Lung (1982) 160:59–84

Lung

Review

The Failing Ventilatory Pump

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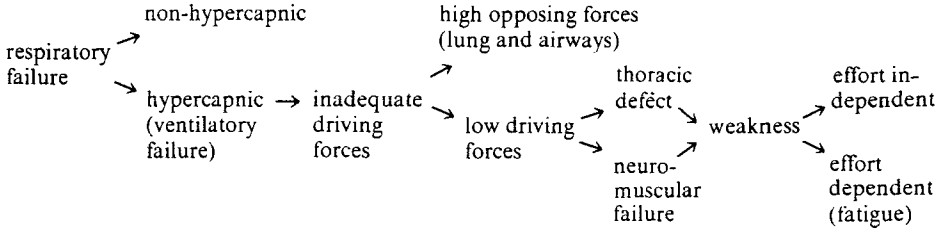
Key words: Respiratory muscle fatigue – Respiratory failure – Respiratory muscle weakness

Introduction

Respiratory failure may be categorized into non-hypercapnic and hypercapnic (ventilatory). Ventilatory failure is due to failure of the thorax[1], (ventilatory pump) to generate the pressure required for ventilation (Schema A). This failure may be due to either high opposing forces from the lung and airways (e.g. airways obstruction) or to low driving forces (weakness) as a result of a defect in the chest wall (e.g. flail chest) or a failure in the neural and/or muscular apparatus. In this review, I will focus on situations resulting from a compromised ventilatory pump due to low driving force (weakness) of the respiratory system. This failure may stem from any

Schema A



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[1] *Thorax.* Originally (Homer) meaning breastplate, curiass, corslet and eventually armour. With Hippocrates, "thorax" signified the area covered by the breast plate, or the entire trunk. In Plato's time, the 'thorax' delimited the walls of the cavity extending from the neck to the genitalia, and was separated by the midrift. Progressively, the region encompassed by the thorax has been reduced to the breast, or the chest.

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Schema B

brain
↓
spinal cord
↓
nerve
↓
neuromuscular junction, cell membrane
↓
excitation contraction coupling
↓
pressure

disturbance in the long chain of events involved in producing pressure originating in the brain and terminating at the chest wall (Schema B). For reasons of convenience and from a functional standpoint, I will categorize the weakness of the thorax into that unrelated to preceding breathing efforts (effort independent weakness) and to weakness resulting from respiratory muscle contraction. This effort dependent weakness represents respiratory muscle fatigue which may be defined as the inability of the thorax to sustain the required pressure [20, 58, 59].

Effort Independent Weakness (Table 1)

Failure of the Central Nervous System

A well known reason for respiratory muscle weakness is lack of neural drive which cannot conceivably be due to loss of motivation as may be the case for other skeletal muscles. The decrease in neural drive therefore suggests a neurological impairment of the respiratory centers as in progressive disorders of motor neurons in the cerebral cortex, brain-stem and spinal cord such as amyotrophic lateral sclerosis, or possibly as a result of the action of drugs like barbiturates.

Nerve and Neuromuscular Junction

Another possible reason for muscle weakness may be impaired neural transmission resulting in reduced muscular force (Schema B) as illustrated by the Landry-Guillian-Barré syndrome [52], which is due to ascending motor paralysis. Myasthenia

Table 1. Factors predisposing to effort independent weakness

1) Depressed neural drive
2) Impaired neural conduction
3) Neuromuscular transmission failure
4) Excitation contraction coupling failure
5) Loss of muscle mass
6) Inadequate energy supply
7) Thoracic volume, chest wall geometry
8) Thoracic defect
9) Cell "poisoning" (e.g. drugs)

gravis, characterized by impaired neuromuscular transmission, is a disturbance affecting the last links of the neural pathway.

Excitation Contraction Coupling Failure

In skeletal muscles the impaired capacity to activate the contractile machinery despite adequate membrane excitation is thought to underlie the muscle weakness seen in familial hypokalaemic periodic paralysis [22], myotonia [70], and with various drugs [48]. The role of excitation contraction coupling in respiratory failure is not as yet documented, but it seems probable.

Loss of Muscle Mass

Disuse atrophy of respiratory muscles after prolonged artificial ventilation may result in respiratory muscle weakness, since it occurs in other skeletal muscles [60, 61]. Destructive processes such as muscular dystrophies or metabolic myopathies are also potential causes of respiratory muscle weakness.

Inadequate Energy Supply

Skeletal muscles, including respiratory muscles, theoretically may become weak and not be able to generate sufficient forces if the energy sources for contraction, particularly ATP and PCr, are inadequate. Patients with extreme inanition for example may have reduced energy supplies resulting in respiratory muscle weakness. In fact, Spande and Schotelius [66] have found a linear relationship between the force developed and the PCr muscle content, and Murphy [51] reported that the contraction force is logarithmically related to muscle ATP content.

Chest Wall Geometry and Thoracic Volume

An important determinant of respiratory muscle strength is the chest wall geometry. Hyperinflation results in a decrease of the pressure developed by the inspiratory muscles. This is due to two factors. Hyperinflation is associated with a shorter length of inspiratory muscles which hence develop reduced forces for a given level of excitation. Furthermore, hyperinflation flattens the diaphragm, increasing its radius of curvature so that according to Laplace's law, ($P = 2T/r$, P = pressure, T = tension and r = radius of curvature) the diaphragmatic pressure developed is diminished. Similarly horizontally parallel ribs, chest wall trauma, diaphragmatic rupture, flail chest and broken bony structures will damage the mechanical advantage of the chest wall resulting in decreased respiratory driving pressures for a given excitation.

