Skeletal muscle fatigue is defined as a loss of the capability of the muscle to generate force and/or the velocity of contraction in response to a load and is accompanied by recovery during rest. Respiratory muscle fatigue may be defined analogously as an inability to continue to generate sufficient pressure to maintain alveolar ventilation in the face of the respiratory loading imposed by lung disease, thus resulting in ventilatory failure. A single measurement of force is necessarily inadequate to detect fatigue, and muscle force-generating or shortening capability must be demonstrated to fall during serial measurements over time. Furthermore, a demonstration that force rises subsequent to rest would be necessary to fully satisfy the definition of fatigue and to exclude the possibility that a given fall in force did not represent muscle injury (the latter does not improve with short periods of rest). Therefore, muscle fatigue can be distinguished from muscle injury (i.e., a slowly reversible or irreversible decrement in muscle contractility) and muscle weakness (i.e., a reduction in force generation that is fixed and not reversible by rest).

Theoretically, fatigue may occur at any point along the extensive chain of command involved in voluntary muscle contraction, beginning with the brain and ending with the contractile machinery (Figure 24-1). Fatigue is subdivided into two types, representing different biophysical mechanisms of fatigue development and having different physiologic characteristics: failure to generate force because of reduced central motor output (central fatigue) and failure to generate force because of fatigue at the neuromuscular junction or distal to this structure (peripheral or contractile fatigue). Davies and colleagues, the first researchers to study respiratory muscle fatigue, affirmed the existence of both types of fatigue, central and peripheral, when the respiratory system is presented with a fatiguing load. It seems that roughly equal proportions of the force decline during diaphragmatic fatigue can be attributed to reduced central motor output (central fatigue) and failure to generate force because of fatigue at the neuromuscular junction or distal to this structure (peripheral or contractile fatigue). As the frequency increases from a single stimulus to a high-frequency train, the muscle responds with a brief twitch (unitary activity), followed by an unfused (oscillatory) contraction, and, finally, when the frequency of stimulation is high enough, by a fused tetanus. Thus, the force–frequency characteristics of a muscle can be conveniently and effectively recorded by programmed electrical stimulation of the nerve in an isolated human nerve–muscle preparation in both limb and respiratory muscles (Figure 24-2). In Figure 24-2, it can be seen in the control (preload) pressure–frequency curve that pressure increases markedly in response to small changes in low-frequency stimulation, whereas pressure is affected very little by large changes in high-frequency stimulation. The importance of this curve is that central factors affecting muscle performance do not influence it. Furthermore, the manner in which it changes shape after loading gives insight into the mechanisms of fatigue. Selective loss of force at high stimulation frequencies (high-frequency fatigue), accompanied by a
Respiratory Muscles and Control of Breathing

making a maximal effort (that is, superimposed electrical stimulation of the diaphragm during such maximal maneuvers does not result in an increase in force generation above that achieved voluntarily)8 (Figure 24-3). As a result, evidence that maximal activation of the diaphragm during a maximal voluntary effort can never be achieved after a period of exercise (that is, the superimposed electrical stimulation can always evoke an increase in force generation) constitutes evidence of central fatigue. Bellemare and Bigland-Ritchie subsequently measured transdiaphragmatic pressure ($P_{di}$) generation over time before, during, and after inspiratory resistive loading in normal human subjects and employed superimposed electrical phrenic stimulation at "Psyche" Brain Spinal cord Peripheral nerve Neuromuscular junction Muscle cell membrane Transverse tubular system Ca$^{2+}$ release Actin-myosin crossbridge formation Force

FIGURE 24-1 Command chain for voluntary contraction of skeletal muscle.

decrease in the amplitude of surface-recorded action potentials of the muscle, indicates fatigue of neuromuscular transmission and/or impaired membrane excitation. Selective loss of force at low stimulation frequencies, not accompanied by a decrease in the amplitude of surface action potentials (low-frequency fatigue), is thought to be due to impairment of excitation–contraction coupling.6

SITE AND MECHANISM OF FATIGUE

Central Fatigue Central fatigue refers to the condition in which muscle force generation during sustained or repetitive contraction decreases owing to reduced central motor output. Central fatigue is judged to be present either when a maximal electrical stimulation is superimposed on a truly maximal voluntary contraction and force generation is still increased or when a certain maximal voluntary effort produces less force than one generated by direct electrical stimulation.3, 8

The technique of twitch occlusion, originally introduced by Merton in peripheral muscles,9 was used by Bellemare and Bigland-Ritchie8 in the diaphragm to distinguish central from peripheral fatigue of the respiratory muscles during respiratory loading. They initially observed that it is possible for well-motivated individuals to fully activate the rested diaphragm during voluntary contractions when

FIGURE 24-2 Pressure–frequency relationships for the human diaphragm at various time points after a loaded breathing trial (ie, a breathing trial in which an external resistive load was applied to increase the work done by the diaphragm and simulate the effects of lung disease). Diaphragm pressure generation was measured through determination of the transdiaphragmatic pressure gradient ($P_{di}$) generated in response to electrical stimulation of both phrenic nerves; $P_{di}$ (expressed as a percentage of $P_{di}$ generated with supramaximal phrenic nerve stimulation at a frequency of 100 Hz; % $P_{di,max}$) is shown on the ordinate, and phrenic stimulation frequency is shown on the abscissa. The time at which each set of curves was obtained is shown in the upper left-hand corner of each panel. For reference, each panel contains both a postload pressure–frequency curve obtained at the designated time (dashed line) and a control preload pressure–frequency curve (solid line). At 2 to 4 minutes postloading, there was a large decrement in pressure generation in response to phrenic stimulation at 20 to 100 Hz (top left panel), indicating diaphragm fatigue. Over time, the pressures generated in response to high-frequency stimulation increased, so that at 25 to 30 minutes postloading, pressure generation in response to 20 to 100 Hz stimulation had returned to preloading levels (bottom right panel). In contrast, however, the response to 20 Hz stimulation remained depressed 25 to 30 minutes postloading. Obviously, both low- and high-frequency peripheral diaphragm fatigue were present 2 to 4 minutes postloading, with rapid resolution of the high-frequency component of fatigue and persistence of the low-frequency component at 25 to 30 minutes. Data from Aubier M et al.7
Various times during the experiment to determine whether subjects were capable of fully activating the diaphragm. At the start of the study, no superimposed force could be detected during the imposition of electrical stimuli on maximal voluntary efforts, indicating that these subjects were capable of maximally activating the diaphragm before respiratory loading. During the course of loading, however, the extent to which the diaphragm could be activated decreased progressively. At the end of the study, maximal voluntary efforts had decreased by 50%, whereas twitch occlusion restored half of this decrease (Figure 24-4), indicating that even though peripheral fatigue was present, a significant portion of the reduction in force was due to failure of the CNS to activate the diaphragm completely. The results of several later studies have also suggested development of central fatigue during respiratory loading.

Central fatigue must not be confused with the progressive decrease in firing rate during maximal contraction, during which superimposed, supramaximal, electrical, tetanic stimulation does not increase muscle force. This decrease in firing frequency is possibly an adaptive, protective mechanism, responding to alteration of muscle contractile characteristics and aimed at preventing muscle exhaustion. Such an adaptation would be beneficial as 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 might occur if high-frequency excitation were maintained. Central fatigue is associated with an even greater decrease in firing rate than can be justified by muscle contractile characteristics. It seems likely that activation of muscle afferents by some fatigue-induced change within the muscle inhibits motor neuron activity and reduces the latter's firing rates. For the diaphragm, it has been shown that afferent information via small (type 3 and type 4) fibers of the phrenic nerve affects the central respiratory controller's discharge in terms of firing rate, firing time, and frequency of breathing. Sensory fibers are activated primarily by extracellular metabolic changes, for example, low pH, ischemia, and increased osmolarity, and by some substances (phenylbiguanide, capsaicin). It has been shown that the reduction in central respiratory output during respiratory loading is signaled by small fiber afferents, which are stimulated by lactic acid accumulation and the fall in pH in the respiratory muscles.

