotropic hormone (ACTH) and β-endorphin release by the pituitary gland. Strenuous inspiratory resistive breathing that induces plasma cytokines stimulates the HPA axis and results in increased levels of circulating β-endorphin and ACTH[86] (Fig. 11.12).

It is tempting to speculate that HPA axis stimulation may occur secondary to the increased levels in circulating proinflammatory cytokines induced by strenuous resistive breathing. This notion is supported by the different time courses of cytokine and hormonal elevations (cytokine elevation appearing first, followed by the

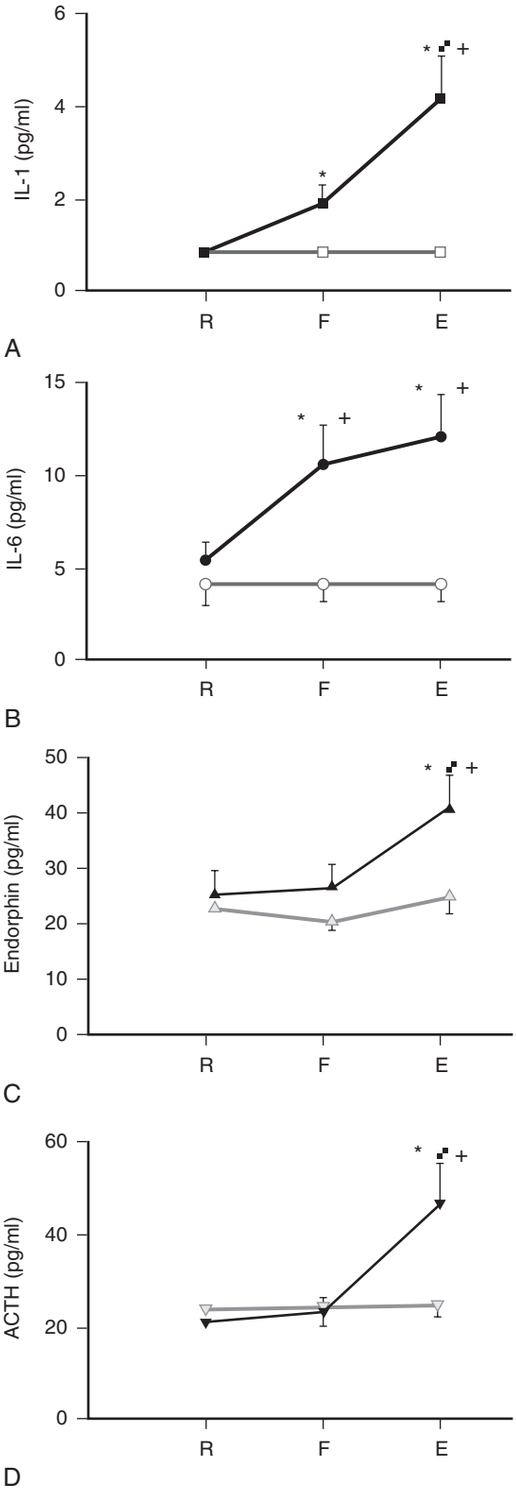

Figure 11.12 The plasma cytokine and hypothalamic pituitary responses to resistive breathing. Mean plasma level of interleukin (IL)-1β *(A)*, IL-6 *(B)*, β-endorphin *(C)*, and adrenocorticotropic hormone (ACTH; *D*) at rest (R), at the point where the subjects could not generate the target maximum inspiratory pressure (75% of maximum, 45 minutes after the beginning of resistive breathing; *F*), and at the end of resistive breathing (15 minutes later, at 60 minutes from the beginning; *E*). From *F* to *E*, subjects were put through an alinear resistance to the maximum they could achieve. Data are presented as mean ±SEM. *Filled squares*, high-load run; *open squares*, moderate-load run; *number sign*, statistically significant difference ($P < .05$) from R; *paragraph sign*, statistically significant difference ($P < .05$) from F; *plus sign*, statistically significant difference ($P < .01$) from the moderate-load run. (From Vassilakopoulos T, Zakynthinos S, Roussos C: Strenuous resistive breathing induces proinflammatory cytokines and stimulates the HPA axis in humans. Am J Physiol 1999;277:R1013–R1019.)