Inspiratory Muscle Fatigue (Effort Dependent Weakness)

Site of Fatigue

The inspiratory muscles are said to be fatigued when they fail to continue to generate the required driving pressure, a failure which has been repeatedly shown to occur in humans and animals [1, 2, 27, 28, 36, 50, 58, 59]. What is the site of such a

failure? Despite a considerable amount of work on the topic for the last century, there is considerable uncertainty about the origin of the failure which occurs when skeletal muscles work against excessive loads. Does the central nervous system get tired and reduce its firing after a period of intensive stimulation of the respiratory muscles? Does the neuromuscular junction gradually lose its ability to transmit neural impulses to the muscle? Or does the problem reside in the muscle's ability to convert chemical energy to mechanical work?

Mosso, in 1892 [47], was perhaps the first to study the phenomenon of muscle fatigue in humans in an objective manner. Mosso pointed out that a subject's endurance time may vary under different conditions. He tested, for example, the finger flexor muscle in one of his colleagues for endurance, immediately before and immediately after he gave an important lecture. The endurance time after the talk was greater than before. Mosso concluded that the excitement during and immediately after his lecture had increased the subject's mental energy to permit him to endure the task for a greater length of time. Thus, from this and other experiments, Mosso concluded that the loss of muscular force can certainly be located in the muscle but is substantially affected by the central nervous system as well.

Two recent studies have dealt with the significance of fatigue of the central nervous system and have acknowledged its role in inducing the loss of force. Ikai et al. [34] used the *adductor pollicis* as a test muscle. The subject contracted his muscle isometrically and maximally at the rate of one contraction per second. It was found that the force developed decreased with time (Fig. 1). However when a strong tetanic electrical stimulation was applied to the ulnar nerve every 5 s the force developed was greater than the voluntary one. It should be pointed out however that the force with each stimulation was also decreasing with time. Thus Ikai et al. concluded that central fatigue may be a very important factor in the process of muscle failure. Bigland Ritchie et al. [9] studied sustained isometric contractions of the quadriceps in humans. The contraction was interrupted every 15 s and a supramaximal tetanizing stimulus applied to the femoral nerve. The authors found that as the force was becoming smaller with time the loss of force with stimulation was less than the loss of force encountered during the voluntary effort (Fig. 2). These results are in ac-

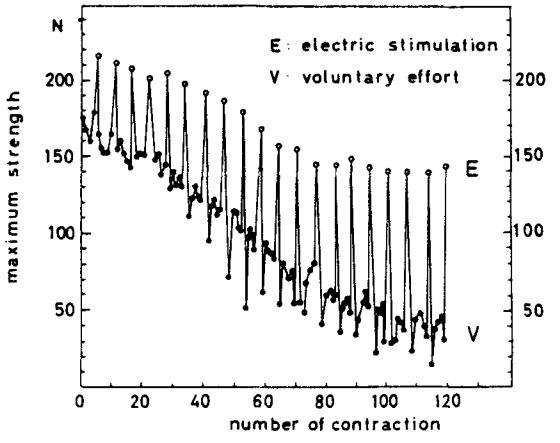

Fig. 1. Maximum isometric voluntary contraction of adductor pollicis muscle (●) interrupted every 5 s by electrical stimulation, applied transcutaneously to the ulnar nerve. Note that the force developed after electrical stimulation (○) is greater than the one developed voluntarily. (After Ikai et al. [34]). Note also that in both cases force decreases with time

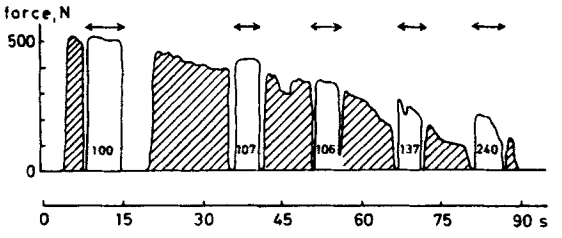

Fig. 2. Maximum isometric voluntary contraction of quadriceps (▨) interrupted by periods of electrical tetanizing stimulation (□) of femoral nerve. Note that with time, the loss of force is greater during voluntary contraction compared to electrical stimulation. (After Bigland-Ritchie et al. [9])

cord with the findings of Ikai et al. How can these conclusions be extrapolated to the respiratory system? Do the respiratory centers reduce their output after a period of high ventilation? We have very little basis for accepting or refuting such a proposition. This will be elaborated below.

Peripheral fatigue can be subdivided into failure at the level of transmission (i.e. neuromuscular junction and muscle membrane) and failure of the contractile machinery. Failure in the transmission mechanism has been shown in nerve-muscle preparations [5, 12] in which force decreases with time during stimulation of the nerve. However, if an intermittent stimulus is applied directly to the muscle the force developed is greater. Stephens and Taylor [67] also found that the area under single action potentials of stimulated muscle decreased to 65% of the original value when the stimuli were applied to the nerves of a muscle during fatiguing voluntary isometric contraction. Thus, these results indicate that, under certain conditions, fatigue may lie in the neuromuscular junction. An important implication of this type of fatigue is that a ceiling is set for all attempts to secure maximum activation of the muscle either by voluntary effort or by electrical stimulation. It is also possible that