Central fatigue may be the result of a decrease in central respiratory motor output in response to endogenous opioid (endorphin) elaboration in the CNS, with the endorphin being generated as a consequence of the stress of loaded breathing. In animals, adequate evidence supports this concept. 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 (Figure 24-6). An increase in β-endorphin in the cisternal cerebrospinal fluid was also detected. In humans, in support of this concept, it was demonstrated
that naloxone could restore the load compensatory reflex in patients with chronic obstructive pulmonary disease (COPD) in whom it was initially absent.\textsuperscript{13} It was postulated that, in such patients, endogenous opioids were elaborated in response to the stress of chronically increased airway resistance, resulting in attenuation of respiratory compensation, perhaps acting as a mechanism to reduce dyspnea.\textsuperscript{13} Moreover, in asthmatic subjects after methacholine challenge inducing severe reductions in forced expiratory volume in 1 second (FEV\textsubscript{1}), naloxone pretreatment resulted in increased breathing frequency, occlusion pressure, and mean inspiratory flow rate.\textsuperscript{15} Endorphin elaboration in the CNS seems to be signaled by small fiber afferents.\textsuperscript{14} In addition, it is possible that CNS endorphin production is also stimulated by circulating cytokines, especially interleukin-6 (IL-6), which is produced by the inspiratory muscles when they are working intensely.\textsuperscript{20–22}

In summary, during fatiguing loaded breathing, the central discharge firing rate decreases, resulting in force decline (central fatigue) as an adaptation to altered chemistry and/or contractile characteristics of the respiratory muscles, in an effort to prevent their self-destruction through excessive activation. During loaded breathing in various clinical states, this response also includes changes in the timing of breathing (firing time, frequency). These changes of central respiratory controller activity seem to be mediated by afferents (via the small fibers) and blood IL-6, which modulate endogenous opioids. Such a strategy, representing an adaptive response much in the way that opioids are generated in response to chronic pain, certainly minimizes breathlessness and may avoid or delay the onset of respiratory muscle peripheral fatigue, protecting the ventilatory pump from exhaustion. However, it may result in hypoventilation and the development of hypercapnia.

**Peripheral Fatigue** Peripheral fatigue refers to failure of transmission at the neuromuscular junction or distal to this structure and is judged to be present when muscle force output or velocity falls in response to direct electrical stimulation. This type of fatigue may occur either because of failure of impulse propagation across the neuromuscular junction and/or over the muscle surface membrane (transmission fatigue) or because of failure of the contractile apparatus of muscle fibers (impaired excitation–contraction coupling). The former is also called high-frequency fatigue as fatigue results in depression of force generation in response to high-frequency electrical stimulation (eg, in humans 50 to 100 Hz), and the latter is called low-frequency fatigue since force generation in response to low-frequency stimuli (ie, 1 to 20 Hz) is reduced (see Figure 24-2). Low-frequency fatigue can occur in isolation, but high-frequency fatigue is invariably associated with some alterations in muscle force generation at lower frequencies.
High-frequency fatigue attributed to transmission failure is constantly produced experimentally during artificial stimulation of a motor neuron, when muscle force declines in association with decline in action potential amplitude. From a teleologic point of view, transmission block could be beneficial as failure at the neuromuscular junction or in excitation of the cell membrane may protect the muscle from excessive depletion of its ATP stores, which would lead to damage.23 High-frequency fatigue has been demonstrated in the diaphragms of normal humans after a trial of high-intensity inspiratory resistive loading; it resolves extremely quickly after cessation of strenuous muscle contractions.7

Low-frequency fatigue is attributed to impaired excitation–contraction coupling, a term that includes all processes linking electrical activation of muscle fibers and the various metabolic and enzymic processes providing energy to contractile machinery. Typically, loss of force is not accompanied by a parallel decline in electrical activity9 and is long-lasting, recovery taking at least 24 hours.24 It is characterized by selective loss of force at low frequencies of stimulation, despite maintenance of force generated by high frequencies of stimulation, thereby indicating that contractile proteins are capable of generating force provided that sufficient Ca2+ is released by the sarcoplasmic reticulum. Therefore, this type of fatigue may result from reduced Ca2+ availability due to alterations in sarcoplasmic reticulum function and/or reduced Ca2+ sensitivity of myofilaments at submaximal Ca2+ concentrations. Both changes have been demonstrated experimentally,25,26 Reduced myofilament Ca2+ sensitivity is caused by increased inorganic phosphate (Pi) concentration and acidosis.25,27 The reason for reduced Ca2+ release by the sarcoplasmic reticulum during contractions is less clear but may be related to declining ATP25 levels or increased production of oxygen-derived free radicals.28–30

Low-frequency fatigue occurs during high-force contractions, and it appears likely that muscle ischemia and reliance on anaerobic metabolism are important factors in its generation. Indeed, low-frequency diaphragmatic fatigue occurs in dogs during cardiogenic or septic shock31,32; despite a three-fold increase in integrated electromyographic activity, Pa decreases (Figure 24-7). Low-frequency fatigue has been demonstrated in the diaphragm and sternocleidomastoid muscles of normal subjects breathing against high inspiratory resistive loads.4,33 Low-frequency diaphragmatic fatigue has also been shown to develop in normal subjects asked to sustain maximum voluntary ventilation for 2 minutes.34

**METABOLIC CONSIDERATIONS IN MUSCLE FATIGUE**

Skeletal muscle is analogous to an engine; it converts chemical energy into heat and work. If the chemical energy available becomes limited or the ability of the muscle to use chemical energy is impaired, the muscle will fail as a force generator.

The authors of most studies have concluded that the major factors underlying fatigue occur within the muscle fibers and mainly result from depletion of muscle energy stores or from pH changes caused by lactate accumulation.1 Substances directly involved in the transformation of chemical energy into mechanical work in skeletal muscle are ATP, ADP, Pi, hydrogen ions (H+), magnesium ions (Mg2+), and phosphocreatine (PCr). ATP leaves mitochondria and diffuses into the contractile machinery, where ATPase enzymes hydrolyze one of the pyrophosphate bonds, liberating large quantities of energy in the process:

\[
\text{MgATP + H}_2\text{O} \rightarrow \text{MgADP} + \text{P}_i + \text{H}^+ + \text{Energy}
\]

In general, metabolic changes can cause fatigue either through a reduction in the amount of high-energy compounds (eg, PCr and ATP) or through accumulation of breakdown products (eg, P_i and H^+). Figure 24-8 shows some important metabolic changes that occur during fatiguing stimulation. Important changes are the breakdown of PCr, with the concomitant formation of P_i, and the formation of lactate, which is usually accompanied by accumulation of H^+ and thus also by reduced intracellular pH.

