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REVIEW ARTICLE

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Fatigue of the respiratory muscles

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Introduction

The word "fatigue" has several meanings: in daily life, it is often used to express tiredness or weakness, whereas a technical definition may also include impaired intellectual or motor performance, increased EMG activity for a given performance, shift of the EMG power spectrum to lower frequencies, and/or the inability of muscle to generate force. In an NHLBI workshop, fatigue was defined as a loss of capacity to develop force and/or velocity in response to a load, which is reversible by rest [1]. As a first approximation, fatigue of the respiratory muscles may be defined as an inability to continue to generate sufficient pressure to maintain alveolar ventilation. Fatigue is distinguished from weakness, a reduction in force generation that is fixed and not reversible by rest, although muscle weakness may be a predisposition to muscle fatigue.

Despite the considerable amount of research that has been done over the past century, the site and mechanism of fatigue remain subjects of controversy. 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 (i.e. brain, spinal cord, nerve, neuromuscular junction, muscle cell membrane, transverse tubular system, calcium release, actin-myosin activation and cross-bridge formation) (Fig. 1). Globally, fatigue is subdivided into two categories: failure to generate force due to reduced central motor output (central fatigue) and failure to generate force due to fatigue either at the neuromuscular junction or within the muscle machinery (peripheral fatigue). The question, first formulated in the early part of this century [2], thus arises: when the respiratory system is presented with a fatiguing load, do the respiratory controllers become too tired to drive the muscles to maintain adequate ventilation, or do the muscles themselves become unable to generate the required force, despite on adequate neural drive? Davies, Haldane and Priestly the first researchers to study respiratory muscle fatigue, affirmed the existence of both types of fatigue, central and peripheral. Recently, an increasing amount of evidence has emerged in support of the notion that roughly equal proportions of the force decline during diaphragmatic fatigue can be attributed to reduced central motor drive and peripheral muscle contractile failure, respectively [1, 3]. However, it is not yet clear whether such a depression of the central nervous system (CNS) is due to a primary central failure or to a protective adaptation of the CNS to changes in the contracting muscle, intended to prevent an undue reduction of intrinsic muscle fiber strength.

Muscle function and pathophysiology of fatigue

Force generation

In the case of voluntary contractions, there is a long chain of command extending from the motor cortex down to the eventual interaction of actin and myosin within the muscle fiber. These events can be broadly divided into three categories: [1] those concerned with delivering sufficient electrical activation from the central nervous system to the muscle, [2] the metabolic and enzymatic processes providing energy to the contractile mechanism, and [3]

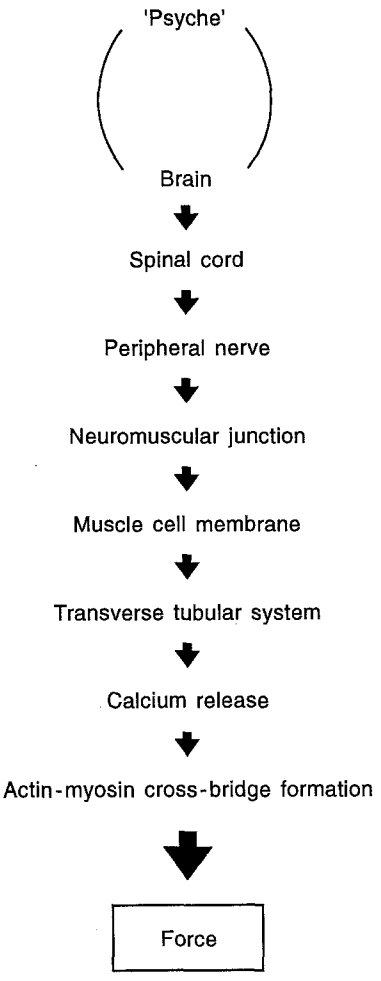


Fig. 1 Command chain for voluntary contraction of skeletal muscle (From [6])

the excitation-contraction coupling processes that link these two.

Muscle tension can be altered either by varying the firing frequency of each of the active motor units or by varying the number of motor units that are active. At low intensities of muscle contraction, force is developed largely by recruitment of motor units; at moderate and high levels of voluntary contraction, the number of additional motor units recruited during a given increment in force decreases sharply, and force is generated by increasing the firing frequency of each motor unit [4].

It is possible experimentally to determine the effectiveness of various firing rates in generating force [4]. 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 by a fused tetanus. Thus, the force-frequency characteristics of a muscle can be conveniently and effectively recorded by programmed electrical stimulation in an isolated muscle preparation [5] in both human limb [6] and respiratory muscles [7, 8] (Fig. 2). In this figure, it can be noted that in the pressure-frequency curve before fatigue (control), 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 electrical stimulation used to establish the pressure-frequency (or force-frequency) curve does not reproduce the true physiological activation. The importance of this curve is that central factors affecting muscle performance do not influence it. Furthermore, the manner in which it changes shape in fatigue gives insight into the mechanisms of fatigue. Selective loss of force at high stimulation frequencies (high-frequency fatigue), accompanied by a decrease in amplitude of surface-recorded action potentials, indicates fatigue of neuromuscular transmission and/or impaired membrane excitation. Selective loss of force at low stimulation frequencies, not accompanied by a decrease in amplitude of surface action potential (low-fre-

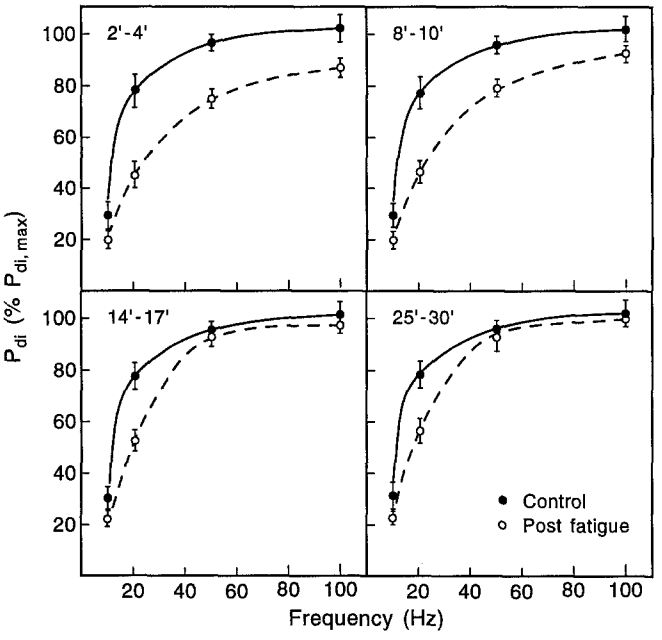


Fig. 2 Time course of changes in pressure-frequency curves of diaphragm of four subjects up to 30 min after fatigue. *Solid curves* represent average of three curves before fatigue (control); *dotted curves* represent average of three curves at different times during recovery period; *bars* indicate 1 SE. Transdiaphragmatic pressure (Pdi) is expressed as percent of Pdi generated with supramaximal phrenic nerve stimulation at frequency of 100 Hz (%Pdi,max). Two to ten minutes after fatigue, the Pdi-frequency curve shifts downward so that at each frequency of stimulation, the Pdi developed is smaller than that developed before fatigue. Obviously, low- and high-frequency fatigue coexist. Thirty minutes after fatigue, Pdi generated at high frequencies of stimulation (50 Hz) approaches control values, whereas low frequencies of stimulation cannot generate pre-fatigue Pdi values (low-frequency fatigue) (From [7])

quency fatigue), is thought to be due to impairment of excitation-contraction coupling [6].

Site and mechanism of fatigue

Central fatigue

In the past, fatigue was frequently attributed to failure of central neural processes [2]. By comparing the forces generated by maximum voluntary and maximum electrically stimulated contractions, an assessment of central fatigue is possible [9]. If maximal electrical stimulation is superimposed on a maximum voluntary contraction, and force generation is thereby increased, a component of central fatigue can be said to exist. Some authors [10] have shown that forces generated with maximal electrical stimulation can exceed those of voluntary contractions, whereas others [9] have found no differences in the forces of voluntary and electrically stimulated contractions.

The technique of twitch occlusion is the only test among those used to detect respiratory muscle fatigue that can distinguish central from peripheral fatigue. This method was originally introduced by Merton in peripheral muscles [9]. However, Bellemare and Bigland-Ritchie expanded its use, extracting very important data in the process [3, 10]. They employed the twitch occlusion method to test whether, following repetitive contractions of the diaphragm to the limits of its endurance in normal human subjects, the nervous system would be able fully to activate the diaphragm in response to a command for maximal voluntary effort [10]. This method examines the transdiaphragmatic pressure (Pdi) response to bilateral phrenic nerve stimulation, superimposed on graded voluntary contractions of the diaphragm. The amplitude of Pdi twitches in response to phrenic nerve stimulation decreases as the voluntary Pdi increases. During maximal voluntary contractions of the diaphragm (Pdimax), no superimposed twitches can be detected. In a later study [3], the same authors induced diaphragmatic fatigue, loading the diaphragm by either resistive loads or expulsive contractions against a bounded abdominal wall, and administered single, bilateral, phrenic shocks during (*Ts*) and between (*Tr*) contractions. Single shocks were also administered during voluntary Pdimax contractions. At the start of the experiment, they found that central respiratory drive was able fully to activate the diaphragm, since no superimposed twitches could be detected during Pdimax contractions, a finding consistent with their previous study [10]. During the course of loaded breathing, the degree to which the full muscle activation could be achieved decreased, as evidenced by the finding that superimposed twitches could be demonstrated at the limits of diaphragmatic endurance. At these limits, voluntary Pdimax had decreased by 50%, whereas the Pdimax estimated from the twitch occlusion had decreased by only 25%. This study showed that even though peripheral fatigue was present at the limits of diaphragmatic endurance, a significant portion of the reduction in the force was due to failure of the central nervous system to activate the diaphragm completely.

Central fatigue must not be confused with the progressive decrease in the firing rate during maximal contraction, during which superimposed, supra-maximal, electric, tetanic stimulation does not increase muscle force [11]. Several investigators have shown clearly that the central firing rate decreases during fatiguing muscle contraction [11, 12]. Experimentally, the gradual loss of force following prolonged maximum voluntary contraction can accurately be mimicked with electrical stimulation if the stimulation frequency can accurately be reduced. Conversely, if high stimulation frequencies are maintained for too long, loss of force is more rapid. Thus, it is possible that the decrease in firing frequency is an adaptive, protective mechanism, responding to the alteration of muscle contractile characteristics and aimed at preventing muscle exhaustion [1, 11].