increase in β-endorphin and ACTH level) (see Fig. 11.12). Furthermore, the increase in IL-6 was strongly correlated with the increase in both β-endorphin and ACTH, thus implying a causative role of the IL-6 for the HPA axis stimulation secondary to resistive breathing. The ACTH response may represent an attempt of the organism to reduce the injury occurring in the respiratory muscles through the production of glucocorticoids by the adrenals, which suppress induction of inflammatory genes, and induction of the acute-phase response proteins from the liver, which serve as antiproteases.[141]

The elaboration of β-endorphins decreases the activation of the respiratory muscles and changes the pattern of breathing, which becomes rapid and shallow. This is probably an attempt by the respiratory controller to reduce the strenuous respiratory muscle contractions (and thus the accompanying muscle injury), through the decline in tidal volume at the expense of increased respiratory frequency. In animals, adequate evidence supports this concept.[119,120,145,146] It was demonstrated that resistive loading resulted in a progressive reduction in tidal volume, which was partially reversed by administration of the opioid antagonist naloxone[146,147] (see Fig. 11.9). An increase in β-endorphin in the cisternal cerebrospinal fluid was also detected.[146] In humans, an increase in the β-endorphin plasma level was measured secondary to resistive breathing.[86,148] It was also demonstrated that naloxone could restore the load compensatory reflex in patients with COPD in whom it was initially absent.[123] Such a strategy, representing an adaptive response much in the way that β-endorphins are generated in response to chronic pain, certainly minimizes dyspnea and may avoid or delay the onset of