A great deal of attention has been focused on the role that lactic acid plays in the development of fatigue as a result of the firm correlation that exists between lactic acid accumulation in the muscle and contractile force. It has been shown that respiratory muscles produce great amounts of lactic acid if they are working under fatiguing conditions.35 However, there is no direct evidence that lactic acid produced by respiratory muscles is the culprit in fatigue.4 The effects of lactic acid on force generation are believed to be mediated by lowering of the pH. Of all the breakdown products of energy metabolism, H^+ and Pi have the greatest effect on the contractile apparatus.25,27 An increased P_i concentration and acidosis result in both reduced maximum tension production (ie, tension at saturating Ca2+ concentrations) and reduced myofibrillar Ca2+ sensitivity25 (Figure 24-9). Furthermore, H^+ ions exert a direct negative effect on the contractile process itself, which is not related to pH.25

In addition to lactic acid accumulation and acidosis of every kind, glycogen depletion,4 inability to use blood-borne substances,4 a decrease in the rate of ATP hydrolysis,36,37 and increased, oxygen-derived free radical production28–30
The metabolites are lactate (La), inorganic phosphate (Pi), ATP, inosine monophosphate (IMP), and phosphocreatine (PCr). Easily fatigued fibers of Xenopus have a very low oxidative capacity, and, during a period of increased energy consumption, they therefore depend on the breakdown of high-energy phosphates (PCr and ATP) and anaerobic glycolysis. The latter process results in accumulation of lactate ions and acidosis. Note that the level of ATP does not start to decline until the store of PCr is almost fully depleted. Note also that the final rapid tension reduction coincides with the reduction in the level of ATP. Data from Nagesser AS et al16 and Westerblad H and Lannergren J.37

probably all play a part in causing loss of force during fatigue. However, the exact interplay of all these factors has not yet been identified in either the diaphragm or the other skeletal muscles.4

INTEGRATED VIEW OF RESPIRATORY MUSCLE FATIGUE

Fatigue is likely to result from 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 and/or metabolite accumulation, and feedback-modulating reflexes.1 Although the three types of fatigue, that is, central, peripheral high frequency, and peripheral low frequency, are usually separately considered, it is likely that they do not occur in isolation but coexist when respiratory muscles face an excessive workload, with the relative importance of each depending on duration of respiratory loading and other physiologic variables (e.g., arterial pressure and arterial blood gas concentrations). Indeed, for an individual muscle, a close relationship exists between excitation and energy metabolism, representing a protective mechanism, so that when depletion of fuel and/or metabolite accumulation occurs (impaired excitation–contraction coupling or low-frequency peripheral fatigue), the activation system fails; in extreme fatigue, this prevents muscle destruction, which would happen if ATP concentrations fell to zero. A decrease in excitation may result from failure of the neuromuscular junction7–23 (transmission fatigue or high-frequency peripheral fatigue), reduced rate of firing by the CNS17 (central fatigue), or both. In the respiratory system, in addition to a reduction in firing frequency, the CNS may respond by altering the timing of breathing (firing time, frequency).18,19 Such alterations in the responses of the central controllers could be brought about by afferents from fatigued respiratory muscles and the chest wall. In particular, free nerve endings within the muscle might inhibit motor neuron activity in response to muscle stretch and fatigue. Afferent information via small (type 3 and type 4) fibers, stimulated by the heavy work (ergoreceptors, type 3) or by noxious substances such as lactic acid (nociceptors, type 4), reduces central respiratory output by modulating endorphins as an adaptive response to avoid or delay respiratory muscle peripheral fatigue.

ENERGY BALANCE: DETERMINANTS OF A CRITICAL TASK

Muscle fatigue develops when the mean rate of energy demand (Ud) exceeds the mean rate of energy supply (Us), that is, Ud > Us.38 Thus, since E = W/Ud and Ud = W/E, W/E > Us or W > UsE, where W is mean muscle power and E is efficiency. Clearly, when W ≤ UsE, the muscle can continue to work indefinitely, but when W > UsE, there will be a finite endurance time limit. Thus, decreases in either efficiency or energy supplies should encourage fatigue, as
would an increase in muscle power. The threshold of fatigue is the lowest level of exercise and/or mechanical loading that cannot be sustained indefinitely. In other words, the threshold of fatigue corresponds to the lowest W, where \( W > U_s E \). For a given value of E, W and \( U_s \) at the point where \( W = U_s E \) are named “critical” power \( (W_{crit}) \) and rate of energy supply \( (U_{s,crp}) \), respectively.

For inspiratory muscles during resistive breathing with mouth pressure developed in a square wave manner, \( W_{crit} \) equals 6 to 8 kg/min. In this situation, \( W = PV_{IT} = PV_T (1/T) \), where \( P \) is mean inspiratory pressure, \( V_T \) is tidal volume, \( f \) is frequency of breathing, and \( T_T \) is total breath time. When numerator and denominator are multiplied by inspiratory time \( (T_I) \), the equation becomes \( W = PV_T (T_I/T_T) \), where \( V_T / T_I \) is mean inspiratory flow and \( T_I/T_T \) is duty cycle. Duty cycle approximates duration of inspiratory muscle contraction as a proportion of the total duration of the breathing cycle. Therefore, \( W_{crit} = P(V_T / T_I)(T_I/T_T) \), indicating that the \( W_{crit} \) of respiratory muscles can be obtained through a variety of combinations of \( P \), \( V_T / T_I \), and \( T_I/T_T \). \( P \) can be expressed as a percentage of the maximal pressure. It was found that the critical pressure of all inspiratory muscles is 50 to 70% of the maximal inspiratory pressure \( (P_{I,max}) \) and that for the diaphragm alone, critical \( P_{di} \) is 40% of maximal \( P_{di} \) \( (P_{di,max}) \) for \( V_T / T_I \) of 0.6 to 0.9 L/s, and \( T_I/T_T \) of 0.3 to 0.4. Furthermore, under conditions of predominant diaphragmatic recruitment, critical \( P_{di} \) decreases as \( T_I/T_T \) increases at constant \( V_T / T_I \). In other words, when the proportion of the time spent in inspiration increases, the pressure that can be sustained falls. When the product \( (P_{di}/P_{di,max})(T_I/T_T) \), called the pressure–time index of the diaphragm \( (PT_{di}) \), exceeds the critical value of 0.15 to 0.18, there is a finite endurance time limit that is inversely related to \( PT_{di} \). Below this critical value, breathing can be sustained without evidence of fatigue. A critical value has also been demonstrated for the pressure–time index of inspiratory rib cage muscles other than the diaphragm \( (PT_{rc}) \); it amounts to 0.30 when inspiratory intercostal/accessory muscles are predominantly recruited. Finally, in keeping with the above-mentioned determinants of \( W_{crit} \), it was shown that the critical value of the esophageal pressure–time index \( (PT_{es}) \) [used as a measure of global inspiratory muscle pressure output and defined as the product \( (P_{es}/P_{es,max})(T_I/T_T) \), where \( P_{es} \) is mean esophageal pressure generated per tidal breath, equivalent to \( P_{tidal} \), and \( P_{es,max} \) maximal esophageal pressure, equivalent to \( P_{I,max} \)] is inversely related to \( V_T / T_I \) over a wide range of flows.

One would predict that if \( U_s E \) is decreased (by decreasing \( U_s \), \( E \), or both), critical values of \( P \) or a combination of \( P \), \( V_T/T_I \), and \( T_T/T_T \), composing \( W \), will decrease (Figure 24-10). For example, decreasing \( U_s \) by reducing cardiac output in dogs readily results in diaphragmatic fatigue (see Figure 24-7). Similarly, decreasing the bloodflow to the diaphragm in dogs causes fatigue that is reversed by restoring normal perfusion or by hyperperfusion. Furthermore, a decrease in \( E \), as might occur with resistive breathing (as opposed to unobstructed hyperventilation), may substantially alter \( W_{crit} \). In fact, it was found that \( W_{crit} \) during hyperventilation

![FIGURE 24-10](image-url) The various determinants of energy supply, energy demand, and neuromuscular competence are schematically represented. Respiratory muscle endurance is determined by the balance between energy supplies and demands (A). Normally, the supplies meet the demands and a large reserve exists. Whenever this balance is in favor of demands, the respiratory muscles ultimately become fatigued. The \( P_{tidal}/P_{I,max} \) ratio is one of the determinants of energy demands, which are shown in B as a balance between the load per tidal breath \( (P_{tidal}) \) and the neuromuscular competence of the ventilatory pump \( (P_{I,max}) \).
is at least four times greater than the $W_{\text{crit}}$ of 6 to 8 kg/min during resistive breathing in normal subjects. If the diaphragm operates at shorter lengths during acute hyperinflation, a similar argument may account for a smaller critical $P_{di}$ when a given force requires much greater excitation. At half inspiratory capacity, $E$ can be reduced by as much as 50%.

In summary, there is clear evidence of the existence of a critical pressure, which, if exceeded, results in fatigue. However, this critical pressure is affected by many factors, including the relative duration of contraction and relaxation per breath (pressure–time index), velocity of contraction, operational length, energy supply, efficiency, and state of muscle training.