It is well known that fatigue is characterized not only by loss of force but also by slowing of muscle contractile speed. In addition, it has been established that for any muscle or motor unit, the minimum excitation frequency required to generate force and tetanic fusion is proportional to its contractile speed. Thus, if during fatigue, the degree of contractile slowing matches the decline in the motoneuron firing rate, the latter does not result in any additional reduction in muscle force. 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. Of course, the interesting question arises of how such an adaptation would take place. It seems likely that activation of muscle afferents by some fatigue-induced change within the muscle inhibits motoneuron activity by reducing the latters' firing rates. In this regard, Hannerz and Grimby [13] have presented evidence that motor neurons receive a tonic inhibitory drive from peripheral sources and that during a maximum voluntary contraction, the motor neuron discharge rate increases if muscle afferents are partially blocked. Whether such an alteration exists in the firing rate of the diaphragm during fatigue is not known. However, it has been shown that afferent information via large (type-1 and type-2) and small (type-3 and type-4) fibers affects the central respiratory controller's discharge in terms of firing rate, firing time and frequency of breathing [14]; the latter is observed in states of diaphragmatic fatigue in both animals and humans [15, 16]. It is tempting, therefore, to hypothesize that as the contractile properties and the diaphragmatic chemistry change during fatigue, chest wall or respiratory muscle afferents may, via the phrenic nerve, affect the output of respiratory centers in

terms of firing rate or timing (frequency of breathing, duty cycle).

The strong interaction between the respiratory muscles and the CNS is well known. The interrelationship between respiratory muscle energy expenditure and central control was first suggested by Otis [17], who concluded that for a given rate of alveolar ventilation and set of mechanical properties in a respiratory system, there is an optimal frequency at which a minimum amount of work is required. Similarly, Mead [18] pointed out that the optimal frequency during spontaneous breathing is most closely associated with the minimum average force. In this regard, it could be proposed that fatigue should be understood primarily not as a failure of physiologic function, but rather as a protective survival mechanism that is activated when the thorax is under excessive stress. Thus, as speculated above, a regulatory mechanism must exist within the CNS to coordinate the discharge of motor neurons with the changes in the contractile speed of the motor unit that they supply and/or the alteration in the muscle chemistry. An alternative hypothesis, which could be called "central fatigue", posits that when fatigue occurs, the CNS alters either its firing output or its rhythmicity. The work of Bellemare and Bigland-Ritchie [3] affirms the existence of a central component of diaphragmatic fatigue. However, the questions of whether "central fatigue" is due to a primary central failure or to an adaptation of the CNS demands further investigation.

The importance of central fatigue in clinical ventilatory failure remains uncertain, and studies on patients are difficult to perform. However, it is possible that the recently described technique of magnetic phrenic nerve stimulation may facilitate process in this area [19]. In patients failing to wean from mechanical ventilation, the findings that the EMG power spectrum shifts [16] and that the maximum relaxation rate (MRR) measured during a sniff slows down [20] suggest that, in this particular clinical situation, respiratory muscle fatigue may play an important role. It seems that the respiratory muscles, at least, are being driven hard. This conclusion is consistent with the earlier findings by Aubier et al. [21] of high occlusion pressures in such patients. Because the level of respiratory muscle activation appears to remain high in these patients during weaning trials, central fatigue is unlikely to be responsible for weaning failure.

In summary, as fatigue sets in, the central discharge firing rate decreases and contractile slowing increases, either as a result of a primary central failure (central fatigue) or as an adaptation to the altered chemistry and/or contractile characteristics of the muscle, in an effort to prevent their self-destruction by excessive activation. These changes in motoneuron activity are postulated to be mediated by chest wall or respiratory muscle afferents.

The role of endogenous opioids and thin fiber afferents in the reduction of central motor output

As the respiratory depressant effects of opiate drugs such as morphine and meperidine had already been well described [22], the discovery of endogenous opioid receptors and ligands in the CNS led to speculation that these peptides might also be involved in ventilatory control. An early study by Santiago and co-workers [23] demonstrated that the opioid antagonist naloxone could restore the flow-resistive load compensation reflex in those patients with chronic obstructive pulmonary disease in whom it initially had been absent. They postulated that in such patients endogenous opioids were elaborated in response to the stress of a chronically increased airway resistance, and that this resulted in attenuation of the respiratory compensation for the increased airway resistance, perhaps as a mechanism by which the sense of dyspnea might be reduced. However, this finding was not confirmed in a subsequent, controlled study by Simon et al. [24].

In an animal model, Scardella et al. [25] demonstrated that relatively short-term but high-intensity, flow-resistive loading could be sufficient to activate the endogenous opioid system and modify the subsequent respiratory response. They found a progressive reduction in tidal volume in the course of resistive loading in unanesthetized goats. This was partially reversed by administration of naloxone (Fig. 3). These authors also demonstrated an increase in beta-endorphin immunoreactivity in the cisternal cerebro-spinal fluid [25]. These and subsequent results from the same laboratory [26, 27] indicate that in animals, endogenous opioid pathways are activated in response to the acute increase in airway resistance, reducing overall ventilatory output. In humans, the role of endorphins in central fatigue remains uncertain, having not been adequately evaluated. One possible example of endogenous opioid activation in humans in the face of an increased respiratory load has been described [28]. In asthmatics with methacholine-induced severe reductions in FEV_1, naloxone pretreatment resulted in increases in breathing frequency, occlusion pressure and mean inspiratory flow rate when compared to saline pretreatment.

Recently the effect of phrenic afferents on central controllers has been investigated by several different groups, with a particular focus on the effect exerted by small (type-3 and type-4) fibers on the timing of breathing and on the sensorimotor cortex [13, 14, 29]. Despite some differences, all of these authors agree that the supraspinal projections of such afferents have an effect on the control of breathing. These sensory fibers are activated primarily by extracellular metabolic changes, e.g. low pH, ischemia, increased osmolarity, and some substances (phenyldiguanide, capsaicin). Recently, Petrozzino et al. [27] demonstrated that the reduction in central respiratory output secondary to increased endorphin activity is signalled by

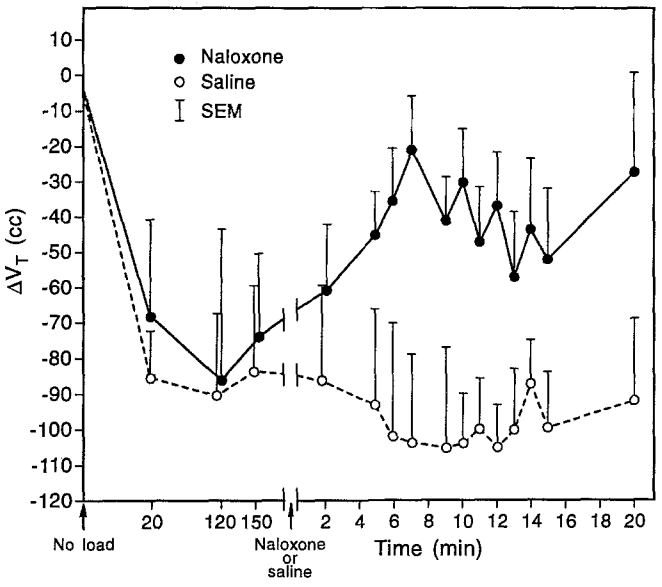


Fig. 3 Tidal volume response of unanesthetized goats to 2.5 h of high-inspiratory, flow-resistive loading prior to and following administration of naloxone. Tidal volume, which fell considerably during loading, increased significantly but transiently after naloxone administration, while saline had no effect. (Note the change in time scale on the x-axis). These 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 prior to 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 (From [25])

small fiber afferents, which are stimulated by lactic acid accumulation and a pH fall in the respiratory muscles. Thus, it is possible that during loaded breathing in various clinical states, afferents (via the small fibers) modulate endogenous opioids as an adaptive response-much in the way that opioids are generated in response to chronic pain. This strategy certainly minimizes breathlessness and may avoid or delay the onset of respiratory muscle fatigue, protecting the ventilatory pump from exhaustion and therby averting what undoubtedly would be a very terminal event.

Peripheral fatigue

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 the muscle fibers (impaired excitation contraction coupling).

During artificial stimulation of a motor neuron, especially at high frequencies, muscle force declines rapidly in association with the decline in action-potential amplitude. This response, known as "high-frequency fatigue", is attributed to transmission fatigue. This type of fatigue may be situated postsynaptically (stemming from a decrease in end-plate excitability) or presynaptically (probably in fine terminal filaments of the motor nerve or, less frequently, stemming from a depletion of synaptic transmitter substance) [30].

The development of this type of failure during voluntary contraction is questionable since 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; furthermore, no unique relation between muscle force and electromyographic (EMG) activity has been observed [1]. Evidence that neuromuscular transmission and cell membrane excitation are adequate during fatigue produced by voluntary contractions has been found in experiments in dogs in cardiogenic and septic shock [15, 31] (Figs. 4 and 5). As the diaphragm became fatigued, the relationship of integrated phrenic nerve activity (Ephr) and diaphragmatic EMG activity remained unaltered. In other words, when the diaphragm started failing as a force generator and greater stimulation was needed per increment of transdiaphragmatic pressure, the relationship between Ephr and EMG was similar to those observed during the control period and in the earlier stage of fatigue [31]. 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 [32], if failure occurs at the neuromuscular junction or in the excitation of the cell membrane, it may protect the muscle from excessive depletion of its ATP stores, which would lead to rigor mortis. If high-frequency fatigue is due to failure of the neuromuscular junction, it may be speculated that such a failure can exist in the human diaphragm. In fact, it has clearly been shown that normal subjects breathing against inspiratory loads develop high-frequency fatigue [7] (Fig. 2), which may reflect neuromuscular junction failure.

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 electrical activity [9]. This type of fatigue is characterized by a selective loss of force at low frequencies of stimulation (low-frequency fatigue), despite maintenance of the force generated by high frequencies of stimulation, thereby indicating that the contractile proteins continue to generate force (Fig. 2). This type of fatigue is not related to depletion of ATP or phospho-

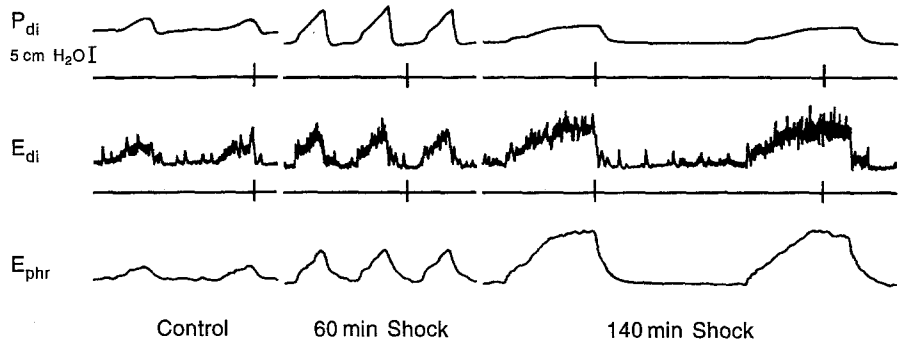


Fig. 4 Tracings from a dog in cardiogenic shock shows typical evolution of transdiaphragmatic pressure (Pdi), integrated electrical activity of the diaphragm (Edi), and integrated electrical activity of the phrenic nerve (Ephr). The *left panel* represents a control. The *middle panel* shows a reading made 60 min after onset of cardiogenic shock. The *right panel* shows a reading made 140 min after onset of cardiogenic shock and just before death from respiratory arrest. While Edi and Ephr continue to increase, Pdi decreases (fatigue). The decrease in size of the electrocardiographic artifact on the Edi trace is a consequence of the injection of saline into the pericardium (From [15])