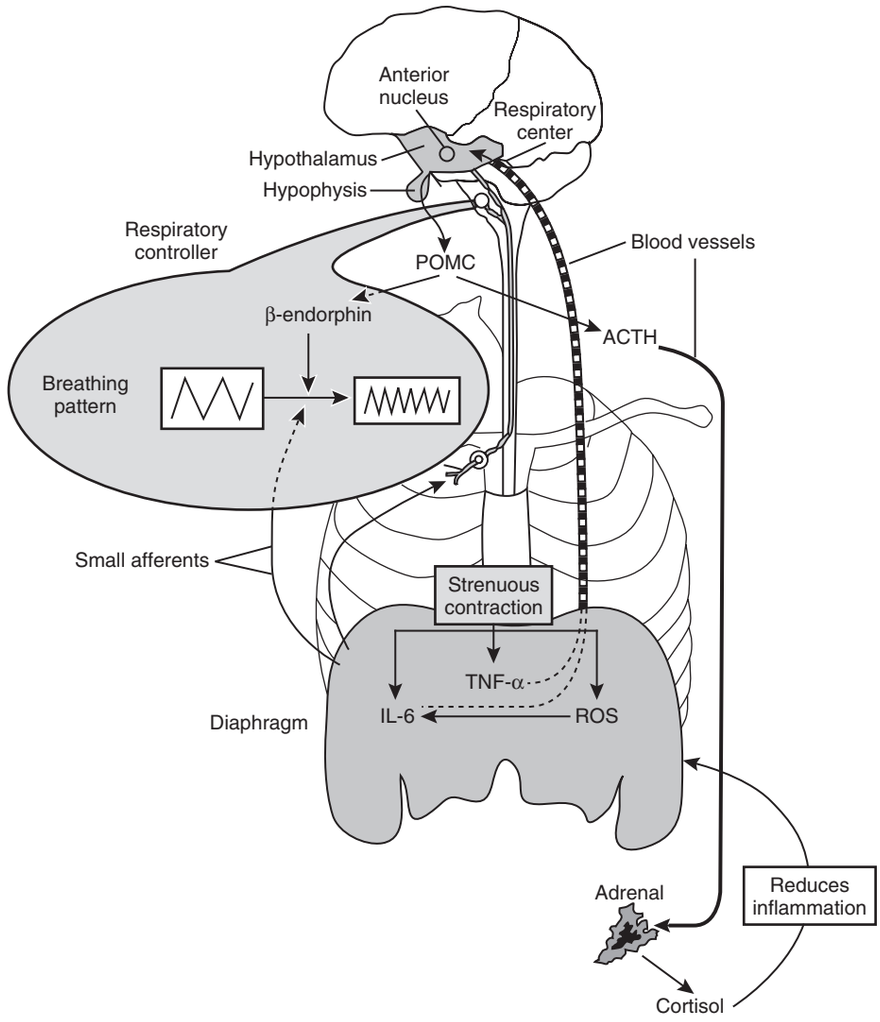

Figure 11.13 Integrated view of the origin and functional consequences of resistive breathing–induced cytokines. Resistive breathing results in the generation of oxidative stress and the induction of cytokines within the diaphragm, secondary to the increased muscle activation. Oxidative stress is a major stimulus for this cytokine induction. Cytokines stimulate the hypothalamic-pituitary-adrenal axis either hematogenously or by stimulation of small afferent nerve fibers, leading to production of adrenocorticotropic hormone (ACTH) and β-endorphins. The ACTH response may represent an attempt of the organism to reduce the injury occurring in the respiratory muscles through the production of glucocorticoids by the adrenals and the induction of acute-phase response proteins. The β-endorphin response would decrease the activation of the respiratory muscles and change the pattern of breathing, which becomes more rapid and shallow, possibly in an attempt to reduce or prevent further injury to the respiratory muscles. POMC, pro-opiomelaninocortin; ROS, reactive oxygen species. (From Vassilakopoulos T, Roussos C, Zakynthinos S: The immune response to resistive breathing. Eur Respir J 2004;24:1033–1043.)

respiratory muscle peripheral fatigue, thus protecting the ventilatory pump from exhaustion. However, it may result in hypoventilation and the development of hypercapnia (Fig. 11.13).

What Is the Role of Fatigue in the Patient Who Fails to Wean?

Consideration of the imbalance between energy supply and energy demand of the respiratory muscles suggests that inspiratory muscle fatigue is frequently a final common pathway leading to inability to sustain spontaneous breathing and thus to weaning failure.[149] In a very influential study, Cohen and associates[150] studied 12 patients with various disorders leading to hypercapnic respiratory failure after discontinuing mechanical ventilation. The power spectrum of diaphragmatic surface EMG activity was analyzed. A sustained reduction of the H/L ratio of the EMG power spectrum to less than 80% of the initial value was taken as indicative that diaphragmatic fatigue would ensue. Seven patients showed evidence on EMG of inspiratory muscle fatigue. Electrical fatigue was followed by respiratory alternans or paradoxic inward movement of the abdominal wall during inspiration (abdominal paradox). However, it is possible that these changes may not reflect inspiratory muscle fatigue per se, but rather alternations in central drive resulting from excessive loading response.[151] Nevertheless, such high inspiratory loads observed during weaning failure eventually lead the ventilatory pump to exhaustion and overt fatigue, which is, undoubtedly, a terminal event.

Respiratory muscle maximum relaxation rate (MRR) has been measured during the weaning process and has been demonstrated to slow in those patients failing to

wean; it has also remained unchanged in patients who were weaned successfully.[152] This finding suggests that during failed weaning trials, a fatigue process is initiated peripherally into the respiratory muscles; associated with the slowing of MRR, it is likely that the central drive is modulated.[153]

Furthermore, using electrical criteria similar to those used by Cohen and associates,[150] Brochard and co-workers[154] found that seven out of eight patients who met the usual criteria for weaning but who failed to wean exhibited a sustained reduction of the H/L ratio of the EMG power spectrum of the diaphragm during spontaneous breathing, followed by decreased tidal volume, an increased respiratory rate, and the development of hypercapnia. All these patients had increased energy demands, as evidenced by the oxygen consumption of the respiratory muscles and the work of breathing per unit of time, W, that was always higher than 8 to 10 L/minute. When pressure support was applied, thus reducing the work performed by the muscles, the reduced H/L ratio was prevented. Impaired diaphragmatic function during weaning was also implicated by Pourriat and co-workers,[155] who studied diaphragmatic function and the pattern of breathing in patients with COPD who were being weaned from mechanical ventilation after acute respiratory failure. These investigators noted that when Pdi was expressed as a fraction of the maximal Pdi (Pdimax), this value reached a mean of 46% in the group failing to wean. According to Roussos and Macklem,[106] a Pdi/Pdimax ratio greater than 40% cannot be tolerated for long periods without fatigue of the diaphragm. It has also been possible in these patients to measure the load imposed on the respiratory muscles and their capacity. When the ratio of load to capacity (i.e., PI/PImax ratio) is high, weaning fails.[156] In fact, PI/PImax had an excessively high mean value amounting to 0.42±0.11 in patients failing at discontinuation of mechanical ventilation.[156] Additionally, dynamic hyperinflation amounting to 0.25±0.19 l was present in almost all patients. When the PI/PImax ratio was plotted against the dynamic increase in FRC to account for the effect of hyperinflation, 13 out of 31 patients (42%) were placed above a hypothetic critical line representing the critical inspiratory pressure above which fatigue may occur. In addition, all patients were gathered around the critical line (Fig. 11.14).[156]