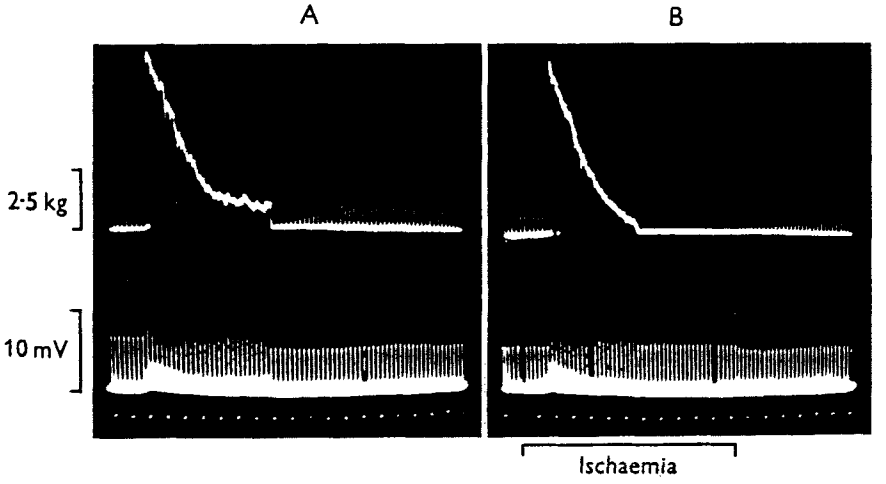

Fig. 3A and B. Maximum isometric voluntary contraction of adductor pollicis muscle until exhaustion with **A** unoccluded and **B** occluded circulation. Upper tracings: force record; single twitches evoked by nerve shocks precede and follow, and are superimposed on the voluntary contraction. Lower tracings: muscle action potentials following the electrical stimulation. Time markers: 30 s. Note the loss of force in the presence of unchanged action potential (After Merton [45])

patients with myasthenia gravis who have an already impaired function of the neuromuscular junction will be more vulnerable to this type of fatigue. In the respiratory muscles, this will be manifested as hypercapnic respiratory failure.

In contrast to the aformentioned experiments, Merton [45] demonstrated in 1954 that fatigue can be located beyond the neuromuscular junction. He used the *adductor policis* muscle, as Ikai et al. [34] did later. Merton's studies were performed on muscles during sustained isometric maximum voluntary contraction and he found, as did Ikai et al. that force decreased with time. However, when strong electrical stimulation was applied to the ulnar nerve during the period in which the force was decreasing, the force developed subsequently did not become greater (Fig. 3). Furthermore, Merton showed that following electrical stimulation the muscle action potentials remained unchanged despite a fall of the mechanical tension to zero or nearly so (Fig. 3). Why is there a difference between Merton's findings and those of others? Differences in motivation and in methodology have been suggested, but the issue remains unresolved. In brief, however, we may say that Merton's experiments provide the most persuasive evidence that fatigue is located solely in the muscles themselves.

In essence, skeletal muscle is analogous to an engine: it converts chemical energy to heat and work. Thus, it is intuitively apparent that if the chemical energy available becomes limited the muscle will fail as a force generator. For example hypoxia and poisoning of the muscle with enzyme inhibitors provoke fatigue [51, 66]. It is also well known that substantial depletion of the PCr stores occurs in sustained ischaemic concentrations [21]. As the circulation is restored phosphocreatine stores are replenished and force recovers in parallel [30]. Bergstrom et al. [8] pointed out that the decrease in high energy phosphates is not, strictly speaking, due to a depletion of the energy stores. Rather, it is caused by a reduced rate of energy transfer from the stores to utilizable ATP and PCr. It was also suggested that the reason for this slowing down process is due to an impairment of the enzymatic processes secondary to the concomitant increase in muscle lactic acid.

New insight into muscle fatigue has been offered in recent years from studies using the radioactive phosphorus (31P) nuclear magnetic resonance technique [16, 17].

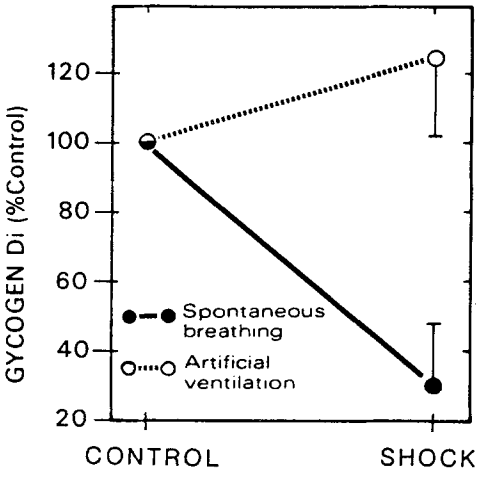

Fig. 4. Changes in diaphragmatic glycogen after 2–3 h cardiogenic shock in a group of animals breathing spontaneously compared to another group artificially ventilated. Note that only the spontaneously breathing animals decreased their diaphragmatic glycogen

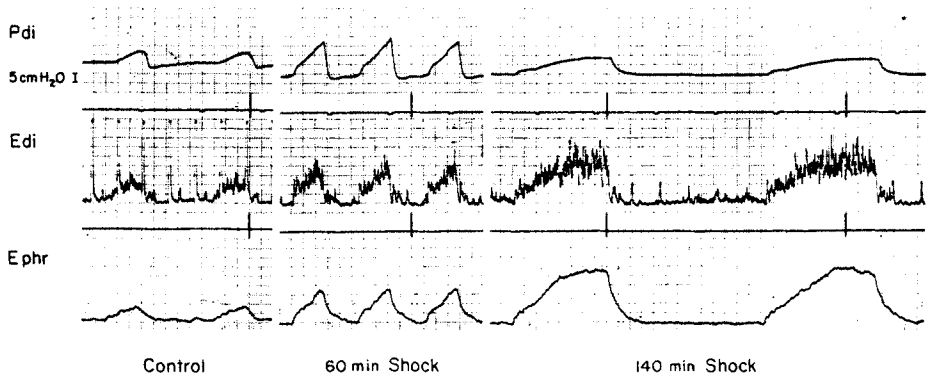

Fig. 5. Evolution of transdiaphragmatic pressure (Pdi), integrated electrical activity of the diaphragm (Edi) and phrenic nerve (Ephr) during cardiogenic shock (tamponade). Left panel during control, middle panel 60 min after the onset of shock and right panel 140 min after the onset of shock, and several minutes before the death of the animals. Note the progressive decrease in Pdi with parallel increase in Edi and Ephr (after Jardim et al. [36])