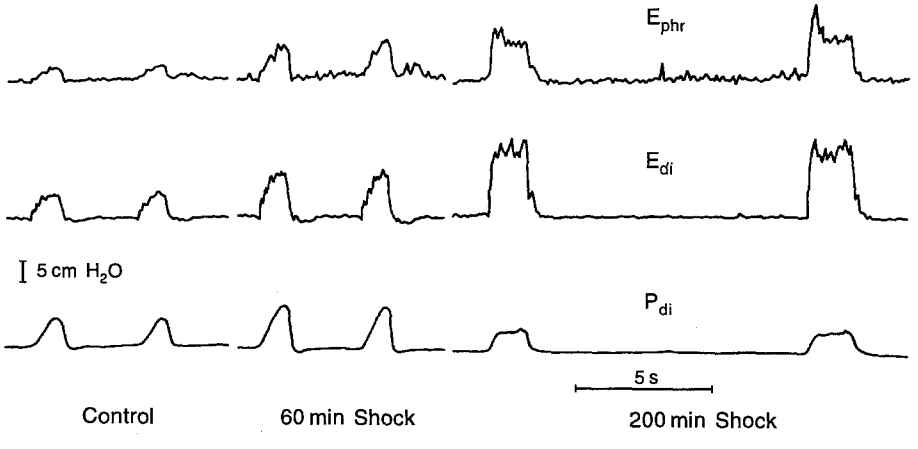
creatine (PCr) and is characteristically long-lasting, recovery taking several hours. The mechanism of this type of fatigue is not well known. It may occur because of a reduced supply of Ca^{2+} or a change in the affinity of the troponin binding site for Ca^{2+}. These defects would reduce the twitch and hence also 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+} [33]. Other possibilities include structural damage [33] or an alteration in the compliance of the series-elastic component of the muscle [34].

Low-frequency fatigue occurs during high-force contractions. It is less likely to develop when the forces generated are smaller, even if these are maintained for longer time periods and thus perform the same total work. It therefore 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 occurs in the diaphragm of the dog during cardiogenic or septic shock [15, 31]; despite a threefold increase in the integrated EMG, Pdi decreased (Figs. 4 and 5). Low-frequency fatigue and, by implication impaired excitation-contraction coupling have also been found in the diaphragm and sternomastoid of normal subjects after breathing against very high inspiratory resistance [7, 8].

Since low-frequency fatigue impairs force generation at physiological firing frequencies, ventilation may be reduced. To compensate for low-frequency fatigue, motor neuron firing frequency must be increased, or additional contractile units recruited, by an increase in central respiratory drive. This can be demonstrated by comparing

Fig. 5 Representative tracing of dog during endotoxic shock showing changes in integrated phrenic neurogram (Ephr), integrated diaphragmatic electromyogram (Edi), and transdiaphragmatic pressure (Pdi). *Left*, during control; *middle*, 60 min after onset of endotoxic shock; *right*, 200 min after onset of endotoxic shock and prior to death of animal. While Ephr and Edi continue to increase, Pdi decreases due to peripheral fatigue (impaired excitation-contraction coupling) (From [31])



smoothed and rectified EMG (SREMG) recordings from the sternomastoid taken during the production of standard forces, when the muscle has low-frequency fatigue, to the response obtained for fresh muscle [8]. Depression of respiratory drive by hypoxia or drugs could therefore impair compensatory responses, and ventilation would then become inadequate.

A similar downward shift in the force frequency curve can occur without fatigue as a consequence of muscle shortening [35]; thus, low-frequency fatigue and muscle shortening, resulting from hyperinflation, may interact to compromise respiratory muscle force generation and increase the likelihood of ventilatory failure. Recent studies have shown that for the normal, in vivo human diaphragm [36], as well as for the isolated rat diaphragm studied in vitro [37], fatigue causes a greater decrease in transdiaphragmatic pressure or force when measured at high lung volumes or short muscle lengths than at lower lung volumes or longer lengths.

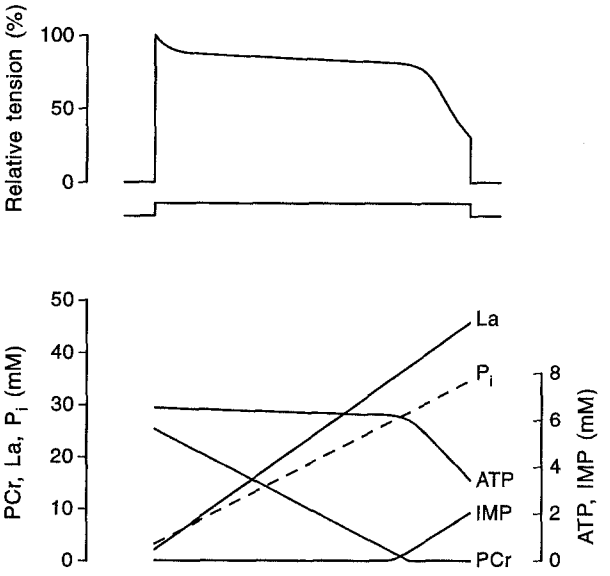


Fig. 6 Characteristic pattern of tension decline (*upper panel*) and metabolic changes (*lower panel*) during fatigue produced by repeated tetanic stimulation. The tension trace in the envelope of the peak force of a large number of tetani. Period of fatiguing stimulation is indicated below the tension record; the duration of this period depends on the fiber's fatigue resistance and the pattern of stimulation (i.e. duration of tetani vs rest period between tetani). Metabolic changes described by *full lines* are replotted from data in Nagesser et al. [38] obtained from easily fatigued fibers of *Xenopus*. The metabolites are lactate (La), ATP, inosine monophosphate (IMP), and phosphocreatine (PCr). The change of inorganic phosphate (P_i; *dashed line*) was calculated from the changes of PCr and ATP. 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 an accumulation of lactate ions and an acidosis of up to 0.8 pH units [39]. Note that 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 decline of ATP

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 utilize chemical energy is impaired, the muscle will fail as a force generator.

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 from pH changes caused by lactic accumulation [1]. The substances directly involved in the transformation of chemical energy into mechanical work in skeletal muscle are ATP, ADP, inorganic phosphate (Pi), hydrogen ions (H^+), magnesium ions (Mg^2), and phosphocreatine (PCr). ATP leaves the mitochondria and diffuses into the contractile machinery of the cell, where ATPase enzymes hydrolyze one of the pyrophosphate bonds, liberating large quantities of energy in the process.

$$MgATP + H_2O \xrightarrow[\text{ATP ases}]{} MgADP + Pi + H^+ + Energy$$

In general, metabolic changes may cause fatigue either through a reduction of high-energy compounds (e.g. PCr and ATP) or through an accumulation of break-down products. Figure 6 illustrates some important metabolic changes that occur during fatiguing stimulation. Important changes are a break-down of PCr with a concomitant formation of Pi and the formation of lactate, which usually is accompanied by an accumulation of hydrogen ions and thus also by reduced intracellular pH.

ATP is the immediate energy source for energy-requiring processes such as cross-bridge cycling and ion pumping; thus, a significant reduction in the myoplasmic ATP concentration would affect cell function. Generally reported reductions in ATP during fatigue are small (from approximately 6 to approximately 5 mm) and if representative would, be unlikely to affect cell function. However, considerably larger reductions (of up to about 50%). capable of influencing some cellular processes, have been found in several studies [38]. It should also be noted that local concentrations at sites where ATP turnover is particularly high may well be lower than the cell average [39].

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. Similarly, blood lactate elevation has been found in subjects breathing through high inspiratory loads to the point of exhaustion [40]. However, there is no direct evidence that the lactic acid produced by the respiratory muscles is the culprit in fatigue. Furthermore, animals in

cardiogenic shock develop substantially less lactic acidosis if they are mechanically ventilated than if they are breathing spontaneously [4], 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. Of all the break-down products of energy metabolism, hydrogen ions and Pi have the greatest effect on the contractile apparatus [42]. 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 [42] (Fig. 7). In addition, hydrogen ions exert a direct negative effect on the contractile process itself, which is not related to pH [42].

Lactic acid accumulation (and pH fall) in the respiratory muscles has recently been linked to the reduction in central respiratory output, which is a secondary effect of increased, endogenous opioid activity during inspiratory, flow-resistive loading [27] (Fig. 8). Increased respiratory muscle lactic acid is considered to be a strong stimulant for afferent fibers (groups 3 and 4), which can signal the release of endogenous opioids.

The increase in energy demands in the working skeletal muscles, including the respiratory muscles, is provided mainly by the combustion of fat, blood glycose and glycogen of the muscle. During sub-maximal prolonged heavy exercise, exhaustion coincides with the depletion of muscle glycogen, whereas exercise capacity is enhanced

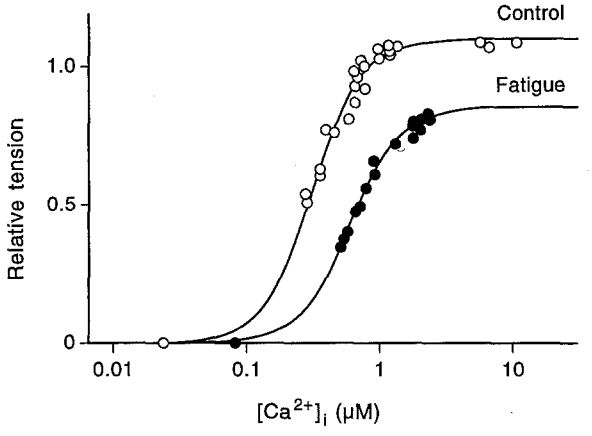


Fig. 7 The relation between tension expressed as percent of maximum and intracellular Ca^{2+} concentration ($[Ca^{2+}]i$) obtained in control (○) and during late fatigue (●) in a single mouse muscle fiber. In fatigue there is both a marked reduction in the stable tension at high $[Ca^{2+}]$ (i.e. reduced maximum tension) and a marked rightward shift of the data points (i.e. reduced Ca^{2+} sensitivity), most likely caused by the combined effect of increased Pi concentration and acidosis. In addition to these two factors, reduced Ca^{2+} release from the sarcoplasmic reticulum may contribute to fatigue. The cause of this factor is less clear, but may be related to declining ATP (From [42])

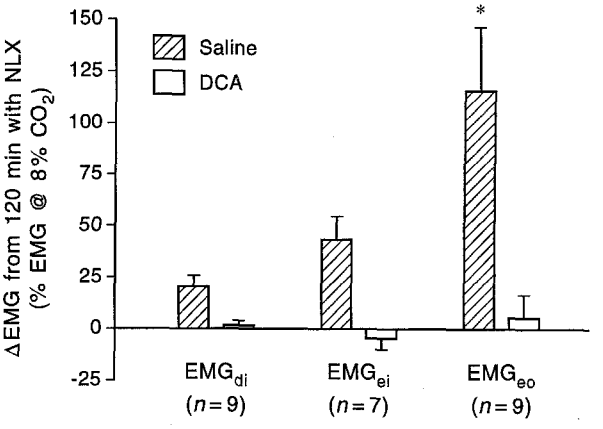


Fig. 8 Respiratory muscles EMG responses to naloxone (NLX) after 120 min of exposure to saline or dichloroacetate (DCA). (*open bars* DCA; *hatched bars* saline; $*P < 0.05$ vs EMGdi). During 2 h of inspiratory loading (50 cm $H_2O\,l^{-1}\,s^{-1}$, goats were exposed to a constant infusion of either saline or DCA, a compound which enhances the activity of pyruvate dehydrogenase and thus lessens the production of lactic acid. NLX (0.3 mg/kg) was given at the conclusion of the loading period. In the goats given saline, NLX significantly increased EMG of the diaphragm (EMG di), external oblique (EMG_{eo}) and external intercostal (EMG_{ei}). DCA infusion completely blocked the NLX effect on respiratory activity, suggesting that lactic acid is the stimulus signaling the activation of the endogenous opioid system (From [27])

when the storage of muscle glycogen is increased [43]. Similar observations have been made in the diaphragm of dogs with low cardiac output [41]. However, why glycogen depletion coincides with fatigue is not clear. During prolonged, intermittent heavy exercise, which is dependent upon the aerobic metabolism, the rate of utilization of fatty acids and glycose is high, and 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 blood-borne fuels, and fatigue will occur when it is depleted.