**DETECTION OF INSPIRATORY MUSCLE FATIGUE**

Fatigue is conveniently and conventionally defined in terms of loss of force. However, other changes in physiologic function (e.g., electromyographic spectral shift, slowing of muscle relaxation rate) can be useful indicators that the fatigue process is under way.

Because muscle fatigue is a complex phenomenon, a test that is well suited to detect one type of fatigue may be incapable of detecting another. Moreover, the need for serial measurements of an index of muscle force generation over time to detect fatigue is a particular problem in the respiratory system because many variables (e.g., lung volume, thoracoabdominal configuration, muscle interaction) can vary over time; all of these factors can influence the relationship between muscle force and pressure generation. For example, consider the utility of measuring $P_{i,max}$ serially to detect respiratory muscle fatigue. This parameter is highly effort dependent, and time-dependent reductions could represent lack of motivation, central fatigue, peripheral high-frequency fatigue, or simply an alteration in lung volume and a resultant mechanical change in the transduction of muscle force into pressure. In addition, failure of $P_{i,max}$ to change does not exclude the development of fatigue because this test would not be suitable for the detection of low-frequency fatigue. As a result, one must keep in mind the potential limitations of a given test for detection of muscle fatigue. Most tests are suitable for detecting the presence of only one component of muscle fatigue, and complete characterization of fatigue requires a complex series of assessments.

**MEASUREMENT OF FORCE (OR PRESSURE)**

**Voluntary Maximal Pressures** In accordance with the definition of respiratory muscle fatigue, it can potentially be documented by measuring a decrease in voluntary maximal respiratory pressures, with demonstration of recovery with rest. Therefore, to detect inspiratory muscle fatigue, either maximal static inspiratory pressure, maximal transdiaphragmatic pressure, or maximal sniff pressure can be measured (see Chapter 60, “Assessment of Respiratory Muscles”).

Maximal static inspiratory pressure ($P_{i,max}$) is measured at the mouth, and its transient fall indicates fatigue of inspiratory muscles as a whole. Such a fall in $P_{i,max}$ has been demonstrated after breathing against external loads, maximal voluntary hyperpnea, marathon running, and labor. The major limitation of $P_{i,max}$ as a test of fatigue is its total dependence on the subject's maximal voluntary effort. Although $P_{i,max}$ is reliable in highly motivated subjects, it cannot be obtained with certainty in patients. Another drawback of $P_{i,max}$ is the potential lack of sensitivity for fatigue detection. Because a maximal static effort is associated with high neuronal firing rate, it reflects mainly high-frequency fatigue and may be a poor indicator of low-frequency fatigue. Therefore, $P_{i,max}$ can be used to detect fatigue in motivated volunteers but has limited utility in patients because of difficulties in ensuring a maximal effort. Twitch interpolation techniques provide a potential means of solving this problem.

Maximal transdiaphragmatic pressure ($P_{di,max}$) is measured with balloon-catheter systems, and its transient fall indicates fatigue of the diaphragm. Such a fall in $P_{di,max}$ has been documented after breathing with an emphasis on diaphragmatic recruitment against external loads, voluntary hyperpnea, or high-intensity exercise. $P_{di,max}$ has the same types of limitation as $P_{i,max}$ in the detection of fatigue, but, additionally, it is invasive, requiring an even more complex maneuver for reliable measurement than that required to measure $P_{i,max}$. Therefore, $P_{di,max}$ can be used to detect diaphragmatic fatigue in motivated volunteers but cannot be recommended for use in clinical settings.

Maximal sniff $P_{di}$ can be used to assess diaphragmatic strength, whereas global inspiratory muscle strength can be assessed either with maximal sniff esophageal pressure or with maximal sniff nasal inspiratory pressure (SNIP). A sniff maneuver is easily performed by almost all subjects and patients, whereas, additionally, the measurement of SNIP is noninvasive, often yielding higher pressures than $P_{i,max}$. However, the usefulness of measuring a transient fall of maximal sniff pressures to detect fatigue in patients remains to be established.

**Muscle Response to External Stimulation**

**Pressure–Frequency Relationship** Peripheral fatigue can be most specifically detected by recording the pressure–frequency or force–frequency curve of a muscle in response to electrical motor nerve stimulation. Of the respiratory muscles, the diaphragm (see Figure 24-2) and the sternocleidomastoid muscles are most amenable to this form of testing (see Chapter 60, “Assessment of Respiratory Muscles” and Chapter 67, “Diaphragmatic Responses to Stimulation”). This technique is nonvolitional, thus overcoming the difficulties associated with voluntary efforts. In addition, the response of a particular muscle can be studied in isolation, providing information on the underlying mechanisms of peripheral fatigue (see Figure 24-2). However, this is a difficult test to perform. Tetanic electrical stimulation can also be uncomfortable. To overcome this problem, partial pressure–frequency curves may be constructed with the use of twin pulses and variation of the intervals between the pulses. This is better tolerated than tetanic stimulation and can provide comparable information regarding the presence of high- and low-frequency fatigue. Partial pressure–frequency curves may
also be constructed with the use of magnetic stimulation. Therefore, although construction of a pressure–frequency curve provides a means of directly detecting the development of muscle fatigue, the applicability of this approach is limited by patient discomfort associated with high-frequency stimulation, equipment expense and complexity, and the need to carefully control for variation in body position, lung volume, and electrode–nerve interface. Advances in magnetic stimulation techniques may allow a variation of this form of testing to have more widespread clinical use in the future, but this test is currently limited to research applications.

Single-Twitch Stimulation Recording of muscle twitches in response to single nerve shocks can be used to detect the presence of low-frequency fatigue. Twitch responses are much easier to obtain but are more variable than tetanic responses and are subject to additional variations caused by twitch potentiation. This technique is nonvolitional and produces much less patient discomfort than construction of the force–frequency relationship. However, application of this test in clinical settings is relatively difficult, partly because, in the case of the diaphragm, stimulation of both phrenic nerves is required but also because it is critical for supramaximality to be attained during electrical stimulation for this test to be useful. Magnetic stimulation seems to overcome some of these difficulties, making it a promising technique for obtaining an objective index of the development of muscle fatigue.

**Electromyography**

**Time Domain Analysis** For respiratory muscles, as for any other skeletal muscles, a nearly linear relationship exists between muscle electrical activity and the pressure generated; the slope is related to muscle length. As a result, for a given muscle length, a decrease in the ratio respiratory muscle pressure/integrated electromyographic activity (pressure-to-integrated electromyographic activity ratio) indicates decreased muscle contractility due to the development of fatigue (see Figure 24-7). As the decrease in pressure is not accompanied by decreased integrated electromyographic activity, a decrease in this ratio indicates that neural or neuromuscular transmission factors are not responsible for the decrease in pressure, which is rather due to impaired excitation–contraction coupling.

For this index to be valid, other factors affecting respiratory muscle contractility, such as muscle length, chest wall configuration, or lung volume, should be controlled or kept constant. The applicability of this method to the respiratory system is limited by the difficulty of recording the electromyographic activity of all muscles involved in normal or augmented breathing that contribute to the measured pressure. Moreover, their relative contributions to the generated pressure are known to change during fatigue development. In practice, the pressure-to-integrated electromyographic activity ratio can be evaluated in the diaphragm, sternocleidomastoid muscles, and abdominal muscles because their electrical activity and force production can be more easily recorded without interference from other muscles. If special precautions are not taken, electromyographic signals (particularly those recorded from the diaphragm with an esophageal electrode) can be subject to artificial changes caused by variations in lung volume or chest wall configuration. Techniques have been described in recent reports that exclude many of the artifacts associated with esophageal diaphragmatic recording, that is, electrocardiographic, electrode motion, noise, and esophageal peristalsis artifacts. Moreover, because multielectrode arrays are used in these techniques, they reliably measure the diaphragm electromyographic amplitude and power spectrum in such a way that these variables are not affected by chest wall configuration and/or diaphragm length. It is obvious that even if electromyographic activity can be accurately recorded, respiratory muscle pressures must also be reliably assessed for the pressure-to-integrated electromyographic activity ratio to be meaningful. Nevertheless, time domain electromyographic assessment in patients enables the detection of fatigue during spontaneous breathing, without the need for special efforts by the patients, and provides a means of determining whether observed reductions in respiratory muscle pressure are due to alterations in action potential transmission or to intrinsic alterations in peripheral muscle function (ie, impaired excitation–contraction coupling or contractile protein myofilament function).