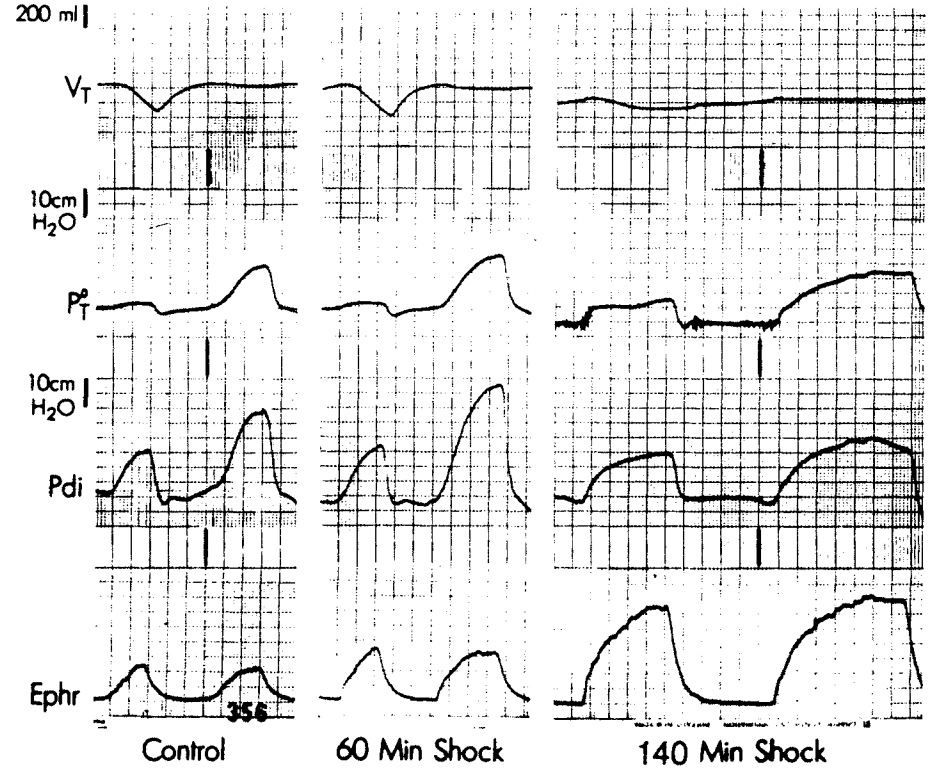

Fig. 6. Typical tracings from one dog, submitted to cardiogenic shock. Tidal volume (V_T), tracheal pressure (P_{φ}), transdiaphragmatic pressure (Pdi) and integrated phrenic activity are shown during control, and at 60′ and 140′ after the onset of shock. At each period an inspiration is followed by an inspiratory effort with occluded upper airways at FRC, resulting in changes only in P_{φ}, Pdi and Ephr. Note that as in Figure 7 the progressive increase of Ephr was not followed by Pdi, P_{φ} and V_T, at 10 min after shock (after Aubier et al. [2])

This technique has been applied to living muscle and has made it possible to monitor the levels and rates of utilization of several key metabolites and the energy changes for ATP hydrolysis. The results conclusively show that force development is closely correlated with metabolic levels rather than with concomitant changes in excitatory conduction. Furthermore it was shown that the decline in isometric force concurrent with muscle fatigue is proportional to the decrease in the rate of phosphorus utilization. Thus, these studies locate the site of fatigue exclusively in the muscle.

The ability to sustain contractions has been found to depend upon intramuscular glycogen stores [14, 26, 31, 32]. A correlation has also been found with glucose levels [66] and with the blood concentrations of free fatty acids [35, 53]. Although we do not know the exact nature of the mechanisms linking the loss of force and these metabolic alterations, the relation is so striking that it cannot be overlooked. One of the most impressive relations between glycogen depletion and loss of force was recently established in our laboratory [2]. Two groups of dogs were subjected to a low cardiac output, 30% of normal control, induced by cardiac tamponade. One group of animals breathed spontaneously while the other group was artificially ventilated. Figure 4 shows that in the spontaneously breathing group diaphragmatic glycogen decreased substantially while in the artificially ventilated group no change was found. Furthermore, the spontaneously breathing group was unable to develop adequate pleural pressure swings at the end of the run, despite an increase in central neural drive and good respiratory muscle excitation as reflected by the relationship between phrenic and diaphragmatic EMG (Figs. 5 + 6) [2]. However, in these experiments glycogen depletion was not the only abnormality observed. Unfortunately we did not measure PCr and ATP concentrations but intramuscular lactic acid and blood lactate levels were about twofold greater in the spontaneously breathing group.

Lactic acid accumulation in muscle has for many years been considered as a potential underlying cause of fatigue. Most of the evidence for this hypothesis came from the studies of Hill and Kupalov [29]. They maintained that fatigue appears at concentrations of muscle lactate above 9 μmoles/g. Since then, the bibliography amassed regarding the role of lactic acid in muscle fatigue is enormous. Fitts and Holloszy [24] found an excellant correlation between contractile force and the intramuscular lactic acid concentration. Similar results were found by Karlson and Saltin [37] who measured lactate concentration in the quadriceps at different levels of exercise. They found that muscular lactic acid increased progressively until exhaustion.

We have also found increases in blood lactate in normal subjects breathing against high inspiratory resistive loads until exhaustion [36]. Subjects performed this test several times breathing room air and 13% O_2. Hypoxia drastically shortened the endurance time. However, at the end of the run, blood lactate was similar to the normoxic runs indicating that the mean rate of lactic acid production was greater during hypoxia (Fig. 7). These results make the hypothesis of lactic acid accumulation an attractive one. However, more studies need to be done to substantiate this old but still appealing proposition of Hill and Kupalov. Currently it is believed that the mechanism through which lactic acid impairs muscular contraction resides in changes in pH which affects the generation of force at different stages of contraction [23].