Recently, an increasing amount of evidence has begun to suggest that oxygen-derived free radicals play an important role in mediating respiratory muscle dysfunction, particularly diaphragm fatigue. In several studies, the effect of free radical production in inducing diaphragmatic fatigue has been evaluated by means of pretreatment with free radical scavengers in order to attenuate the rate of diaphragmatic impairment. Pretreatment with free radical scavengers (N acetylcysteine [44]. Dimethylsulfoxide, Lazeroids, etc.) resulted in a reduction in the rate at which diaphragm fatigue developed in response to oxidative stress [44]. 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 [45].

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

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]. Fatigue may occur at any point 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 or beyond the site of the action potential, so that when a depletion of fuel occurs the activation system fails; in extreme fatigue, this prevents the muscle destroying itself, which would happen if the ATP level fell to zero. A decrease in excitation may result from failure of the neuromuscular junction [32], a reduced rate of firing by the CNS [12], 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 [15]. Although it has not yet been proven, such an alteration in the responses of central controllers could be brought about by afferents from the fatiguing inspiratory muscles and the chest wall. During fatigue, the normal inhibitory influence from Golgi tendon organs presumably declines with the loss of force; however, concomitant fatigue of intrafusal fibers might reduce the excitatory response of muscle spindles. Furthermore, free nerve endings within the muscle might inhibit motoneuron activity in response to muscle stretch and fatigue. Afferent information via small (type-3 and type-4) fibers possibly reduces central respiratory output by modulating endorphins as an adaptive response to avoid or delay respiratory muscle fatigue.

Energy balance: Determinants of critical task

The threshold of fatigue is the lowest level of exercise and/or mechanical loading that cannot be sustained indefinitely. This level can be expressed as a percentage of maximum performance. Monod and Scherrer [46] used this approach for intermittent contractions to determine the critical force above which fatigue ensues. The authors also suggest that fatigue will develop when the mean rate of energy demand ($\dot{U}d$) exceeds the mean rate of energy supply ($\dot{U}s$)

$$\dot{U}d > \dot{U}s \ . \tag{1}$$

Thus, since $E = \dot{W}/\dot{U}d$ and $\dot{U}d = \dot{W}/E$,

$$\dot{W}/E > \dot{U}s \quad \text{or} \quad \dot{W} > \dot{U}sE \ , \tag{2}$$

where $\dot{W}$ is mean muscle power and E is efficiency. Clearly, when $\dot{U}sE \geq \dot{W}$, the muscle can continue to work indefinitely, but when $\dot{U}sE < \dot{W}$, there will be a finite endurance time (*Tlim*). Thus, a decrease in either efficiency or energy supplies should encourage fatigue, as would an increase in muscle power. Fatigue (like angina pectoris) can be analyzed in terms of the balance between energy supply and demand. For the inspiratory muscles during inspiratory resistive breathing, with the mouth pressure developed in a square-wave manner, the endurance time becomes infinite when $\dot{W} = 6-8$ kg/min [47]. This implies that $\dot{U}sE$ is also 6–8 kg/min: these values are named "critical power" and "rate of energy supply", respectively.

If the pressure generated by the inspiratory muscles assumes a square waveform, the term $\dot{W}$ becomes

$$\dot{W} = P \cdot V_T \cdot f = P \cdot V_T \cdot (1/T_T) \ , \tag{3}$$

where P is mean inspiratory pressure and f is frequency of breathing. $V_T f$ or $V_T(1/T_T)$ equals minute ventilation. Multiplying numerator and denominator by T_I, Eq. 3 becomes

$$\dot{W} = P(V_T/T_I)(T_I/T_T) \ , \tag{4}$$

where the product of mean inspiratory flow (V_T/T_I) and duty cycle (T_I/T_T) denotes minute ventilation. As a first approximation, T_I/T_T expresses the duration of inspiratory muscle contraction as a proportion of the total duration of the breathing cycle. Substituting the value given in Eq. 4 for $\dot{W}$ in (inequality) 2 yields

$$P(V_T/T_I)(T_I/T_T) > \dot{U}sE \ . \tag{5}$$

Clearly, the power of the respiratory muscles can be greater than, equal to, or smaller than the available energy in a variety of combinations of P, V_T/T_I and T_I/T_T. Thus, Roussos et al. [47] found that the critical pressure of all the inspiratory muscles is 50%–70% of the maximum and that for the diaphragm alone, it is 40% of the maximum for V_T/T_I of 0.6–0.9 l/s and T_I/T_T of 0.3–0.4. Furthermore, under predominant diaphragmatic recruitment, Bellemare and Grassino [48] found that the critical Pdi decreases as the T_I/T_T increases at a constant V_T/T_I. They found that when the product (Pdi/Pdi max) (T_I/T_T) exceeds the threshold value of 0.15, there was a finite endurance *Tlim*. This threshold value was recently

demonstrated, amounting to 0.30 when the intercostal/accessory muscles were predominantly recruited (48a). Subsequently, McCool et al. [49] measured the esophageal pressure-time index (*PTes*) as a measure of inspiratory muscle pressure output and, in keeping with the predictions of inequality [5], showed that for a given *PTes*, *Tlim* was inversely related to V_T/T_I over a wide range or flows. The critical value of *PTes* that could be sustained for prolonged periods of time (> 10 min) was also found to be inversely related to V_T/T_I.

One would predict that if $\dot{U}sE$ decreases (either decreasing the energy supply, efficiency or both), the critical values of pressure or the combination of pressure, flow, and duty cycle will change (Fig. 9). For example, reducing *Us* by reducing cardiac output in dogs readily results in diaphragmatic fatigue [15] (Fig. 4). Similarly, decreasing the blood flow to the diaphragm in dogs causes fatigue to this muscle, an effect which is reversed by restoring normal perfusion [50]. Supinski et al. [51] have also shown that diaphragmatic fatigue in the dog can be reversed by hyperperfusion achieved by increasing arterial blood pressure, thereby increasing *Tlim*. Furthermore, an alteration in efficiency, as might occur with resistive breathing (as opposed to unobstructed hyperventilation), may substantially alter critical pressure or power. In fact, Tennney and Reese [52] found that the critical power ($\dot{W}crit$) during hyperventilation is at least four times greater than the $\dot{W}crit$ (and $\dot{U}sE$) of 6–8 kg/min found during resistive breathing in normal subjects [47], corresponding to 55% of maximum breathing capacity. If the diaphragm operates at shorter lengths during acute hyperinflation, a similar argument may account for the smaller critical *Pdi*, when a given force requires much greater excitation [35]. At half inspiratory capacity, *E* can be reduced by as much as 50% [53].

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

Detection of inspiratory muscle Fatigue

In the sense of failure of force generation, muscle fatigue is best understood as a continuous process that starts whenever a muscle is subjected to an unsustainable load. Fatigue is therefore a normal physiological response to excessive load and is associated with a multitude of complex changes in muscle physiology that can affect any link in the chain of command extending from the central nervous system to the peripheral contractile machinery. Although fatigue is conveniently and conventionally defined in terms of loss of force, detection of other changes in physiological function can be useful indicators that the fatigue process is underway; indeed, the notions that fatigue is a single end point (loss of force) and that all tests of fatigue should center on the detection of force loss is too narrow, from both a practical and an intellectual stand point.

Measurement of force (or pressure)

Fatigue can be detected by techniques that directly measure the force of voluntary or electrically stimulated contractions, or by measurements from which force is inferred (maneuvers such as VC). The measurement of force-frequency curves, as discussed previously, is a useful and specific technique for detecting peripheral fatigue. Mea-

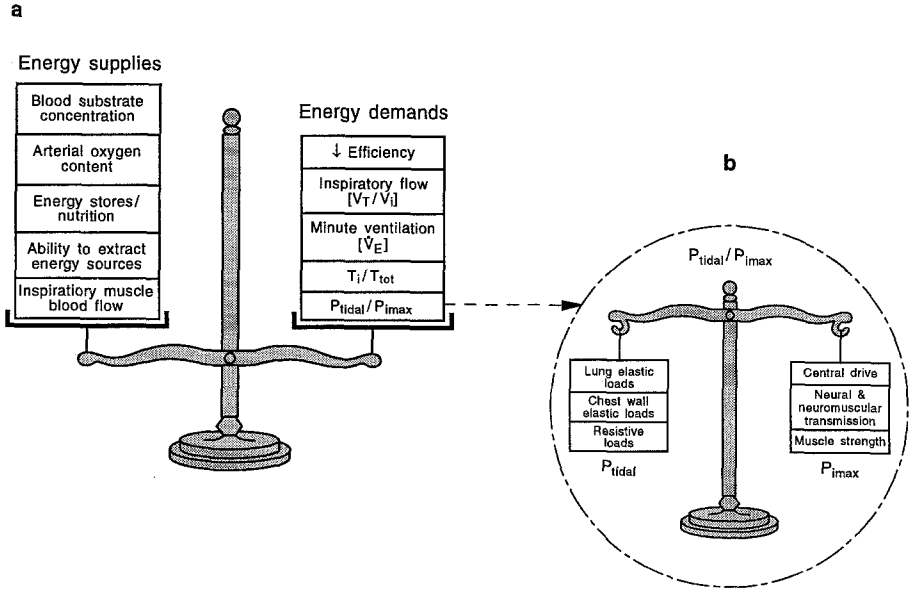


Fig. 9 The various determinants of energy supplies, demands, and neuromuscular competence are schematically represented. Respiratory muscle endurance is determined by the balance between energy supplies and demands (a). Normally the supplies meet the demands and a large reserve exists. Whenever this balance weighs in favor of demands, the respiratory muscles ultimately become fatigued. The Ptidal/Pi,max ratio is one of the determinants of energy demands that is shown (b) as a balance between the load per tidal breath (Ptidal) and the neuromuscular competence of the ventilatory pump (Pi,max)

surement of the force-frequency curve of the diaphragm is made possible by stimulating the phrenic nerve and recording transdiaphragmatic pressure [7]; the curve for the sternomastoid can easily be documented by stimulating the muscle with surface electrodes [8]. Changes in the shape of the force-frequency curve provide information about the underlying mechanism of force loss. Loss of force at low frequencies indicates impairment of excitation-contraction coupling, whereas loss of force at high frequencies indicates impairment of neuromuscular junction transmission or membrane excitation.