**Frequency Domain Analysis** Frequency domain analysis of electromyographic signals from the respiratory muscles allows detection of the occurrence of respiratory muscle fatigue because the power spectrum of electromyographic signals typically shifts to lower frequencies during fatiguing contractions. Several indices of the power spectrum have been used for this purpose, including an assessment of the “center” or “centroid” frequency of the power spectrum and a “power ratio” of a high-frequency band over a low-frequency one. Both of these indices decrease with fatigue and increase with recovery. With appropriate instrumentation, these analyses can be done “on-line” in spontaneously breathing subjects or patients. Shifts in the electromyographic power spectrum indicative of diaphragmatic fatigue have been documented during severe whole body exercise, during loaded breathing in normal subjects, in female patients during delivery, and in ventilator-dependent patients during weaning failure. As the electromyographic power spectral shift occurs in the diaphragm before there is failure to develop adequate force, this is a useful objective measure with which to predict the onset of fatigue. Moreover, power spectral shifts are rapidly reversed on rest or with reduced activity, even though the muscle may remain in a fatigued state. Therefore, this test cannot be taken as a reliable index of the development of muscle fatigue.

**Respiratory Muscle Relaxation Rate** On cessation of contraction, skeletal muscles relax at a rate determined by their relative proportions of fast and slow fibers. When muscles fatigue, their relaxation rate declines as a result of slower uptake of Ca$^{2+}$ previously released from...
the sarcoplasmic reticulum. During various types of intermittent contraction, the rates of decay of \( P_{es} \) and \( P_{di} \) reflect the relaxation rate of the global inspiratory muscles and the diaphragm, respectively. Relaxation rate typically declines before the occurrence of muscle failure, following a time course similar to that of the change in electromyographic power spectrum. On cessation of loading, relaxation rate recovers quickly and reaches baseline values within 5 to 10 minutes. The relaxation rate of \( P_{es} \) or \( P_{di} \) can be measured during intermittent contractions against loads, during sniffs with airway occlusion or without airway occlusion, and during phrenic nerve stimulation. The most useful and simple maneuver is the unoccluded sniff, which is easy to perform for most subjects and provides large and consistent changes in relaxation rate after fatigue. Inspiratory muscle relaxation rate can also be assessed in a less invasive manner by measuring nasopharyngeal or mouth pressure during sniffs with balloons positioned in these locations or entirely noninvasively by using SNIP. However, these less invasive techniques have been validated only in normal subjects; the transmission of brief pressure swings from the alveoli to the upper airways is likely to be dampened in patients with abnormal lung mechanics.

Relaxation rate change is determined from the change in maximal relaxation rate (MRR), which is calculated as the first derivative of pressure with respect to time \( (dp/dt) \) over the first half of the relaxation curve. Because MRR increases with the amplitude of pressure swing, it is usual to normalize the MRR and to express it as a percentage of pressure fall in 10 ms. The range of normal values for MRR is wide, with overlap between the fresh and fatigued states. Serial measurements are thus required to detect the onset of inspiratory muscle fatigue in an individual.

Measurement of MRR can be used with confidence as an early sign of fatigue in healthy humans subjected to high external inspiratory loads or to high-level hyperpnea. MRR can also be used to detect fatiguing contractions during exercise in patients with COPD or during trials of weaning from mechanical ventilation. Because interpretation of changes in MRR is not straightforward, this test can be considered useful only for clinical research.

**PRESSURE–TIME INDEX OF INSPIRATORY MUSCLES**

As previously reported in this section, \( PT_{es} \), \( PT_{di} \), and \( PT_{rc} \) (ie, pressure–time index of the global inspiratory muscles, diaphragm, and inspiratory muscles other than the diaphragm, respectively) characterize the operational conditions of the inspiratory muscles with respect to their fatigue threshold. Therefore, these indices may allow assessment of the risk of fatigue before actual task failure occurs. However, as their critical values were established in healthy subjects breathing against external loads, critical thresholds may be different in clinical circumstances, in which a number of pathologic factors (eg, levels of tissue perfusion, presence of hypoxemia) may influence muscle performance. In addition, pressure–time index assessment is dependent on accurate measurement of maximal muscle pressure (eg, \( P_{di,max} \) for \( PT_{di} \)), which is often difficult in patients. Moreover, the shortening velocity of muscle fibers, that is, inspiratory flow pattern, strongly influences critical values of the pressure–time index. Finally, some clinical conditions (malnutrition, steroid myopathy) change the muscle fiber populations, altering the relationship between muscle strength and fatigability. For example, conditions that result in a shift to a greater concentration of slow fibers in muscle may well result in better tolerance of a given

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**FIGURE 24-11** Changes in the peak values of integrated spontaneous electromyographic activity of the diaphragm (\( E_{di} \)) and the corresponding spontaneous transdiaphragmatic pressure (\( P_{di} \)) (A), ratio of \( E_{di} \) to \( P_{di} \) (\( E_{di}/P_{di} \)) (B), and centroid frequency (\( f_c \)) and ratio of high and low frequencies of diaphragmatic electromyographic activity (H/L) (C) during shock induced by balloon inflation in the inferior vena cava in a canine model and recovery. Means ± SE.

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\( \text{PT}_{es} \) and \( \text{PT}_{di} \) are pressure–time indexes of the global inspiratory muscles and the diaphragm, respectively.
absolute level of pressure–time index and an increase in critical pressure–time index. Therefore, as fatigue thresholds have been reported only in patients with COPD, remaining largely untested in other pathologies, the pressure–time index should be considered a measure of inspiratory load rather than an instrument for the clinical diagnosis of fatigue.

**Clinical Detection of Fatigue**

**Breathing Pattern: Tidal Volume and Breathing Frequency** Rapid shallow breathing, characterized by high breathing frequency and low tidal volume, commonly develops in progressive respiratory failure or in unsuccessful attempts to wean patients from mechanical ventilation. These conditions are associated with increased ventilatory load and/or reduced respiratory muscle capacity and therefore potentially may lead to respiratory muscle fatigue (see Figure 24-10). However, the relationship between fatigue and breathing pattern is complex, and rapid, shallow breathing is most likely a reflex response to an increase in respiratory workload and not the consequence of respiratory muscle fatigue per se. Thus, although rapid, shallow breathing may accompany respiratory muscle fatigue, it cannot be considered a specific marker of fatigue.