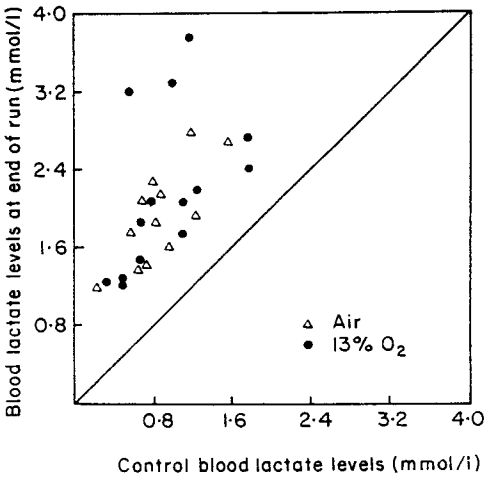

Fig. 7. Relationship between control blood lactate and lactate concentration measured at the end of the run in man breathing through high inspiratory resistance. Note that blood lactate is higher at the end of the run and there is no difference between breathing room air and 13% O_2

The view that the site of fatigue lies in the muscle itself has received additional credence from studies demonstrating that the three different types of muscle fibers fatigue at different rates. The slow twitch oxidative (SO) fibers are resistant to fatigue. The fast twitch oxidative-glycolytic are less resistant to fatigue (FOG) and the fast twitch glycolytic (FG) are easily fatiguable. Thus it appears that the fatiguability of a muscle is largely dependent on its oxidative capacity [13]. 55% of the fibers of the diaphragm are SO fibers in adults [40] and 45% in full term infants [38]. These values correlate reasonably well with our finding [59] that the adult diaphragm can sustain about 40% of the maximal pressure without fatiguing.

It becomes obvious that since Mosso and particularly since Merton's work most of the literature speaks in favor of peripheral fatigue and more specifically of fatigue located distal to the neuromuscular junction. This implies that as the force of muscle contraction decreases during submaximal contraction, the recorded electromyographic intensity may remain constant or may even increase. This sequence of events is rather common in submaximal contraction leading to fatigue, i.e. an increase in the ratio between electromyographic intensity and mechanical response, the "E/T ratio" of Lippold et al. [41]. The explanation is that, as the mechanical response of the individual active muscle fibers decline with fatigue, some compensation can be achieved by increasing the innervation frequency and/or the number of active motor units. This behaviour was recently demonstrated for the diaphragm in our laboratory [2] in experiments performed during a low cardiac output state, as previously described. Figure 5 depicts a typical example. Transdiaphragmatic pressure (Pdi) at 60 min of the run was greater than control while towards the end of the run (140 min) Pdi decreased. On the contrary, the integrated electrical activity of the diaphragm (EMG) and of the phrenic nerve (EPh) continuously increased. These results unequivocally argue that in respiratory muscles the failure during fatigue can be due neither to inadequate neural drive per breath (as witness the continuously increasing phrenic activity) nor to poor excitation (as witness the progressive increase of diaphragmatic EMG). An impaired contractile machinery appears to be the culprit.

Towards an Integrated View

The preceding brief review of the literature indicates that fatigue may be unequivocally located in the contractile machinery. However, fatigue of the neuromuscular junction or of the central nervous system also are possible under certain circumstances. For example, Mosso's colleague could conceivably perform better when excited. In fact it is well known that motivation can appreciably prolong the time to exhaustion in a fatiguing experiment. The important question however is whether the automatic respiratory controllers can be affected by the fatigued respiratory muscles and adapt their drive to the thorax.

Minute ventilation is given by the equation

$$\dot{V}_E = V_T \cdot f = V_T \cdot 1/T_{TOT} \quad (1)$$

where V_T = tidal volume, f = frequency of breathing and T_{TOT} = total duration of breathing cycle. Assuming that the mechanical properties of the respiratory system remain constant, any change in the output of the central respiratory controllers may alter $\dot{V}_E$ by changing either f or flow ($\dot{V}$), the integral of which is V_T. Inspiratory flow may be reduced by reducing the number of impulses per unit time to the periphery, for example after an overdose of barbiturates. Alternatively inspiratory flow may be reduced as a result of respiratory muscle failure despite adequate neural drive and muscle excitation. The latter is exemplified in Figs. 5 and 6. We observe that at 140 min the phrenic activity and the corresponding diaphragmatic excitation is the largest throughout the run while the V_T, the tracheal pressure during an inspiratory effort with occluded upper airways at FRC (P^oT_I), the transdiaphragmatic pressure (Pdi) and the mean inspiratory flow (V_T/T_I, where T_I = inspiratory time) are the smallest. Note that no changes occurred in the mechanics of the respiratory system. The respiratory muscles were unable to generate the pressure needed to maintain or increase the mean inspiratory flow. This failure occurred without an increase in the end expiratory lung volume which could otherwise account for such a result by altering the length and geometry of inspiratory muscles. However inspection of Fig. 5 and 6 reveals that the fall of $\dot{V}_E$ was not only due to decrease of pressure and V_T but also due to a drop in frequency. We may conclude therefore that a peripheral component (muscle fatigue) and a central depression of the rate of breathing resulted in a drop of $\dot{V}_E$. Why do not lightly anaesthetized animals increase their frequency of breathing to compensate for the failure of the contractile machinery to avert the hypercapnic respiratory failure?