Pressure-frequency relationships, obtained with unilateral phrenic stimulation, are complicated by uncontrolled movement and distortion of the contralateral hemidiaphragm. Bellemare et al. [54] have shown that the pressure developed for any given frequency of stimulation is about 2.5 times greater during bilateral than unilateral phrenic nerve stimulation, thus showing that the pressures developed by the two sides are not simply additive. Bilateral tetanic phrenic nerve stimulation is difficult, particularly at frequencies greater than 35 Hz, and is likely to be of limited clinical use. However, partial pressure-frequency relationship can be constructed using paired stimuli, and by varying the interval between the stimuli of each pair [55]. This technique is simpler and better tolerated than tetanic stimulation and can provide information about high and low-frequency fatigue of the diaphragm.

When normal subjects undertake treadmill exercise at 85–95% of maximum oxygen uptake to the point of exhaustion, twitch *Pdi* is reduced [56]. Therefore, when pushed to the limit, the normal human diaphragm develops peripheral fatigue, which is reliably detected by twitch *Pdi*. However, applying the twitch technique to patients with ventilatory failure is more difficult. For this purpose, the more recently developed method of magnetic stimulation [19] may be advantageous. Recently, in order to minimize the invasivity of the balloon-catheter technique of measuring twitch *Pdi* pressure, which limits its clinical use, the measurement of mouth pressure twitch against an occluded airway has been developed [57]. Although it could potentially be used as a twitch occlusion test, more rigorous evaluations is needed before this method can be recommended for general use [1].

A progressive decrease in maximum mouth pressure (P_i,max) during an inspiratory task at a defined lung volume may provide some information regarding fatigue. However, under such conditions, there is always the possibility that inadequate effort may give false results. In this context, the measurement of esophageal pressure during maximal sniffs (sniff Pes), or the noninvasive sniff nasal inspiratory pressure [57a], is a useful alternative method for detecting a progressive fall in inspiratory muscle strength. It is probably easier and less unpleasant, for most people to perform than the P_i,max maneuver.

EMG spectral shift

Analysis of the EMG at its frequency part delineates its power spectrum; in fatigue, this spectrum shifts to lower frequencies. This approach has been used for many years in other skeletal muscles and in the past few decades, in the respiratory muscle [58]; however, the underlying cellular mechanisms remain unknown.

The relationship between the power-spectral shift and fatigue is empirical. The former occurs in the diaphragm before there is failure to develop adequate force and thus is a useful objective measure to predict the onset of fatigue (Fig. 10). With the new definition of respiratory muscle fatigue [1], which posits that fatigue may be present long before a muscle becomes unable to continue to perform a particular task, it is possible that the power-spectral shift tracks the development of fatigue with considerable accuracy. However, a single measurement of the power spectrum is unsufficient, and a change must be observed in order to predict fatigue. In addition to the fact that the electrical activity of inspiratory muscles are influenced by changes in the spatial relationship between the recording electrodes and the muscle, power-spectrum changes can result from conditions other than muscle fatigue. Thus, some doubt is cast on the sensitivity and specificity of this technique [1].

Respiratory muscle relaxation rate

An early physiological event in the progress of a fatiguing contraction is the slowing of the muscle relaxation rate. This has the important effect of facilitating a reduction in central firing frequency whilst maintaining plateau tension [11].

Maximum relaxation rate (MRR) is conventionally defined as the percentage of force or pressure lost in 10 ms. By recording respiratory pressures during a brief inspiratory effort and subsequent relaxation, MRR has been measured for the diaphragm in terms of transdiaphragmatic pressure and for the respiratory muscles as a whole, by measuring mouth, nasopharyngeal, or esophageal pressures [59, 60]. Muscle relaxation is an active, energy-consuming process, and MRR is affected by temperature, thyroid status, the inherent speed of muscle, and fatigue. When skeletal muscle is subjected to an excessive load, an early slowing of MRR is observed. Thus, MRR slows following exhaustive inspiratory resistive loading as well as maximum sustained ventilation. The MRR of the respiratory muscles is numerically similar to that of limb muscles, and slows with exhaustive inspiratory loading in a similar way as loaded limb muscles. Furthermore, the recovery of MRR following exhaustive loading of the respiratory muscles is very similar to that of fatigued limb muscles. These observations suggest that respiratory mus-

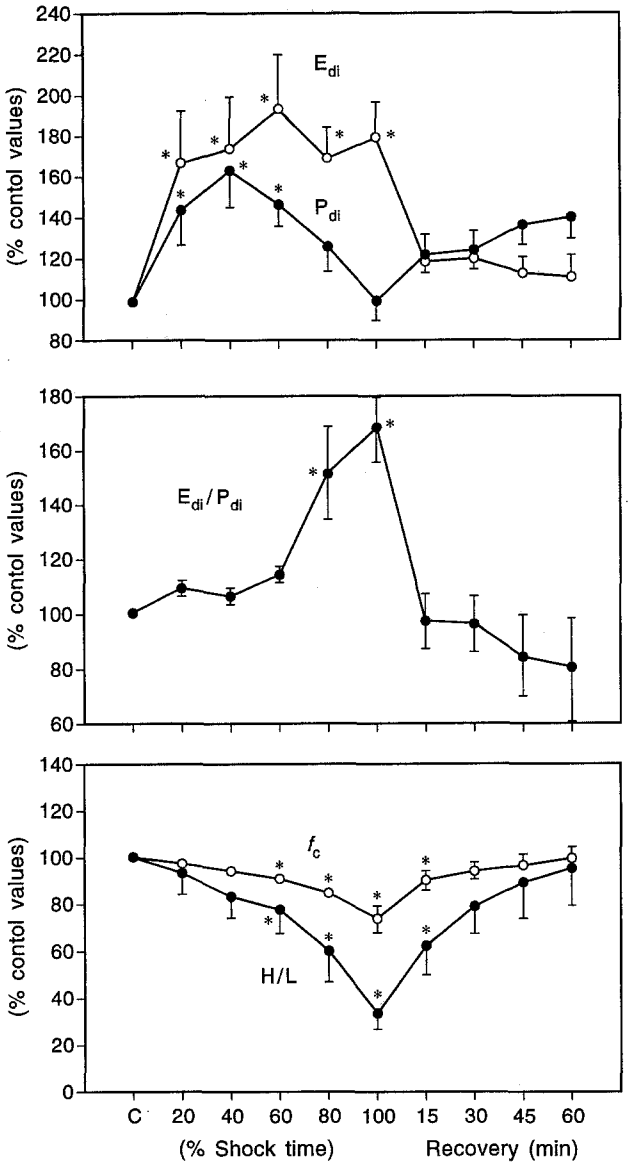


Fig. 10 Changes in the peak values of integrated spontaneous EMG activity of the diaphragm (Edi) and corresponding spontaneous transdiaphragmatic pressure (Pdi; *top*), ratio of Edi to Pdi (Edi/Pdi, *middle*), and centroid frequency (fc) and ratio of high and low frequencies of diaphragmatic EMG (H/L, *bottom*) during shock induced by a balloon inflation in the inferior vena cava in a canine model and recovery. Means±SE. $P<0.05$ compared with control values. Although Edi/Pdi rose at 80% and 100% of shock time only, both fc and H/L declined immediately and progressively after decline in arterial pressure (From [86])

cle MRR, measured from respiratory pressures, reflects the relaxation rate of the respiratory muscles.

To date, although a number of studies on normal subjects have demonstrated slowing of MRR when the respiratory muscles are loaded, few investigations of MRR in patient populations have been made. In a study of intubated patients in an intensive care unit, MRR was measured from sniff-like inspiratory maneuvers before and during weaning [20]. Sequential measurements of MRR demonstrated that in patients who weaned successfully, MRR remained unchangesd, whereas in patients failing to wean, it slowed.

Although there are many advantages to measuring MRR when studying respiratory muscle fatigue, there are, in practice, many problems, as well. The wide range of normal values for MRR makes it difficult to obtain useful information from a single measurement. Obtaining sequential measurements of MRR of sufficient quality is another difficulty. As with limb muscles, the measurement of MRR during voluntary respiratory efforts, like sniffs, is dependent upon the magnitude of the effort developed, presumably reflecting the recruitment of different motor units types [61]. Theoretically, some of these problems could be overcome by measuring the relaxation characteristics of twitch responses. However, the slowing of MRR, like the changes of the EMG power spectrum, is associated with high-intensity exercise and high-frequency fatigue [59]. As low-frequency fatigue is not associated with changes in relaxation rate, it cannot be detected with this measurement alone [36].

Clinical detection of fatigue

An interesting and important feature of fatiguing inspiratory muscles is the alternation in the contribution made by each group of muscles (diaphragm or intercostal/accessory) to the breathing task [47]. For a normal subject breathing against a fatiguing load while attempting to maintain a constant mouth pressure, three stages of breathing have been observed from the point of view of breathing pattern and ability to continue to perform the required task (Fig. 11). At the beginning, the timing of breathing and the mouth pressure remain constant. This period is called the stage of "infinite possibilities"; that is, the subject has been given no indication of the duration of the task, which might be anything from very short to very long. The last period, consisting primarily of the terminal 4–5 breaths, the stage of "exhaustion", is when the subject can no longer sustain the breathing task and stops the effort. Between these two periods is an intermediate one, the stage of "alternative strategies". During this period, whenever the breathing task threatens to lead to exhaustion because it is above the critical level, the subject uses all possible strategies to maintain the target pressure or work to preserve ventilation. During this stage, although mouth pressure remains constant, the pleural, or gastric and transdiaphragmatic, pressure vary almost in an alternative fashion. These changes may be interpreted as the result of recruitment and de-recruitment between the diaphragm and the intercostal/accessory muscles.This alternation has also been observed in

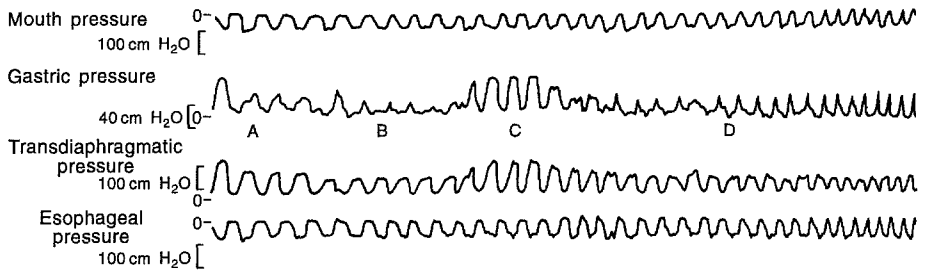


Fig. 11 Tracings of experimental run in man breathing against an inspiratory resistive load. With each breath, subject generated 75% of maximum mouth pressure. All pressures, except transdiaphragmatic pressure, were measured relative to atmospheric pressure. Only gastric and transdiaphragmatic pressure 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 alternation of inspiratory muscle recruitment (From [47])

patients breathing against a load that might lead to fatigue, as well as in those who cannot be weaned from the ventilator [16]. These patients had also demonstrated respiratory muscle fatigue, as detected by electromyographic measurements (Fig. 12). Very early, after discontinuation of mechanical assistance, there is an increase in frequency of breathing (tachypnea), while the muscles are still able to generate adequate ventilation. In many of these patients, paradoxic chest wall respiration results from either inward motion of the abdominal wall (abdominal paradox) or alternating breathing (respiratory alternans). Finally, if artificial ventilation is not instituted, bradypnea ensues, followed by central apnea.