Following these observations, patients who had initially failed to wean from mechanical ventilation but who were successfully weaned on a later occasion were prospectively studied.[157] Compared with success, during failure, patients had greater intrinsic positive end-expiratory pressure, dynamic hyperinflation, total resistance, ratio of mean to maximum inspiratory pressure, TTI and power, less maximum inspiratory pressure, and a breathing pattern that was faster and shallower (ratio of frequency to tidal volume, f/VT). To clarify on pathophysiologic

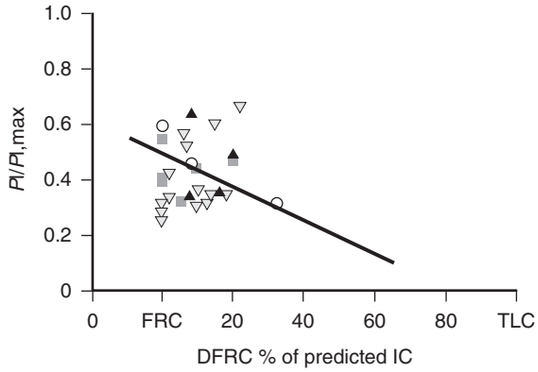

Figure 11.14 Pressure-volume diagram similar to that of Roussos and associates[48] plotting the PI/PImax ratio against a dynamic increase in FRC (DFRC) expressed as a percentage of predicted inspiratory capacity (IC). The PI/PImax ratio is the mean inspiratory pressure per breath expressed as a fraction of the maximum. Each *closed symbol* refers to a patient. The *solid line* was constructed from data in normal subjects and represents the critical inspiratory pressures above which fatigue may occur. At normal FRC, the critical inspiratory pressure per breath above which fatigue may occur in normal subjects is about 50% of PImax, whereas at FRC + 1/2 IC, this critical pressure is 25% to 30% of the maximum. All patients had excessively high values of the PI/PImax ratio, clustering around the critical line, rather than remaining away from it, as happens in normal subjects. *Closed circles*, exacerbated chronic obstructive pulmonary disease (COPD); *closed squares*, adult respiratory distress syndrome (ARDS); *closed downward triangles,* other pulmonary diseases; *closed upward triangles*, acute respiratory failure of extrapulmonary origin. (From Zakynthinos SG, Vassilakopoulos T, Roussos C: The load of inspiratory muscles in patients needing mechanical ventilation. Am J Respir Crit Care Med 1995;152:1248–1255.)

grounds what determines an inability to wean from mechanical ventilation, multiple logistic regression analyses with the weaning outcome as the dependent variable were performed. The TTI and the f/VT ratio were the only significant variables in the model. Thus, the TTI and the f/VT were the major pathophysiologic determinants of the weaning outcome. The increased TTI, which was higher than the critical threshold of 0.15 during failure, was again suggestive of the presence of fatigue (Fig. 11.15). However, the diagnosis of diaphragmatic fatigue requires the demonstration of reduced force generation by the diaphragm on constant levels of stimulation.[108]

Evidence does not support the existence of low-frequency fatigue (the type of fatigue that is long lasting, taking more than 24 hours to recover) in patients who fail to wean despite the excessive respiratory muscle load.[158] The twitch transdiaphragmatic pressure elicited by magnetic stimulation of the phrenic nerve was not

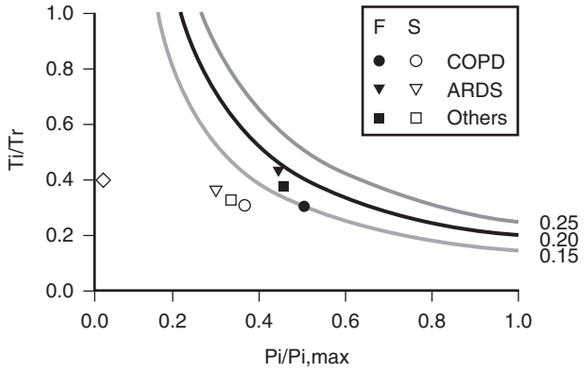

Figure 11.15 Diagram similar to the isodiaphragmatic tension-time index (iso-TTdi) plot of Bellemare and Grassino[45] constructed from the data of our patients. *Ordinate,* Inspiratory to total cycle duration ratio (TI/Ttot) at the end of the spontaneous breathing trial. *Abscissa*, Mean inspiratory pressure, expressed as a fraction of maximum (PI/PImax). The product of each combination of the two variables is the TTI of global inspiratory muscles. Three iso-TTI isopleths are drawn for reference. Each *closed symbol* refers to the mean value of each group during weaning failure. Each *open symbol* refers to the mean value of each group during weaning success. The *open diamond* represents the average TTI of 10 normal subjects breathing with a minute volume similar to the mean minute volume of our patients. ARDS, adult respiratory distress syndrome; COPD, exacerbated chronic obstructive pulmonary disease; F, weaning failure; S, weaning success. (From Vassilakopoulos T, Zakynthinos S, Roussos C: The tension-time index and the frequency/tidal volume ratio are the major pathophysiologic determinants of weaning failure and success. Am J Respir Crit Care Med 1998;158:378–385.)