A similar question is raised by rearranging Eq. 1 multiplying and dividing by the factor T_I.

$$\dot{V}_E = \frac{V_T}{T_I} \cdot \frac{T_I}{T_{TOT}} \quad (2)$$

where V_T/T_I = mean inspiratory flow and T_I/T_{TOT} represents the ratio of inspiratory time to total duration of breathing cycle. This ratio is a first approximation expressing the proportion of time that the inspiratory muscles spend contracting (inspiratory duty cycle). Inspecting Figs. 5 and 6 it is clear that from control to 60 min $\dot{V}_E$ increased by increasing V_T/T_I (mean inspiratory flow) and T_I/T_{TOT} ($p < 0.01$, for 12 animals), however at 140 min $\dot{V}_E$ decreased, mainly by decreasing V_T/T_I, and at

later stages in some animals also by decreasing T_I/T_{TOT}. Why did the respiratory centers not further increase T_I/T_{TOT} to compensate ventilation? In this connection it should be noted that in humans and animals breathing against high loads T_I/T_{TOT} can reach values of 0.7.

It seems premature to draw firm conclusions from the observed adaptations of respiratory centers in anaesthetized animals during a low cardiac output state without first systematically examining other factors that probably affected the response of the animals, particularly the effect of vagal reflexes, a subject elegantly reviewed recently by D'Angelo [15]. Be that as it may, the respiratory muscles can be considered as an engine which consumes chemical energy to produce mechanical work (work of breathing). This engine is under the control of an engineer (respiratory centers) who sets the rate of work ($\dot{W}$) according to the demands. Thus, for a given mechanical efficiency (E), the muscles have a corresponding rate of energy ($\dot{C}$) consumption, according to

$$\dot{C} = \frac{\dot{W}}{E} \tag{3}$$

Rearranging Eq. 3 and assuming a square wave profile for changes in pressure (P)

$$\dot{C} = \frac{P}{E} \cdot V_T \cdot f = \frac{P}{E} \cdot V_T \cdot \frac{1}{T_{TOT}} \tag{4}$$

$$= \frac{P}{E} \cdot \frac{V_T}{T_I} \cdot \frac{T_I}{T_{TOT}} \tag{5}$$

In the experiments represented in Figs. 5 and 6, as the energy available decreased the rate of energy consumed ($\dot{C}$) decreased by virtue of decreasing the P and V_T/T_I. Equations 4 and 5 may offer a reasonable proposition as to why the respiratory controllers did not increase the f or T_I/T_{TOT} by shortening the expiratory time, the only available mechanism remaining. Such a strategy would have resulted in an increase in $\dot{C}$, which was however incompatible with the shortage of energy. A decrease in the frequency of breathing without an increase in the T_I/T_{TOT} allowed the muscles to rest for sufficient time in order to replenish the consumed energy, wash-out the byproducts and hence increase the endurance.

To summarize the hypothesis, the respiratory muscle is the primary source of loss of force as the chemical free energy decreases. This failure is sensed by the respiratory controllers which modify the pattern of their drive to the muscles. If this hypothesis is correct one may expect that the adaptation of central drive to the respiratory muscles, which we may call central fatigue, may vary under different conditions. In the example of a low cardiac output state the modification was expressed by a reduction in frequency. It is possible however under different condition to be expressed as decrease in the number or intensity of the outgoing signals to the muscle as occurred in the experiments of Ikai et al. [34] and Bigland Ritchie et al. [9]. Finally, the neuromuscular transmission may serve as an additional protective mechanism of the muscle to avert exhaustion and rigor. However such a mechanism has not yet been shown nor can it as yet be inferred for the respiratory pump.

The substances most directly involved in the transduction of chemical free energy into mechanical work in striated muscles are ATP, ADP, orthophosphate (Pi), hydrogen ion (H^+), magnesium ion (Mg^{2+}) and phosphocreatine (PCr). The force development in muscle is currently accepted to result from the cyclic attachment and detachment of myosin cross-bridges to and from active sites on actin filaments. The energy required for this cycling process of cross-bridges is derived from the hydrolysis of ATP to which the actomyosin ATPase is structurally and functionally integrated. It has been shown that ATP hydrolysis in myosin solutions is reversed in the late stages by high concentrations of product [69]. If a similar effect occurs with actomyosin, changes in product concentrations could well affect cross-bridge cycling and therefore force development. It is also very possible that (H^+) formation affect various stages in the process of contraction [23]. One may argue, therefore, that certain nerve afferents from the fatigued respiratory muscles inhibit the central controllers (for example by stimulating the inhibitory part of the reticular formation) resulting in a decrease in the outgoing signals.

The observation of failure of respiratory frequency to increase in presence of respiratory muscle fatigue is intriguing. Although telelogically it makes sense, it is difficult to explain. Perhaps it is not too difficult to conceive of some negative feedback system at the level of lower motor neurons operating either by antidromic inhibition in the nervous systems or by afferents from one or other of the muscle receptors. However, the decrease in the frequency of discharge of the medullary centers is more complex and difficult to explain.

Pathophysiology of Respiratory Muscle Fatigue

It is helpful in understanding the pathophysiology of respiratory muscle fatigue to further relate force development of the contracting muscle to the energy available for mechanical work output. Admittedly many steps in doing this will only be briefly touched upon. However the simple model of respiratory muscle fatigue that I shall propose emphasises some general principles and questions that need to be confronted.