Tobin et al. [62], studying healthy subjects breathing against severe resistances, presented results indicating that rib cage-abdominal asynchrony and paradox are due predominantly to increases in respiratory load rather than muscle fatigue. However, even if abnormal rib cage-abdominal motion is not due to respiratory muscle fatigue per se, it may still be considered a harbinger of fatigue since it is a direct reflection of increased, fatiguing respiratory load [62]. The clinician then can observe abdominal paradox and/or alternating breathing by a simple examination and/or palpation of the chest and abdominal wall and detect an excessively increased respiratory load, leading to fatigue or pre-established respiratory muscle fatigue.

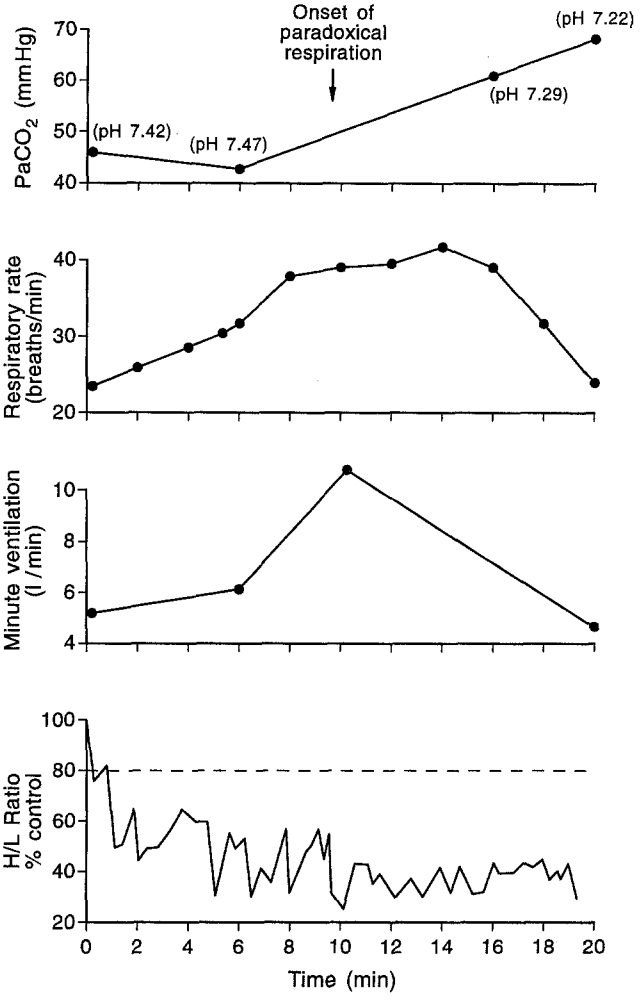


Fig. 12 Sequence of changes in P_aCO_2, respiratory rate, minute ventilation, and high/low (H/L) ratio of the diaphragm in a patient during a 20-min attempt at discontinuation of mechanical assistance. The initial change was the fall in high/low ratio (indicating fatigue), followed by a progressive increase in respiratory rate. The P_aCO_2 initially fell and the patient became alkalemic. Paradoxic abdominal displacements were not noted until after there had been a substantial increase 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 reinstituted, there was a sharp fall in respiratory frequency and minute ventilation (From [16])

Management of respiratory muscle fatigue

Experimental muscle fatigue develops when the demands on the respiratory pump exceed pump energy supply (Fig. 9). 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 [1]. The three components of the system (demand, supply, and neuromuscular competence) (Fig. 9) 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, as well as at 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, the energy requirements will also increase and fatigue may develop. This may explain the inability of normal subjects to maintain high levels of ventilation for long periods [52] or to sustain normal ventilation when the work of breathing is excessive. Therefore, in patients with increased work of breathing, fatigue may be avoided therapeutically 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 pulmonary compliance.

Muscle strength is an important factor influencing muscle energy demands; therefore pressure should be normalized by expressing it as a fraction of Pi,max at the same fiber length. The greater the work required to sustain adequate ventilation, the greater the value of Ptidal/Pi,max and the greater the energy demand (Fig. 9). Thus, at constant pressure, the energy demand will increase as Pi,max decreases. This is of considerable physiological significance, since Pi,max is a function of fiber length; for the respiratory muscles, therefore, it is determined in part by lung volume. Hyperinflation strongly predisposes respiratory muscles to fatigue, not only by increasing the driving pressure but also by decreasing Pi,max [35, 47]. Furthermore, if the efficiency of the respiratory muscles decreases, which occurs with an increase in airway resistance [47, 53], the O_2 cost of breathing and energy demands increase for the same external power, further predisposing them to fatigue. Airway obstruction frequently leads to hyperinflation, which further decreases the efficiency of the respiratory muscles by shortening fiber length and obliging the muscles to perform an isometric contraction at the beginning of inspiration in order to overcome internal PEEP.

Improving contractility and endurance of the respiratory muscles

Rational therapy of respiratory muscle fatigue includes training, nutritional repletion, rest, and muscle pharmacotherapy. These measures prevent fatigue by improving respiratory muscle contractility and endurance 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 thyroid-, alcohol-, steroid-, and drug-induced and inflammatory myopathies [1].

Pharmacological agents

Only recently has attention been focused on the effects that various pharmacological agents may have on improving the contractility and endurance of the respiratory muscles. Respiratory muscle function can be modulated pharmacologically either by acting at the level of the excitation-contraction coupling process or by increasing the energy supply to the muscles. Drugs that act at the level of excitation-contraction coupling are xanthies [63] and digitals [64], while those that increase the energy supply are isoproterenol [65] and dopamine [66]. Studies in animals, isolated preparations, normal subjects, and patients have all shown that theophylline has a positive inotropic effect on respiratory muscles, enhancing their contractility at the therapeutic dose level; hence, it restored the ability of the fatigued diaphram to generate adequate forces, increasing its endurance. The effects of theophylline appear to be greater in the fatigued than in the nonfatigued state. The mechanism of action is not yet clear, but recent studies indicate that theophylline may facilitate the influx of Ca^{2+} through the slow channels and perhaps activate a Ca^{2+}-induced Ca^{2+} release from the sarcoplasmic reticulum [67].

Training

Specific training of the respiratory muscles, like other skeletal muscles, can enhance their strength and endurance, the latter being most relevant to patients with chronic ventilatory loads or weaning difficulties. Ventilatory muscle strength has been increased by 55% in subjects performing repeated maximum static inspiratory and expiratory pressure maneuvers [68]. By increasing inspiratory muscle strength, the pressure developed per breath expressed as a fraction of the maximum will diminish, thus reducing vulnerability to fatigue.

Inspiratory resistive training constitutes the most direct approach to improving the strength and endurance of patients with ventilatory failure and who are unable to

return to spontaneous ventilation [69]. In the study by Aldrich and co-workers [69], patients were exposed to five conditioning sessions per week. Each session consisted of spontaneous breathing through an adjustable, nonlinear resistor. The length of each session and the degree of resistance were increased gradually. With this conditioning protocol, MIP increased by 24% and VC by 60%. After 10–46 days of conditioning, 44% of the patients were weaned completely and 20% were weaned to spontaneous nocturnal ventilation. However, the results of this stimulating study need to be confirmed by controlled trials and the administration of training for difficult-to-wean patients is not yet standard practice.

Respiratory muscles, like limb muscles, usually respond to high-frequency/low-load contractions with an endurance-conditioning response and low-frequency/high-load contractions with a strength-conditioning response [70]. Under some circumstances, however, the specificity of conditioning is not so precise and dual-response (i.e., endurance and strength) conditioning may occur in response to a single conditioning stimulus [68]. Dual-response conditioning is most likely to occur when muscles are severely deconditioned as it occurs in ventilatory muscles following prolonged periods of mechanical ventilation, total bed rest, undernutrition, debilitating disease, or surgical trauma [69, 70]. Thus, in mechanically ventilated patients with difficulties in weaning, less precise forms of conditioning stimuli, like low-frequency and low-load activities, may produce improvement in both endurance and strength [70].

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 [71]. Nutritional repletion can improve the strength and endurance of the ventilatory pump [1].

Rest

A logical approach to restore the contractility and endurance of a fatigued muscle would be to allow the muscle to rest. Available data clearly demonstrate the long-term benefit as evidenced by improvements in P_aCO_2 and maximum respiratory muscle pressures to patients with chronic neuromuscular and chest wall disorders of the noninvasive use of assisted ventilation, usually nocturnal, using both positive and negative pressure ventilators [72, 73]. Similarly, several studies have shown a significant improvement in patients with severe stable COPD and CO_2 retention, e.g. decreased CO_2 and increased strength of the respiratory muscles, using both negative [74] and positive [75] pressure ventilating devices. 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 the improvement in these patients is a result of respiratory muscle rest reversing muscle fatigue remains speculative [1]. This is because the reduction in P_aCO_2 during the periods off the ventilator may be due to the resetting of the CO_2 setpoint, resulting from the forced reduction of P_aCO_2 in the ventilation phase, and the improvement in maximum 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. In this regard, Elliott et al. [75] failed to find any relationship between the improvement in P_aCO_2 and increased inspiratory muscle strength in patients with severe, stable COPD after 6 months of overnight, nasal, intermittent, positive-pressure ventilation. Since the reduction in P_aCO_2 was correlated with a decrease in gas trapping and residual volume, as well as with a better response to CO_2 rebreathing, the authors concluded that the improvement in blood gases was not the result of increased respiratory muscle strength achieved through relief of muscle fatigue, but was due rather to changes in respiratory load and central drive.

Fatigue as cause of ventilatory failure

In dogs, respiratory muscle fatigue is recognized as a cause of respiratory failure in cardiogenic [15] or septic shock [31]. In clinical conditions, however, as well as in patients undergoing weaning from ventilators [16, 20], it is very likely that hypoventilation is due to fatigue. Because hypercapnia occurs either acutely – as in cardiogenic shock with pulmonary edema or chronically, as in chronic obstructive pulmonary disease – it follows that if fatigue plays a role in CO_2 retention, it may occur either acutely or chronically.