**Thoracoabdominal Motion** Analysis of breathing movements gives some insight into the level of recruitment and function of the respiratory muscles (in particular of the diaphragm, rib cage inspiratory muscles, and abdominal muscles). Two unusual patterns of muscle recruitment may be observed in healthy subjects subjected to fatiguing inspiratory loads. The first is increased variability in compartmental contributions to tidal volume, with breaths characterized by clear rib cage predominance alternating with other breaths in which abdominal motion predominates (alternating breathing or respiratory alternans) (Figure 24-12). This pattern reflects alternate predominant recruitment of the inspiratory rib cage (intercostal/accessory) muscles and of the diaphragm. Because fatigue may develop separately in the diaphragm and in the inspiratory rib cage muscles, such alternation may represent a way to postpone respiratory muscle failure. The second pattern is paradoxical movement of one compartment, generally the abdomen, that is, an inward movement of the abdominal wall during inspiration (abdominal paradox). Abdominal paradox indicates weak, absent, or inefficient contraction of the diaphragm. These two patterns may also be observed in patients breathing against loads that might lead to fatigue, as well as in patients who cannot be weaned from the ventilator (Figure 24-13). However, these abnormal patterns of thoracoabdominal motion are not specific for respiratory muscle fatigue as respiratory alternans and abdominal paradox can appear immediately after institution of loaded breathing due predominantly to increased respiratory load rather than muscle fatigue. Furthermore, these

![Figure 24-12](image-url)

**Figure 24-12** Tracings of an experimental run in a man breathing against an inspiratory resistive load. With each breath, the subject generated 75% of maximum mouth pressure. All pressures, except for transdiaphragmatic pressure, were measured relative to atmospheric pressure. Only gastric and transdiaphragmatic pressure varied: mouth and esophageal pressures remained constant throughout the run. Gastric pressures increased during periods A and C and declined during periods B and D, indicating alteration of inspiratory muscle recruitment. Data from Roussos C et al.

![Figure 24-13](image-url)

**Figure 24-13** Sequence of changes in $P_{a}CO_2$, respiratory rate, minute ventilation, and high-frequency/low-frequency (H/L) ratio of the diaphragm in a patient during a 20-minute attempt at discontinuation of mechanical assistance. The initial change was the fall in H/L (indicating fatigue), and this was followed by a progressive increase in respiratory rate. The $P_{a}CO_2$ initially fell, and the patient became alkalemic. Paradoxical abdominal displacements were not noted until after there had been substantial increases in respiratory rate and minute ventilation. Hypercapnia and respiratory acidosis did not develop until after abdominal paradox and alternation between rib cage and abdominal breaths were noted. Just before the artificial ventilation was re instituted, there was a sharp fall in respiratory frequency and in minute ventilation. Data from Cohen C et al.
patterns can also occur, albeit to a lesser degree, during application of low, nonfatiguing respiratory loads. Therefore, abnormal thoracoabdominal motion should be viewed as reflecting specific forms of respiratory muscle dysfunction (eg, diaphragmatic paresis) and/or increased ventilatory load, which in itself may or may not induce respiratory muscle fatigue.

CONCLUSIONS
Of the measures and indices described, breathing pattern and thoracoabdominal motion analysis, as well as pressure–time index measurement, are useful but nonspecific tests of fatigue. Serial measurement of maximal voluntary pressures, assessment of maximum relaxation rates, time domain and frequency domain electromyographic analysis, and measurement of respiratory muscle pressures in response to electrical or magnetic nerve stimulation are all techniques that can be used to assess the evolution of respiratory muscle fatigue in the research environment. Of these techniques, serial measurement of respiratory muscle pressures in response to electrical or magnetic nerve stimulation is arguably the best technique with which to directly assess the development of respiratory muscle fatigue at the present time, and it offers the greatest promise for assessment in the clinical setting.

MANAGEMENT OF RESPIRATORY MUSCLE FATIGUE
Experimental muscle fatigue develops when demands on the respiratory pump exceed pump energy supply (see Figure 24-10). However, it is not yet clear whether, in the clinical setting of ventilatory failure, overt peripheral muscle fatigue develops or whether an adaptive feedback reduction of central drive avoids such fatigue, albeit at the cost of hypoventilation. The three components of the system (demand, supply, and neuromuscular competence) (see Figure 24-10) are closely linked, and for the patient proceeding to ventilatory failure, a small alteration in one variable may crucially determine outcome. It is rational, therefore, to direct therapeutic efforts at minimizing demand, maximizing neuromuscular competence by improving contractility and optimizing respiratory drive, and increasing energy supply to the respiratory muscles.

DECREASING THE DEMANDS ON THE RESPIRATORY MUSCLES
If either the work of breathing or the pressure–time index increases to such a point that it exceeds a critical value, energy requirements will increase excessively and fatigue may develop. This explains the inability of normal subjects to maintain high levels of ventilation for long periods or to sustain normal ventilation when the work of breathing is excessive. Therefore, in patients with increased work of breathing, fatigue may be avoided with therapy if it reduces the load on the ventilatory pump to below the fatigue threshold. In the clinical situation, this is most often achieved by treatment directed at reducing airway resistance and increasing lung compliance.

Muscle strength is an important factor influencing muscle energy demands. Therefore, pressure should be normalized by expressing it as a fraction of $P_{i,max}$ at the same fiber length (for example, $P_{i,tidal}$ should be expressed as a fraction of $P_{i,max}$ measured at functional residual capacity [FRC]). The greater the work required to sustain adequate ventilation, the greater the value of $P_{i,tidal}/P_{i,max}$ and the greater the energy demand (see Figure 24-10). Thus, at constant pressure, energy demand will increase as $P_{i,max}$ decreases. This is of considerable physiologic significance since $P_{i,max}$ is a function of fiber length; for the respiratory muscles, therefore, it is determined in part by lung volume. Dynamic hyperinflation strongly predisposes respiratory muscles to fatigue, not only by increasing $P_{i,tidal}$ but also by decreasing $P_{i,max}$. Furthermore, if the efficiency of the respiratory muscles decreases, which occurs with an increase in airway resistance, the oxygen cost of breathing and energy demands increase for the same muscle power, further predisposing them to fatigue. Airway obstruction frequently leads to dynamic hyperinflation, which further decreases the efficiency of the respiratory muscles by shortening fiber length, by altering the geometry of the diaphragm, and by obliging the muscles to perform an isometric contraction at the beginning of inspiration in order to overcome intrinsic positive end-expiratory pressure (PEEP).

IMPROVING THE CONTRACTILITY AND ENDURANCE OF THE RESPIRATORY MUSCLES
Rational therapy for respiratory muscle fatigue includes training, nutritional repletion, rest, and muscle pharmacotherapy. These measures prevent fatigue by improving the contractility and endurance of respiratory muscles and thereby increasing their capacity. Furthermore, as weak muscles are susceptible to fatigue, treatable or avoidable causes of weakness must not be ignored. These include hypercapnia, acidosis, hypocalcemia, hypokalemia, and hypophosphatemia, as well as inflammatory-, thyroid-, alcohol-, steroid-, and drug-induced myopathies.

Pharmacologic Agents Respiratory muscle function can be modulated pharmacologically either by action at the level of excitation–contraction coupling process or by an increase in energy supply to the muscles. Drugs that act at the level of excitation–contraction coupling are xanthines and digitalis, and those that increase energy supply are isoproterenol and dopamine. It has been shown in many studies that theophylline at a therapeutic dose enhances respiratory muscle contractility and restores the ability of fatigued muscles to generate force, thus increasing their endurance. The effects of theophylline appear to be greater in the fatigued than in the nonfatigued state and at shorter muscle lengths (eg, during hyperinflation). Theophylline acts by facilitating the influx of Ca$^{2+}$ through slow channels and perhaps activates Ca$^{2+}$-induced Ca$^{2+}$ release from the sarcoplasmic reticulum.

Training Specific training of the respiratory muscles, like that of other skeletal muscles, can enhance their strength and endurance, the latter being most relevant to patients...
with chronic ventilatory loads or weaning difficulties. Respiratory muscle strength has been increased by 55% in subjects performing repeated maximal static inspiratory and expiratory pressure maneuvers. When inspiratory muscle strength is increased, pressure developed per breath expressed as a fraction of the maximum will diminish, thus reducing vulnerability to fatigue.

Inspiratory resistive training in a gradually increasing, conditioning protocol constitutes the most direct approach to improving the strength and endurance of patients with ventilatory failure who are unable to stop using mechanical ventilation in order to facilitate their weaning. Respiratory muscles, like limb muscles, usually respond to high-frequency/low-load contractions with an endurance-conditioning response and to low-frequency/high-load contractions with a strength-conditioning response. Under some circumstances, however, specificity of conditioning is not so precise, and dual-response (ie, endurance and strength) conditioning may occur in response to a single conditioning stimulus. Dual-response conditioning is most likely to occur when muscles are severely deconditioned, as may occur in ventilator muscles following prolonged periods of mechanical ventilation, total bed rest, undernutrition, debilitating disease, or surgical trauma. Thus, in mechanically ventilated patients with difficulties in weaning, less precise forms of conditioning stimuli, such as low-frequency and low-load activities, may produce improvements in both endurance and strength. Nevertheless, as controlled trials are lacking, administration of training for difficult-to-wean patients is not yet standard practice.