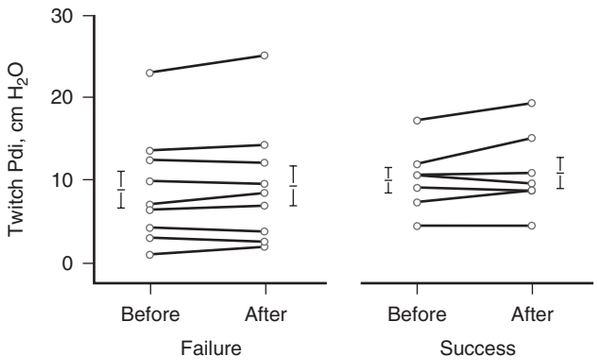

Figure 11.16 Transdiaphragmatic twitch pressure (twitch Pdi), recorded before and 30 minutes after a weaning trial in nine patients with weaning failure *(closed symbols, left panel)* and seven weaning success patients *(open symbols, right panel)*. Twitch Pdi did not differ between the groups before the trial, and it did not decrease after the trial in either group. *Bars* represent group mean ± SE. (From Laghi F, Cattapan SE, Jubran A, et al: Is weaning failure caused by low-frequency fatigue of the diaphragm? Am J Respir Crit Care Med 2003;167:120–127.)

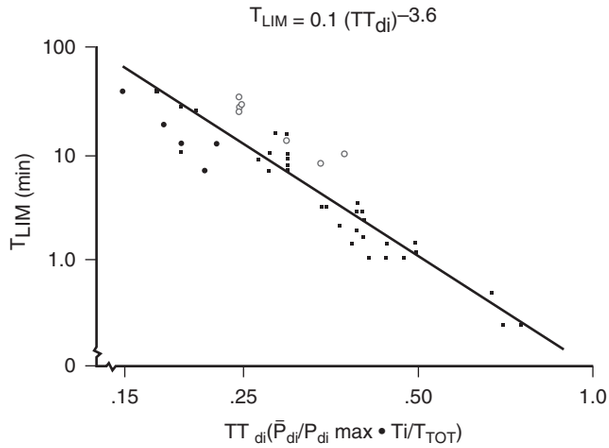

Figure 11.17 Relationship between time limit (TLIM) and tension-time index of the diaphragm (TTdi) The two scales are logarithmic. TLIM, the time elapsed from the onset of the contraction to the time at which a target tension can no longer be sustained. (From Bellemare F, Grassino A: Effect of pressure and timing of contraction on human diaphragm fatigue. J Appl Physiol 1982;53:1190–1195.)

altered before and after the failing weaning trials (Fig. 11.16).[158] The TTI of the diaphragm was 0.17 to 0.22 during failing weaning trials.[158] Bellemare and Grassino[45] reported that the relationship between the TTI of the diaphragm (TTdi) and time to task failure in healthy subjects follows an inverse power function: time to task failure = 0.1 (TTdi) - 3.6 (Fig. 11.17). Based on this formula, the expected times to task failure would be 59 to 13 minutes. The average value of the TTI of the diaphragm during the last minute of the trial was 0.26, and the patients with weaning failure would be predicted to sustain this effort for another 13 minutes before developing of diaphragmatic fatigue.[158] Thus, the reason for the lack of low-frequency respiratory muscle fatigue development despite the excessive load is that physicians have adopted criteria for the definition of spontaneous breathing trial failure and thus termination of unassisted breathing that lead them to put patients back on the ventilator before the development of low-frequency respiratory muscle fatigue.

The lack of fatigue, however, does not mean that the loaded breathing associated with weaning failure is not injurious for the respiratory muscles. Both animal models and human data have shown that breathing against such loads (TTIdi, 0.17 to 0.22) can injure these muscles.[90] Nevertheless, this injury peaks at about 3 days after the excessive loading, a time that coincides with the documented decline in the force-generating capacity of the diaphragm at this later point.[90] Thus, although weaning failure is not associated with low-frequency fatigue of the diaphragm at the

time of termination of spontaneous breathing trials, it may lead to the onset of an injurious process in the respiratory muscles that is expected to peak later.