During muscular contraction leading to exhaustion the total number of ATP molecules hydrolysed may be considered to consist of 1) the number freely available in the muscle and those potentially available in the stored energy source (i.e., glycogen) in the muscle (the energy coming from these two sources may be termed "stored energy" (A)) and 2) the equivalent number of ATP molecules given to the muscle from the circulation. The energy delivered by the circulation during a period t_{lim} can be considered as transferred to the muscle with an average rate, B. Thus, during the t_{lim} the energy offered to the muscles by the circulation will be equal to $B \cdot t_{lim}$. It follows, therefore, that during muscular contraction leading to exhaustion the total amount of energy (C) transformed to work and heat is:

$$C = A + B\, t_{lim} \tag{6}$$

or

$$\dot{C} = \frac{A}{t_{lim}} + B \tag{7}$$

where $\dot{C}$ = average rate of energy consumption

Rearranging Eq. 7 we obtain

$$t_{lim} = \frac{A}{\dot{C} - B} \tag{8}$$

$$= \frac{A}{\dot{W}/E - B} \tag{9}$$

Equation 9 reveals that when $B = \dot{W}/E$ the muscle can continue to work indefinitely without becoming fatigued, but when $B < \dot{W}/E$ there will be a finite endurance time. Thus a decrease in E or B or A will predispose to fatigue as will an increase in muscle power. Combining Eqs. 9 and 5 we obtain;

$$t_{lim} = \frac{A}{\frac{P}{E} \cdot \frac{V_T}{T_I} \cdot \frac{T_I}{T_{TOT}} - B} \tag{10}$$

Equation 10 suggests that apart from A, B and E the respiratory muscles' endurance will be determined independently by the driving pressure, the mean inspiratory flow and the inspiratory duty cycle, all of which, at a given efficiency, determine the rate of energy consumption ($\dot{C}$).

Critical Rate of Energy Consumption ($\dot{C}_{crit}$). Equations 9 and 10 indicate that when $B = \dot{C}$ there is a critical value of the first term of the denominator above which t_{lim} is finite, and below which t_{lim} is undetermined; namely, fatigue will not occur. This value of $\dot{C}$ (when $\dot{C} = B$) is called the critical rate of energy consumption ($\dot{C}_{crit}$). It is obvious from Eq. 10 that $\dot{C}_{crit}$ can be obtained by several combinations of P, V_T/T_I, T_I/T_{TOT} and E.

Critical Pressure. Assigning certain values to T_I/T_{TOT} we may appreciate the state of muscle contraction. When $T_I/T_{TOT} = 1$ it implies that we consider only the period during which a muscle contracts. We face an isometric contraction, during which the V_T/T_I, which may be considered as expressing the mean velocity of shortening, and E approaches zero. But for all practical purposes the ratio of velocity of shortening to efficiency remains constant for a large range of velocities of shortening. Thus, the magnitude of $\dot{C}$ is grossly dependent on the pressure developed. In fact it has been shown with human skeletal muscles during isometric contraction that when they generate forces of about 15% of their maximum, that force can be sustained indefinitely [46, 57]. Similarly assigning different values of V_T/T_I and T_I/T_{TOT} during dynamic contraction, as during breathing, we obtain a certain value of P which we call critical pressure, P_{crit}. Thus, we have measured the critical transdiaphragmatic pressure (Pdi_{crit}) at FRC in humans breathing with a mean inspiratory flow of about 0.4 and Pdi_{crit} was found to be 40% of the maximum Pdi [59], while for all the inspiratory muscles the critical mouth pressure (Pm_{crit}) was found to be 50 – 70% of the maximum mouth pressure (Figs. 8 and 9) [58].

Pressure – Time (P × T) Index. For several years circulatory physiologists have used the product of intraventricular pressure and the time over which it developed as a very useful index of myocardial energy requirements [10, 11, 62]. This assumes that $\dot{C}$ is proportional to the product of pressure and time and requires the assumption

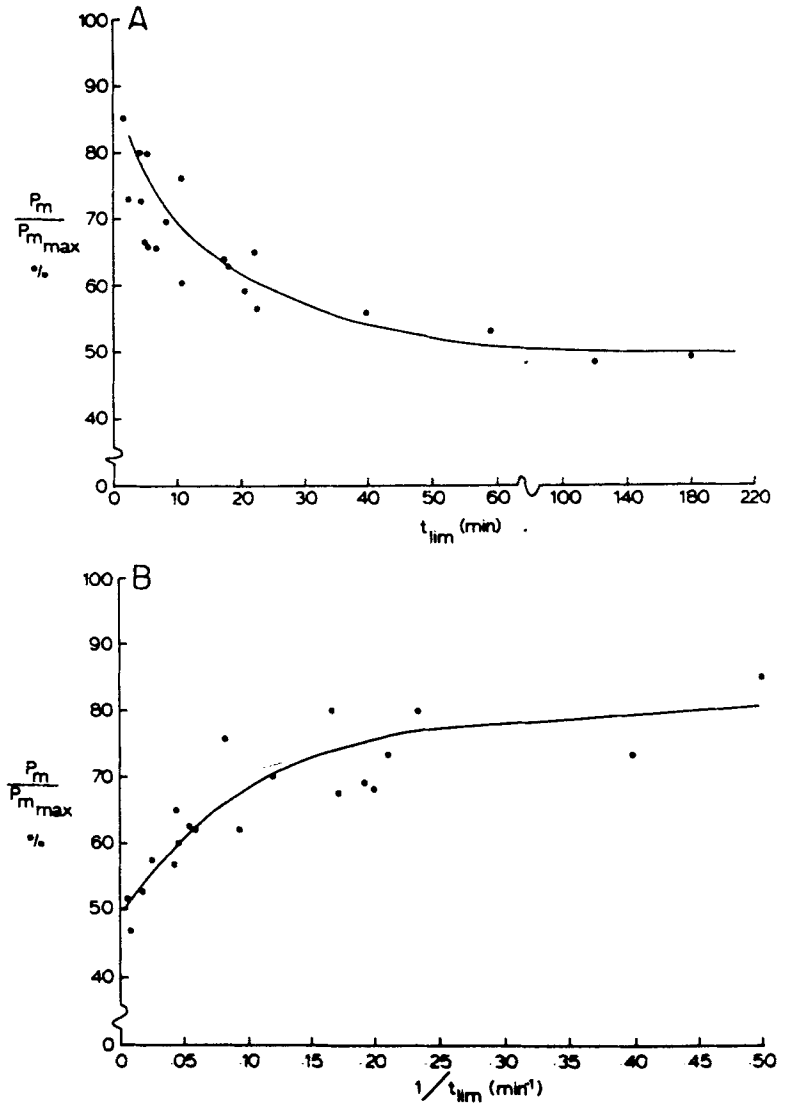

Fig. 8A–B. Mouth pressure (Pm) as a percentage of maximum inspiratory pressure (Pm_{max}) plotted as a function of endurance time (t_{lim}) (**A**) and against reciprocal of endurance time ($1/t_{lim}$) (**B**). Results are shown from one subject. Intercept of best fit curve drawn by eye through date points in **B** gives approximate value of Pm that individual can sustain indefinitely (Pm_{crit}). (After Roussos et al. [58])