**Nutritional Repletion** Malnutrition is a very important complicating factor in critically ill patients requiring mechanical ventilation, as well as in patients with a variety of chronic lung diseases. It has been shown to be associated with impaired respiratory muscle structure and function in humans; nutritional repletion can improve the strength and endurance of the ventilatory pump.

**Rest** A logical approach to the restoration of the contractility and endurance of a fatigue muscle would be to allow the muscle to rest. Available data clearly demonstrate long-term benefit, as evidenced by improvements in the arterial partial pressure of carbon dioxide ($P_aCO_2$) and maximal respiratory muscle pressures, in patients with either chronic neuromuscular and chest wall disorders or severe stable COPD and carbon dioxide retention ventilated with positive-or negative-pressure noninvasive mechanical ventilation. Although such mechanical ventilation rests the respiratory muscles, the mechanism whereby respiratory function, ventilatory failure, and symptoms are improved is not yet clear. The hypothesis that improvement in these patients is a result of respiratory muscle rest reversing muscle fatigue remains speculative. This is because reduction in $P_aCO_2$ during periods off the ventilator may be due to resetting of the carbon dioxide setpoint, resulting from the forced reduction in $P_aCO_2$ in the ventilation phase, and improvement in maximal respiratory muscle pressures may be secondary to better $P_aCO_2$ and $P_aO_2$ and to a general improvement in well-being attributable to better sleep and/or to resolution of cor pulmonale.

**FATIGUE AS CAUSE OF VENTILATORY FAILURE**

Respiratory muscle fatigue is recognized as a cause of ventilatory failure in animal studies of shock, either cardiogenic or septic. However, in clinical conditions with ventilatory failure, clear evidence is lacking, and fatigue remains a very likely cause of hypoventilation. Because hypercapnia occurs either acutely, as in cardiogenic shock with pulmonary edema, or chronically, as in COPD, it follows that if fatigue plays a role in carbon dioxide retention, it may do so either acutely or chronically.

**Acute Hypercapnia**

Fatigue and, in turn, hypercapnia of acute onset are usually due to a combination of increased mechanical load on the lung, reduced muscle strength, decreased efficiency, and reduced energy supplies to the inspiratory muscles. The mechanisms responsible for carbon dioxide retention are a decrease in minute ventilation ($V_{E}$) and an increase in dead space to $V_{T}$ fraction ($V_{D}/V_{T}$). The sequence of events is as follows. In patients with weak and/or loaded respiratory muscles, $V_{E}$ is reduced by lowering of the central discharge firing rate and inspiratory time, in order to reduce pressure per breath ($P_{tidal}$) and energy demand per breath (expressed by the pressure–time index) (central fatigue). In addition, according to this strategy, the respiratory muscles operate at a more optimal length that will not substantially affect their geometry since large tidal breaths force greater shortening of the muscles than small tidal breaths. This reduction in $V_{T}$ is compensated for, at least in the beginning, by an increase in breathing frequency, such that $V_{E}$ is maintained or increased. Consequently, since such a pattern of breathing increases $V_{D}/V_{T}$, $P_aCO_2$ will increase if $V_{E}$ is preserved or may remain stable if $V_{E}$ is increased proportionately. Such a frequency of breathing, however, is no longer optimal, and, for the same alveolar ventilation, energy demand will increase. Thus, although nonoptimal frequency seems to be a better option than long $T_I$, when coupled with the inadequate energy supply, it will finally lead to respiratory muscle peripheral fatigue. Pressure will then decrease and, as a result, $V_{T}$ and $V_{E}$ will decrease while $V_{D}/V_{T}$ further increases. The reduction in pressure will obviously decrease the pressure–time index and energy demands per breath, but alveolar ventilation will be further reduced and $P_aCO_2$ will rise. At a later stage (eg, in patients during weaning failure or in animal models with shock), via central mechanisms, $T_I$ increases again and respiratory frequency gradually decreases, resulting in a drop in $V_{E}$ and $V_{T}$ (see Figures 24-7 and 24-13). Finally, in extreme fatigue, the CNS reduces the output signals per breath, further reducing tidal pressure and $V_{T}$, and eventually leading to respiratory arrest.

In asthma and exacerbations of COPD, which are common causes of acute hypercapnic respiratory failure, severe airway obstruction results in increased flow resistance and, in rapid, shallow breathing. These factors increase the work of breathing and energy demand, leading to breathlessness...
and potentially to fatigue. The latter is a very probable hazard as dynamic hyperinflation, which reduces respiratory muscle strength and efficiency, can be severe. At the same time, $P_{\text{tidal}}$ increases excessively due to PEEP, and high resistive and elastic inspiratory loads. Hyperinflation decreases $P_{i,\text{max}}$ and, hence, $P_{\text{tidal}}/P_{i,\text{max}}$ substantially increases, potentially leading to fatigue. The blood supply to the respiratory muscles may eventually be impaired as muscular contractions become very strong, impairing bloodflow. Finally, severe lung disease may lead to hypoxemia and may reduce the amount of energy available, resulting in lactic acid production. Therefore, a constellation of factors decreases $P_{\text{tidal}}/P_{i,\text{max}}$ leading to dyspnea, fatigue, or both. Such a situation forces alveolar hypoventilation by reducing $V_T$, either as a way of protecting the muscles or as a consequence of failure (fatigue) of the muscles. It must be noted that, because of hyperinflation, values of $P_{\text{tidal}}/P_{i,\text{max}}$ lower than those needed at FRC are adequate to cause fatigue of the respiratory muscles.39

In cardiogenic shock, there is an increase in energy demand (stiff lungs, hyperventilation) and a decrease in the supply of blood to the respiratory muscles. In such a disease state, the respiratory muscles may fail. The condition has been well described in animal models, with respiratory muscle fatigue leading to severe alveolar hypoventilation, followed by bradypnea and respiratory arrest31 (see Figure 24-7). In noncardiogenic pulmonary edema, patients need increased pressure and energy to ventilate the lungs. Coexistent severe hypoxemia due to lung damage may reduce the energy supply to the muscles. Furthermore, weakness of the respiratory muscles may be present as a result of malnutrition or sepsis. This imbalance between the capacity of the ventilatory pump and the demands placed on it may again lead to alveolar hypoventilation.

Despite the above-mentioned considerations, data on respiratory muscle function and fatigue in clinical conditions with acute ventilatory failure are sparse. A useful clinical model of acute ventilatory failure is provided by patients who are failing to sustain spontaneous breathing after discontinuation of mechanical ventilation. Recent results indicate that, in at least some patients, high inspiratory load accompanied by hyperinflation or other detrimental factors (eg, high inspiratory flow, hypoperfusion) may lead to inspiratory muscle fatigue90 (Figure 24-14). Therefore, respiratory muscle fatigue may result in or contribute to severe acute respiratory failure requiring mechanical ventilation.