ADAPTATION OF THE RESPIRATORY MUSCLES TO INACTIVITY

Respiratory muscles adapt not only when they function against increased load but also when they become inactive, as happens when a mechanical ventilator undertakes their role as force generator to create the driving pressure permitting airflow into the lungs. Evidence supports the finding that the inactivity and unloading of the diaphragm caused by mechanical ventilation are harmful, resulting in decreased diaphragmatic force-generating capacity, diaphragmatic atrophy, and diaphragmatic injury, conditions described by the term *ventilator-induced diaphragmatic dysfunction* (VIDD).[159]

In the intact diaphragm of various animal species (including primates) studied in vivo after a period of controlled mechanical ventilation (CMV), transdiaphragmatic pressure generation caused by phrenic nerve stimulation declines at both submaximal and maximal stimulation frequencies (20 to 100 Hz) in a time-dependent manner.[160–162] The decline is evident early and worsens as mechanical ventilation is prolonged. Within a few days (3 days in rabbits,[162] 5 days in piglets,[161] 11 days in baboons[160]), the pressure-generating capacity of the diaphragm declines by 40% to 50%. The endurance of the diaphragm is also significantly compromised, as suggested by the reduced ability of animals to sustain an inspiratory resistive load.[160]

The decreased force-generating capacity is not secondary to changes in lung volume because transpulmonary pressure and dynamic lung compliance do not change. Moreover, it is not caused by changes in abdominal compliance, given the nearly stable abdominal pressure over the observation period and the similar results obtained with abdominal wrapping, which prevents changes in abdominal compliance.[160,161]

Neural or neuromuscular transmission remains intact, as reflected by the lack of changes in phrenic nerve conduction (latency) and the stable response to repetitive stimulation of the phrenic nerve.[161] In contrast, the decrease in the compound muscle action potential suggests that excitation-contraction coupling or membrane depolarization may be involved in the dysfunction.[161] Thus, the mechanical ventilation–induced impairment in force-generating capacity appears to reside within the myofibers.[159]

In vitro results of isometric (both twitch and tetanic) tension development in isolated diaphragmatic strips confirm the in vivo findings,[85,163–166] and they suggest that the decline in contractility is an early (12 hours)[165] and progressive phenomenon.[165,167] Isometric force development declines by 30% to 50% after 1 to 3 days of CMV in rats and rabbits, although this time course may be prolonged in piglets,[161] a finding that could suggest that the bigger the species, the longer it takes for VIDD to develop.

The mechanisms of VIDD are not fully elucidated. Muscle atrophy, oxidative stress, structural injury, and muscle fiber remodeling have been documented after CMV.[159] The precise contribution of each in the development of VIDD has to be defined.

Muscle atrophy results from a combination of decreased protein synthesis and increased proteolysis,[168] and both mechanisms have been documented in VIDD.[169,170] From the three intracellular proteolytic systems of mammalian cells (lysosomal proteases, calpains, and proteasome), both calpains and the proteasome are activated to induce atrophy secondary to CMV.[170] The proteasome is a multiple-subunit multicatalytic complex that exists in two major forms: the core 20S proteasome can be free or bound to a pair of 19S regulators to form the 26S proteasome (Fig. 11.18). The 26S proteasome is activated in ventilator-induced cachexia.[167,171] Shanely and colleagues showed that CMV resulted in a fivefold increase in 20S proteasome activity,[170] which is specialized in degrading proteins oxidized by reactive oxygen species.[172] Oxidative damage of a protein results in its partial unfolding, exposing hidden hydrophobic residues; therefore, an oxidized protein does not need to be further modified by ubiquitin conjugation to confer a hydrophobic patch, nor does it require energy from ATP hydrolysis to unfold (Fig. 11.19).[173]

This result is in concert with evidence of oxidative stress–induced modification of proteins obtained from the diaphragms of animals subjected to CMV.[170,174] Oxidative stress is augmented in the diaphragm after CMV, as indicated by increased protein oxidation and lipid peroxidation byproducts.[170,174] The onset of oxidative modifications is rapid, occurring within the first 6 hours of the institution of CMV.[174] Oxidative stress can modify many critical proteins involved in energetics, excitation-contraction coupling, and force generation. Accordingly, CMV-induced diaphragmatic protein oxidation was evident in insoluble (but not soluble) proteins with molecular masses of approximately 200, 128, 85, and 40 kDa.[174] These findings raise the possibility that actin (40 kDa) and myosin (200 kDa) undergo oxidative modification during CMV.[174] This intriguing possibility awaits confirmation by more specific identification of the modified proteins.