Acute hypercapnia

Fatigue and, in turn, hypercapnia of acute onset are usually due to a combination of increased mechanical load of the lung, reduced muscle strength, decreased efficiency, and reduced energy supplies to the inspiratory muscles. The mechanisms responsible for CO_2 retention are both decreasing $\dot{V}_E$ and increasing V_D/V_T. The sequence of events and their potential explanation is as follows: in patients with weak and/or loaded respiratory muscles, tidal volume is reduced by diminishing inspiratory time in order to diminish Ptidal and the energy de-

mand per breath (expressed by the pressure-time index, *PTI*). 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 the small tidal breaths. This reduction in V_T is compensated for, at least in the beginning, by increasing breathing frequency such that minute ventilation is maintained or increased. Consequently, since such a pattern of breathing increases V_D/V_T, P_aCO_2 will increase if $\dot{V}_E$ is preserved, or may remain stable if $\dot{V}_E$ is increased proportionately. Such a frequency of breathing, however, is no longer optimal and, for the same alveolar ventilation, the energy demand will increase. Thus, although the non-optimal frequency seems to be a better option than the long T_I, it coupled with the inadequate energy supply, will finally lead to muscle fatigue. Pressure will then decrease and, as a result, V_T and $\dot{V}_E$ will decrease while V_D/V_T further increases. The reduction in pressure will obviously decrease the *PTI* and energy demands per breath, but alveolar ventilation ($\dot{V}_A$) will be further reduced and P_aCO_2 will rise. At a later stage (for example, 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 drop in $\dot{V}_E$ (15, 16). Finally, in extreme fatigue, the central nervous system 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 reduced dynamic compliance and in rapid, shallow breathing. These factors increase the work of breathing and the energy demand, leading to breathlessness and potentially to fatigue. The latter is a very probable hazard, as hyperinflation, which reduces the strength and efficiency of muscles, can be severe. At the same time, the required pressure per breath (Ptidal) is increased excessively due to auto-PEEP and high-elastic and resistive inspiratory load. Hyperinflation increases the likelihood of a decrease in maximum inspiratory pressure (Pi,max) and, hence, an increase in Ptidal/Pi,max potentially leading to fatigue. The blood supply may eventually be impaired as muscular contractions become very strong in order to maintain higher end-expiratory lung volumes [76]. Finally, severe lung disease may lead to hypoxemia and may reduce the amount of energy available, resulting in lactic acid production. A constellation of factors encourages maximum inspiratory pressures to decrease and Ptidal/Pi,max to increase, leading to dyspnea, fatigue, or both. Such a situation forces alveolar hypoventilation by reducing tidal volume, either as a protective mechanism for the muscles or as a consequence of failure (fatigue) of the muscles. It must be noted that, because of hyperinflation, values of Ptidal/Pi,max lower than those needed in FRC, i.e. about 0.50 [47], are adequate to cause fatigue of the inspiratory muscles.

Muscles that are used most often, such as the inspiratory muscles (particularly the diaphragm), atrophy the fastest. Artificial ventilation may be followed by weakness of the inspiratory muscles due to atrophy (secondary to disuse). Thus, it is probable that patients who fail to wean suffer from disuse atrophy, which leads to shortness of breath and fatigue [16]. In addition, after prolonged stays in the intensive care unit, patients often suffer from malnutrition, which clearly affects both muscle strength and ventilatory drive [71, 77].

In most neuromuscular diseases with acute onset (e.g. diaphragmatic paralysis), weakness of the respiratory muscles is a very common feature leading to ventilatory failure. Under such conditions, the remaining normal muscle cells cannot develop sufficient force to maintain adequate alveolar ventilation and hypercapnia ensues. This may be the result of central nervous system adaptation, muscle fatigue, or both. It is apparent that the clinical expression of failure (acute vs chronic) depends on the nature of the underlying disease. It may vary from rapid onset, as in Guillain-Barre syndrome, to stable chronic failure, as in long-standing poliomyelitis. In the latter case, it is extremely likely that the chronic failure will be compounded by acute failure under a variety of conditions (e.g. infection, CO_2 production, sedation, anaesthesia, surgery).

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 is well described in animal models, with respiratory muscle fatigue leading to severe alveolar hypoventilation, followed by bradypnea and respiratory arrest [15]. In non-cardiogenic pulmonary edema, patients need increased pressure and energy to ventilate the lungs. Coexistent severe hypoxemia due to lung damage may diminish 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 again leads to alveolar hypoventilation.

Despite the abovementioned 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 that of patients who are failing to sustain spontaneous breathing after discontinuation of mechanical assistance. Recent results indicate that, in at least some patients, the high inspiratory load accompanied by hyperinflation or other detrimental factors (e.g. high inspiratory flow, hypoperfusion) may lead to inspiratory muscles fatigue [78] (Fig. 13). Hence, respiratory muscle fatigue may result in or contribute to severe acute respiratory failure requiring mechanical ventilation.

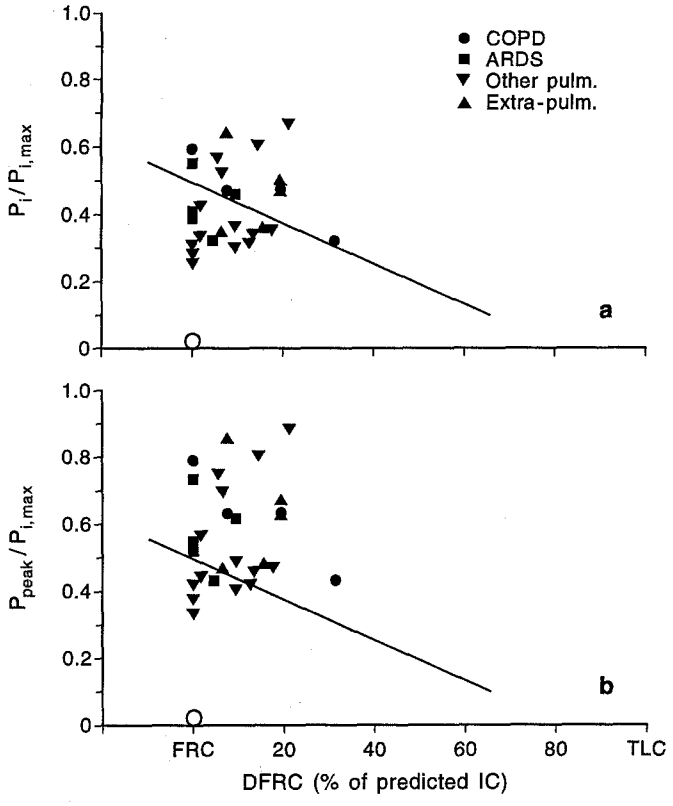


Fig. 13 Pressure-volume diagram similar to that of Roussos et al. [47], plotting the ratio Pi/Pi,max (A) and Ppeak/Pi,max (B) against dynamic increase in FRC (DFRC), expressed as percentage of predicted inspiratory capacity (IC). The ratios Pi/Pi,max and Ppeak/Pi,max are mean and peak inspiratory pressure per breath, respectively, expressed as a fraction of maximum. Each *closed symbol* refers to a patient. *Open circles* represent the mean values of mean and peak esophageal pressure, respectively, expressed as a fraction of maximum in ten normal subjects. *COPD* exacerbated chronic obstructive pulmonary disease; *ARDS* adult respiratory distress syndrome; *Other pulm* other pulmonary diseases; *Extra-pulm* acute respiratory failure of extrapulmonary origin. 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 normals is about 50% of maximum inspiratory pressure, while at FRC+1/2 IC, this critical pressure is 25–35% of the maximum. All patients had excessively high values of both ratios, clustering around the critical line, rather than away from it, as happens in normal subjects (From [78])

Insidious onset of hypercapnia

Patients who insidiously retain CO_2 invariably need to generate high pressure per breath that is a large fraction of their maximum inspiratory pressure. 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 a category of patients, Ptidal, although normal, may be a large fraction of Pi,max, since the latter is reduced (neuromuscular disorders). It is difficult to ascertain the mechanism of CO_2 retention in such patients. However, reduction of V_T is a frequent feature and therefore may be the common pathway to CO_2 retention by increasing in V_D/V_T. Two alternative pathways are proposed, which are not mutually exclusive. As disease progresses, the pressure, *PTI*, or power required to maintain adequate ventilation is increased and the muscles become more vulnerable to dyspnea and fatigue. In this process, the central nervous system may set a lower level of ventilation or may alter the pattern of breathing in order to avoid dyspnea or exhaustion. Alternatively, it is possible that the ventilatory pump may become chronically fatigued (centrally or peripherally), so that the decrease in alveolar ventilation is the result of pump failure. Both mechanisms may be operative.

When COPD patients who retain CO_2 were compared to those who did not, it was found that V_T and T_I were reduced in the CO_2 retainers, while frequency was increased [79]. At equal minute ventilation, V_D/V_T was higher in the CO_2 retainers and hence, CO_2 increased. The increased V_D/V_T may be explained as follows: Patients who retain CO_2 have lower forced expiratory volume in 1 s (FEV) and Pi,max values, higher effective impedances and higher weights, functional residual capacities (FRCs) and FRC/total lung capacity (TLC) ratios than do nonretainers of CO_2 [79, 80] (Fig. 14). At equal driving force (P 0.1) such a patient is better off terminating T_I early, thus avoiding substantial deviation from optimal lenght and, perhaps, avoiding substantial geometric alterations of the diaphragm and intercostal muscles than by taking 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 ecxeeding the "critical" inspiratory pressure, leading to severe dyspnea or fatigue. In fact, although hypercapnia can be reduced in COPD patients by voluntary changing of the breathing pattern, i.e. increasing V_T and decreasing frequency, it has been shown that this type of breathing leads to fatigue of the inspiratory muscles and that the imposed pattern cannot be tolerated for more than a few minutes [81]. In this regard, patients with COPD and severe hypercapnia developed a mean tidal inspiratory pressure (Ptidal) that was 27% of Pi,max, whereas the Ptidal in patients with no CO_2 retention was only 10% of Pi,max [80]. Using the results from normal subjects, in which the critical pleural pressure for developing fatigue of FRC plus one half inspiratory capacity is 25–30% of the maximum [47], we may place CO_2 retainers above or in the critical zone of fatigue, whereas non-retainers remain in the nonfatiguing zone (Fig. 15). In patients with COPD and P_aCO_2 of less than 45 mmHg, this was especially evident. The Ptidal/Pi,max was 10% and the residual volume (RV)/TLC ratio was 50% [80]; that is, the tidal