**Chronic Hypercapnia**

Patients who insidiously retain carbon dioxide invariably need to generate a higher inspiratory pressure per breath ($P_{\text{tidal}}$) that is a large fraction of their $P_{i,\text{max}}$. The pressure is generated to overcome forces imposed by the chest wall (kyphoscoliosis, thoracoplasty, pleural thickening, severe obesity), by the lung (bronchitis, emphysema, bronchiectasis), or by both (scleroderma, polymyositis). In one category of patients, $P_{\text{tidal}}$, although normal, may be a large fraction of $P_{i,\text{max}}$ since the latter is reduced (neuromuscular disorders). It is difficult to determine the mechanism of carbon dioxide retention in such patients. However, reduction of $V_T$ is a frequent feature and therefore may be the common pathway to carbon dioxide retention through an increase in $V_T/N_T$. The sequence of events is as follows. As disease progresses, $P_{\text{tidal}}$, $P_{\text{tidal}}/P_{i,\text{max}}$, pressure–time index, or the power required to maintain adequate ventilation increases, and the muscles become more vulnerable to dyspnea and fatigue. In
When COPD patients who retain carbon dioxide were compared with those who do not, it was found that $V_T$ and $T_i$ were reduced in carbon dioxide retainers, whereas frequency was increased. At equal $V_E$, $V_D/V_T$ was higher in carbon dioxide retainers, and hence carbon dioxide levels increased. Increased $V_D/V_T$ may be explained as follows. Patients who retain carbon dioxide have lower FEV$_1$ and $P_{i,max}$ values and higher effective impedance, weight, FRC, and FRC/total lung capacity (TLC) than do nonretainers of carbon dioxide$^{91,92}$ (Figure 24-15). At equal driving force ($P_{0.1}$), such a patient is better off terminating $T_i$ early and taking a small $V_T$, thus avoiding substantial deviations from the optimal length and, perhaps, avoiding the substantial geometric alterations of the diaphragm and intercostal muscles that might occur with a large $V_T$ (long $T_i$). In the latter case, at the end of inspiration, this type of patient may have to develop pressure approaching or exceeding the critical inspiratory pressure, leading to severe dyspnea or fatigue. In fact, although hypercapnia can be reduced in COPD patients by a voluntary change in the breathing pattern, that is, increasing $V_T$ and decreasing frequency, it has been shown that this type of breathing cannot be tolerated for more than a few minutes before inspiratory muscle fatigue occurs.$^{79}$ In this regard, patients with COPD and severe hypercapnia developed a $P_{tidal}$ that was 27% of $P_{i,max}$ whereas $P_{tidal}$ in patients with no carbon dioxide retention was only 10% of $P_{i,max}$. Using the results from normal subjects, in which the critical pressure for the development of fatigue at FRC is about 50% of $P_{i,max}$ and the critical pressure at FRC plus one-half inspiratory capacity is 25 to 30% of $P_{i,max}$, we may place carbon dioxide retainers above or into the critical zone of fatigue, whereas nonretainers remain in the nonfatiguing zone (Figure 24-16). In patients with COPD and $P_{a,CO_2}$ values of less than 45 mm Hg, this was especially evident.$^{92} P_{tidal}/P_{i,max}$ was 10%, and residual volume (RV)/TLC was 67%$^{92}$; that is, patients were certainly below the critical zone for the development of fatigue. In contrast, in patients who retained carbon dioxide, RV/TLC was 67% and $P_{tidal}/P_{i,max}$ was 27%, that is, a value very likely to predispose the muscles to fatigue. Thus, in some patients, the combination of increased work of breathing due to lung disease and/or obesity, decreased mechanical efficiency due to hyperinflation and/or airway resistance, and muscle weakness due to hyperinflation and/or atrophy and undernutrition pushes the respiratory muscle to its limits. In such a predicament, central controllers (through feedback mechanism mediated by endogenous opioids and afferents via small fibers) reduce $T_i$ and $V_T$, and hence $P_{tidal}$ (central fatigue). Therefore, inspiratory muscle peripheral fatigue is avoided. In this regard, hypercapnic patients weigh their options and choose hypoventilation rather than respiratory muscle peripheral fatigue.$^4\&8,92$

In many other diseases characterized by chronic hypercapnia (eg, severe obesity and kyphoscoliosis), the mechanism leading to carbon dioxide retention seems to be the same as or similar to that in COPD patients.

![FIGURE 24-15 Relationships among lung volume, tidal pressures, and maximal inspiratory pressures (MIP) in normocapnic and hypercapnic groups of patients with COPD. The shaded area on the right was produced from MIP values plus 95% confidence intervals obtained at FRC in all patients and plotted against their FRC/TLC values. On the left, vertical bars represent the tidal volume ($V_T$) excursions and horizontal bars represent the mean (± SD) inspiratory transpulmonary pressure swing ($P_{tit}$) for the normocapnic (N), moderately hypercapnic (MH), and severely hypercapnic (SH) groups. A subgroup of 15 patients from the normocapnic group with the smallest FRC/TLC, with values near normal, is shown in the left lower corner. The line enclosing the area on the left connects the SD values for each group. The inspiratory muscle load ($P_{tit}/MIP$) for each group is given at the level of the midinspiratory volume. Data from Begin P and Grassino A.$^{92}$](image1)

![FIGURE 24-16 Effect of lung volume on critical pressure of the respiratory muscles. The diagram was constructed from findings in normal subjects breathing against high inspiratory resistance. Subjects who, at functional residual capacity (FRC) or higher lung volume, generate per-breath pressure (mouth and/or transdiaphragmatic) above the critical zone become fatigued; in contrast, in subjects whose pressure is below the critical zone, fatigue does not occur. Note that patients with chronic obstructive pulmonary disease (COPD) and carbon dioxide retention ($P_{a,CO_2} > 45$ mm Hg) are above or barely within the upper limit of the critical zone, whereas patients with no carbon dioxide retention ($P_{a,CO_2} < 45$ mm Hg) are below or barely within the lower limit of the critical zone. RV = residual volume; TLC = total lung capacity.](image2)
WEANING FAILURE AND FATIGUE

The muscles that are used most often, such as the inspiratory muscles (particularly the diaphragm), atrophy the fastest. Artificial ventilation can induce inspiratory muscle atrophy. In addition, many ventilator-supported patients are malnourished, and this will further contribute to atrophy. Thus, patients who are not weaned usually have inspiratory muscle weakness, which leads to shortness of breath and predisposes to fatigue. The question of whether respiratory muscle fatigue occurs in weaning failure patients is of major clinical importance, partly because the development of peripheral fatigue might superimpose structural injury on the already weak respiratory muscles, adversely affecting final weaning outcome. However, the presence of respiratory muscle fatigue during weaning failure remains uncertain, mainly because of technical difficulties, especially in the clinical setting. Indeed, the development of inspiratory muscle fatigue has been shown in several studies (Figures 24-13, 24-14, 24-17, and 24-18), but most of the experimental techniques used were nonspecific, raising doubt as to whether fatigue truly occurred. In a recent study, it was shown that weaning failure was not accompanied by low-frequency fatigue of the diaphragm, with the use of the best current technique of serial measurement of $P_{di}$ in response to phrenic nerve stimulation. However, the presence of neither central nor high-frequency fatigue could be excluded in this study. Moreover, during weaning trials in clinical practice, mechanical ventilation is invariably resumed prior to inspiratory muscle exhaustion in patients failing to wean since many symptoms and clinical signs presage the onset of overt fatigue and task failure. Peripheral fatigue could eventually ensue, at least in many patients, in a limited time period had patients with clinical signs of weaning failure been allowed to breathe for longer.

CONCLUSIONS

The inability of respiratory muscles to generate pressure, caused by fatigue and leading to ventilatory failure, is well documented only in shock. For the remaining patients with hypercapnia—acute or chronic—the evidence is not as clear. It seems that, as the work of breathing increases (eg, decreased lung and/or chest wall compliance), $P_{i,max}$ decreases (eg, neuromuscular disease, hyperinflation), or both occur concurrently (eg, acute asthma attack), and then $P_{tidal}$ becomes a large fraction of $P_{i,max}$. The central discharge firing rate and inspiratory time are thereby reduced, and a
decrease in $V_T$ ensues. This strategy possibly involves the small type 3 and type 4 afferents from the muscles and the endogenous opioids (central fatigue), avoids high values of $P_{tidal}$, and therefore minimizes dyspnea and, ultimately, peripheral fatigue. Peripheral fatigue may occur if this strategy fails.

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