Structural abnormalities of different subcellular components of diaphragmatic fibers have been found after CMV.[162,175,176] The changes consist of disrupted myofibrils, increased numbers of lipid vacuoles in the sarcoplasm,

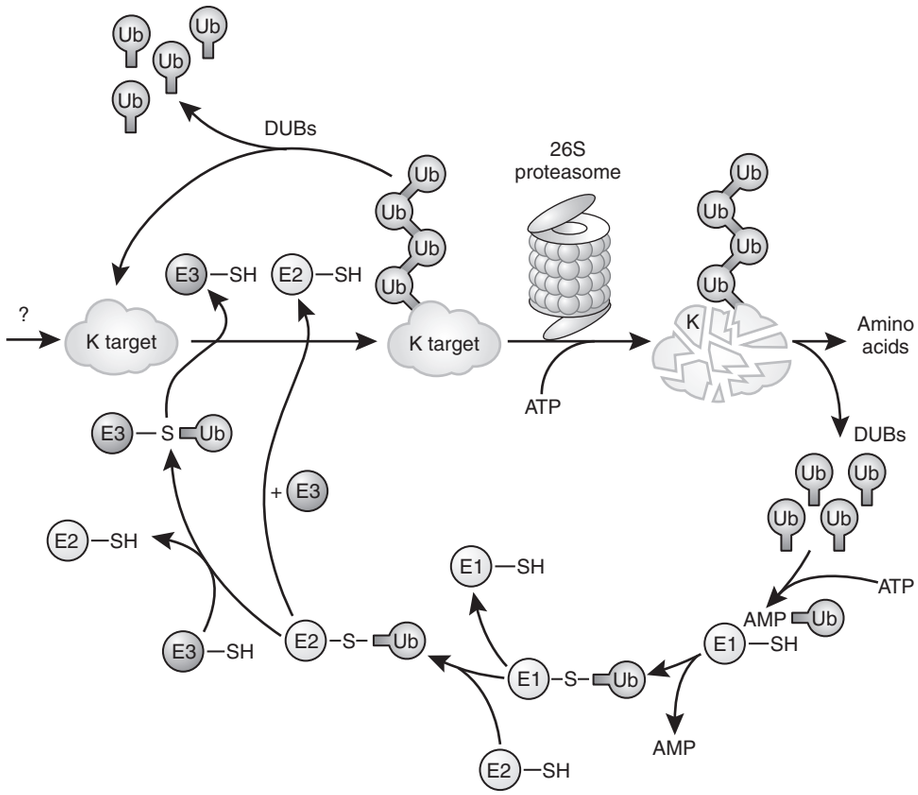

Figure 11.18 The ubiquitin-proteasome pathway of proteolysis. Proteins degraded by the ubiquitin-proteasome pathway are first conjugated to ubiquitin (Ub in *A*). The process of linking ubiquitin to lysine residues in proteins destined for degradation involves the activation of ubiquitin by the E1 enzyme in a reaction dependent on adenosine triphosphate (ATP). Activated ubiquitin is transferred to an E2 carrier protein and then to the substrate protein, a reaction catalyzed by an E3 enzyme. This process is repeated as multiple ubiquitin molecules are added to form a ubiquitin chain. In ATP-dependent reactions, ubiquitin-conjugated proteins are recognized and bound by the 19S complex, which releases the ubiquitin chain and catalyzes the entry of the protein into the 20S core proteasome *(B)*. Degradation occurs in the 26S core proteasome, which contains multiple proteolytic sites within its two central rings. Peptides produced by the proteasome are released and are rapidly degraded to amino acids by peptidases in the cytoplasm or are transported to the endoplasmic reticulum and used in the presentation of class I antigens. The ubiquitin is not degraded but is released and reused. ADP, adenosine diphosphate; PP1 pyrophosphate; SH, sulfhydryl.

and abnormally small mitochondria containing focal membrane disruptions. Similar alterations were observed in the external intercostals muscles of ventilated animals, but not in the hind limb muscle.[175] The structural alternations in the myofibrils have detrimental effects on diaphragmatic force-generating capacity; the number of abnormal myofibrils is inversely related to the force output of the diaphragm.[162] However, further studies are needed to elucidate the amount of activity that the respiratory muscles should have to prevent VIDD and whether periods of intermittent activity (i.e., "exercise" of the respiratory muscles) can prevent or attenuate VIDD.