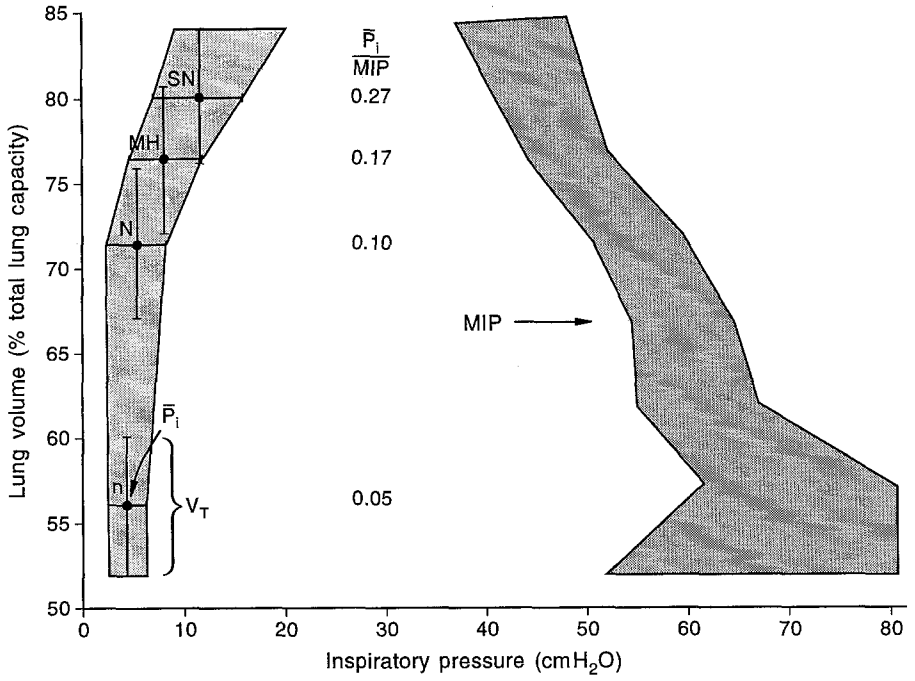


Fig. 14 Relationship among lung volume, tidal pressures, and maximal inspiratory pressures (MIP) in normocapnic and hypercapnic groups of patients with COPD. The *right band* is drawn from MIP values plus 95% confidence intervals obtained at FRC in all patients and plotted against their FRC/TLC values ($r = 0.32$, $P < 0.001$). On the left, *vertical bars* represent the tidal volume (V_T) excursions and *horizontal bars* represents the mean (±SD) inspiratory transpulmonary pressure swing (P_I) for the normocapnic, moderately hypercapnic, and severely 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 *left band* connects the SD values for each group. The inspiratory muscle load (P_I/MIP) for each group is given at the level of their mid-inspiratory volume (From [80])

inspiratory pressure was certainly below the critical zone for developing fatigue. In contrast, in patients whose RV/TLC was 67% and who retained CO_2, Ptidal/Pi,max was 27% [80] – 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 the limits. In such a predicament, there are two alternative pathways. First, the central controllers (via a feedback mechanism) reduce the T_I and V_T and hence, the Ptidal. Thus, fatigue is avoided. If this is so, hypercapnic subjects weigh their options and choose hypoventilation rather than respiratory muscle fatigue [80]. Second, the muscles pass into a stage of chronic failure (fatigue), leading to reductions in the driving pressure and V_T. From all that is known about the nature of central fatigue and peripheral, high-frequency fatigue, it is very unlikely that these fatigue states persist in a stable form. On the con-

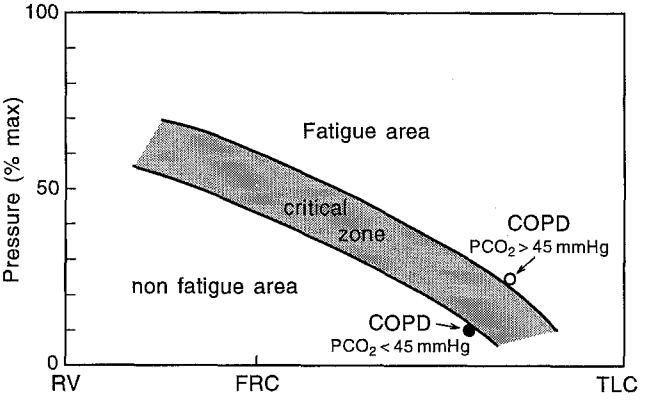


Fig. 15 Effect of lung volume on critical pressure of the respiratory muscle. Diagram is constructed from findings in normal subjects breathing against high inspiratory resistance. Subjects who, at functional residual capacity (FRC) or higher (lung volume), generate per-breath pressure (mouth and/or 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 CO_2 retention ($PCO_2 > 45$ mmHg) are above or barely within the upper limit of the critical zone, whereas patients with no CO_2 retention ($PCO_2 < 45$ mmHg) are below or barely within the lower limit of the critical zone. *RV* residual volume; *TLC* total lung capacity (From [87])

trary, chronic fatigue in the form of low-frequency fatigue is possible as it recovers slowly and is relatively more stable. However, as previously discussed, the hypothesis that the improvement in respiratory muscle strength observed in patients with severe, stable COPD and treated with assisted ventilation is a result of rest reversing chronic muscle fatigue remains as yet speculative. The authors of this article favor the first strategy. We also speculate that afferents from the small (type-3 and type-4) fibers, stimulated by the heavy work (ergoreceptors, type 3) or by noxious substances like lactic acid (nociceptors, type 4), modify the CNS output. The mechanism is not known, but the production of endogenous opioids may play an important role.

In many other diseases characterized by the presence of chronic hypercapnia (for example, severe obesity and kyphoscoliosis), the mechanism leading to CO_2 retention seems to be the same as or similar to that in COPD patients.

Weaning failure and fatigue

Fatigue of the inspiratory muscles probably precipitates the inability to sustain spontaneous breathing, which is the most frequent cause of weaning failure. In fact, during unsuccessful weaning trials, the pattern of breathing alters [82, 83], discoordinate respiratory movements appear [16], and the diaphragmatic EMG high/low ratio falls [16, 84] (Fig. 12, 16). However, it is possible that these changes may not reflect inspiratory muscle fatigue per se, but rather alterations in central drive due to excessive loading response [62]. Nevertheless, such high inspiratory loads observed during weaning failure will eventually lead the ventilatory pump to exhaustion and overt fatigue, which is undoubtedly a very terminal event. 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 signal the forthcoming task failure.

Some of the controversy regarding the exact role of inspiratory muscle fatigue during weaning failure stems

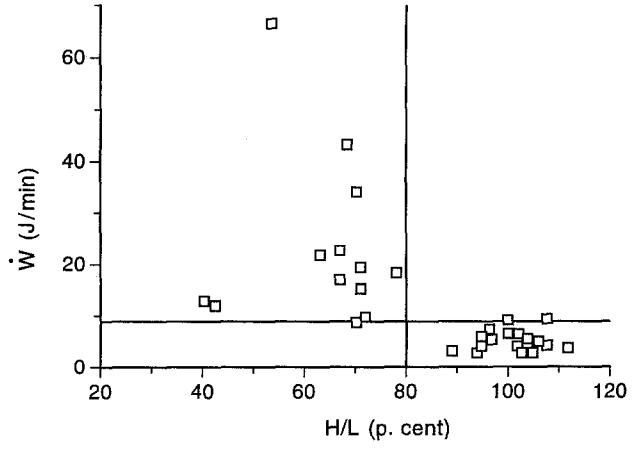


Fig. 16 Plot of individual values of the respiratory muscle power ($\dot{W}$) against H/L ratio of the diaphragm during weaning trials. H/L was expressed as a fraction of its initial value in each period. Two regions can be distinguished: (1) above a certain amount of $\dot{W}$ (*horizontal line*), values of H/L were in the zone fatigue (*vertical line*) and patients were failing at weaning; (2) below this level of $\dot{W}$, no evidence of fatigue occured and patients were weaned successfully (From [84])

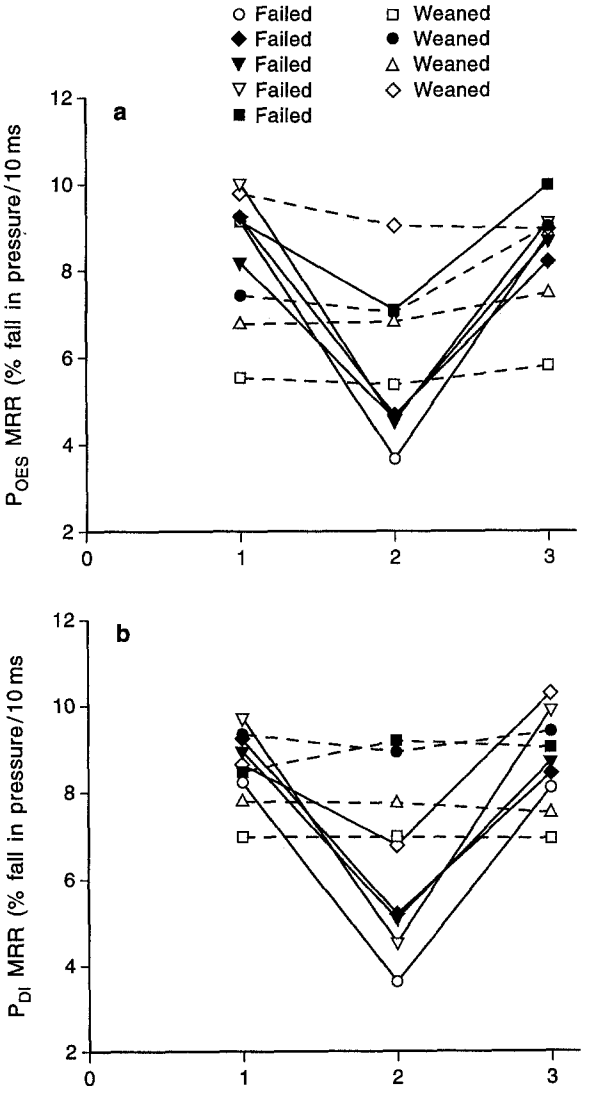


Fig. 17 Sniff esophageal and transdiaphragmatic pressure maximum relaxation rates (MRR) in nine patients undergoing a weaning trial. MRR was measured before (1), during (2), and after (3) the weaning trial. MRR slowed in the five patients who failed to wean, returning to normal when mechanical ventilation was resumed. In the four patients who were weaned successfully, MRR remained unchanged (From [20])

from the fact that fatigue has been defined in dichotomous terms (present or absent), but the impairment in contractility is more likely to exist in the form of a continuum [85]. Furthermore, the bedside clinical diagnosis of fatigue is hampered by the inability to measure the baseline before fatigue and by the lack of a universally agreed-upon, objective physiologic or clinical test (or set of tests) to determine fatigue [1]. However, recent data offer significant support for fatigue. 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, while remaining unchanged in those weaning successfully [20] (Fig. 17). These data suggest that during unsuccessful weaning trials, a fatigue process is initiated peripherally in the respiratory muscles; as this is associated with the slowing of MRR, it is likely that the central drive is modulated [11]. It has also been possible to measure the load imposed on the respiratory muscle pump in these patients, as well as the capacity of the respiratory muscles. When the ratio of load to capacity is high, weaning fails [20, 83]. Furthermore, in such patients, the combination of a decrease in inspiratory load and an increase in ventilatory capacity is adequate to make the weaning successful [83].

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. The favored hypothesis is that, as Ptidal becomes a large fraction of Pi,max, the breathing work load increases (e.g. decreased lung and/or chest wall compliance), Pi,max is reduced (e.g. neuromuscular disease, hyperinflation), or both (e.g. acute asthma attack). Inspiratory time is thereby reduced and a decrease in V_T follows. This strategy possibly involves the small type-3 and type-4 afferents from the muscles and the endogenous opioids, avoids high values of Ptidal, and therefore minimizes dyspnea and, ultimately, fatigue. Fatigue may occur if this strategy fails, and it is certainly a very terminal event.

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