Clinical Relevance of Ventilator-Induced Diaphragmatic Dysfunction

Do we have evidence of VIDD in patients? Although conclusive data do not exist, several intriguing observations suggest that VIDD may occur clinically. The twitch transdiaphragmatic pressure elicited by magnetic stimulation of the phrenic nerves is reduced in ventilated patients compared with physiologically normal subjects[177] and in patients ready to undergo weaning trials.[158] Diaphragmatic atrophy was documented (by ultrasound) in a tetraplegic patient after prolonged CMV[178]; the time course of atrophy, however, was not

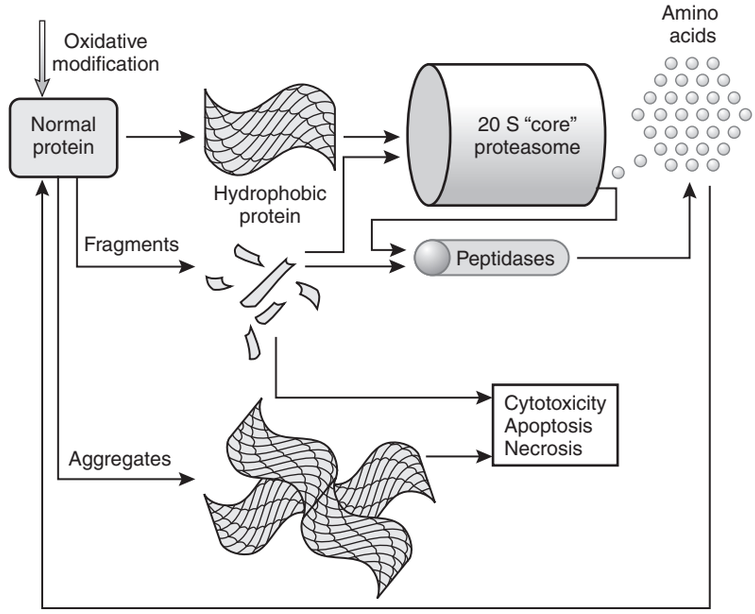

Figure 11.19 Proposed scheme for oxidation-induced protein degradation by the 20S proteasome or fragmentation and aggregation. Mild oxidative stress modifies cellular proteins, thus generating hydrophobic protein patches that bind to the 20S proteasome and ensure rapid degradation. Because most oxidatively modified proteins are efficiently degraded, there is little chance for further oxidation reactions to cause protein fragmentation or aggregation. Under conditions of severe oxidative stress, however, or if proteasome activity declines during aging or disease, the production of protein fragments and of cross-linked and oxidized protein aggregates increases. Some of the fragments are still degraded by the 20S proteasome (alone or in cooperation with cellular peptidases), but some may have cytotoxic biomimetic effects. Cross-linked and oxidized protein aggregates still tend to bind to the proteasome, which they then irreversibly inhibit. This process can cause a progressively worsening cycle of protein oxidation and increasing accumulation that is ultimately cytotoxic.

established. Furthermore, denervation atrophy removes substances originating from the nerve that are trophic for the muscle, and this is not the case for VIDD, because neural and neuromuscular functions remain intact. The presence of confounding factors, such as disease states (e.g., sepsis) and drug therapy (e.g., corticosteroids, neuromuscular blocking agents), makes documentation of VIDD difficult in a clinical setting.[159] Nevertheless, retrospective analysis of postmortem data from neonates who received ventilator assistance for 12 days or more immediately before death revealed diffuse diaphragmatic myofiber atrophy (small myofibers with rounded outlines) that was not present in extradiaphragmatic muscles.[179]

The typical clinical scenario in which to suspect VIDD is a patient who fails to wean from CMV because of respiratory muscle dysfunction.[159] Other known causes of respiratory muscle weakness such as shock, ongoing sepsis, major malnutrition, electrolyte disturbances, and neuromuscular disorders, are excluded. For example, prolonged neuromuscular blockade can be ruled out by the lack of an abnormal response to train-of-four stimulation; critical illness polyneuropathy can be excluded by the absence of neuropathic changes on electrophysiologic testing; and acute quadriplegic myopathy can be excluded by the lack of corticosteroid exposure history (or by muscle biopsy in indeterminate cases).[180]

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