that the ratio of the velocity of contraction to efficiency is constant. In fact this assumption has proven to be valid for a large range of velocities of shortening and the tension-time index has proven extremely powerful in the study of myocardial energetics [10, 11]. Furthermore McGregor and Becklake [44] developed a similar relationship for the respiratory musculature. They found a different relationship between mechanical work and oxygen cost of breathing when they compared unload-

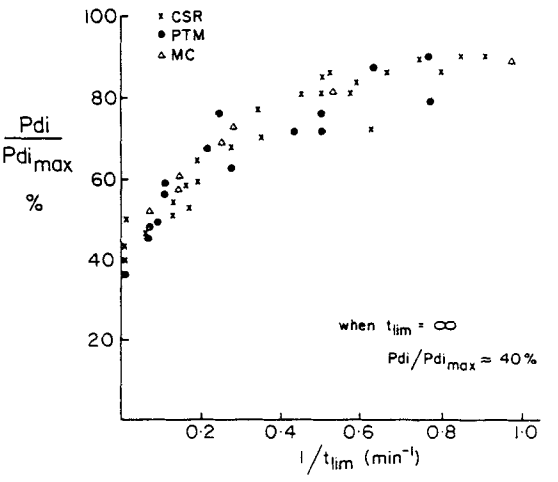

Fig. 9. Relationship between Pdi/Pdi_{max} and reciprocal of endurance time ($1/t_{lim}$). Intercept of curve gives as in Fig. 8B, the Pdi_{crit} (after Roussos and Macklem [59])

ed hyperventilation to breathing through resistances. However the relationship between the tension and the oxygen consumption was the same for the two conditions. More recently a linear relationship between oxygen cost of breathing and Pdi · t has been demonstrated in dogs [56].

We have also used the Pdi-time index in humans in order to compare the endurance of the diaphragm under normoxic and hypoxic conditions [59] under equal rates of energy consumption. Hypoxia increased the inspiratory time and T_I/T_{TOT}; therefore, at a given P, $\dot{C}$ is increased. Thus by altering the inspiratory duty cycle the comparison of endurance time at equal P is incorrect, because the higher the T_I/T_{TOT} the greater the $\dot{C}$ will be, as indicated in Eq. 10 by the fact that t_{lim} will be shorter. The relationship of T_I/T_{TOT} to the critical pressure has also been studied by Bellemare and Grassino [7]. As predicted, the Pdi_{crit} becomes smaller as T_I/T_{TOT} increases (Fig. 10).

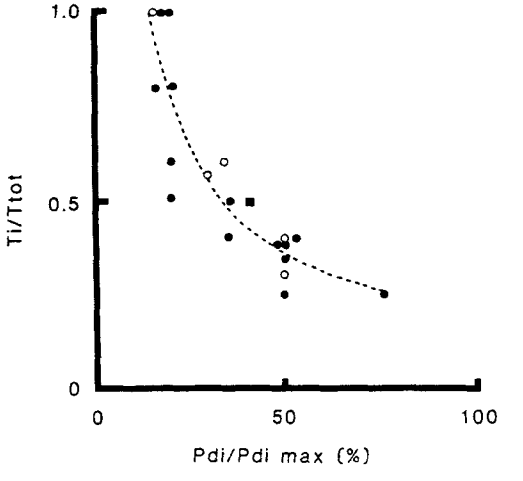

Fig. 10. Relationship of T_i/T_{tot} (duty cycle) to critical transdiaphragmatic pressure expressed as % of Pdi_{max}. Note that Pdi_{crit} becomes less as the T_i/T_{tot} increases. Different symbols indicate different subjects (derived from Bellemare and Grassino [7])

Table 2. Factors predisposing to inspiratory muscle fatigue

1) Imbalance of energy supply and demands
   A) Factors determining energy available
      a) oxygen content (Hb concentration, O_2 saturation)
      b) blood flow (cardiac output, distribution of perfusion, ability to increase perfusion)
      c) stores of substrates (nutrition, previous exercise)
      d) blood substrate concentration
      e) ability to extract energy sources
   B) Factors determining energy demands
      a) work of breathing, ($\dot{V}_E$, V_T, f, T_I/T_{TOT}, resistance, compliance)
      b) efficiency of respiratory system (breathing through resistance vs. hyperventilation, nutrition)
      c) strength (lung volume, atrophy, prematurity, neuromuscular disease, nutritional status)
2) Alteration of "Milieu interne"
   Acidosis, histochemical adaptations, drugs

Factors Predisposing to Inspiratory Muscle Fatigue. Perusing the equations of the preceding section, we can draw some logical conclusions regarding the factors that predispose the inspiratory muscles to fatigue. Regardless of the ultimate cause of skeletal muscle fatigue, there is no question that fatigue occurs when the energy demand of the muscle exceeds the ability of the blood to supply sufficient energy. We can also envisage situations which may predispose to respiratory muscle fatigue in the absence of shortage in chemical energy, such as general acidosis. For convenience we name these eonditions affecting the "milieu interne" (Table 2).

Of paramount importance with regard to the energy supply is the blood flow to the muscle, which is determined by the cardiac output and by the ability of the muscles to increase their blood flow in parallel to the increase of the work output. We have shown the significance of this factor in animals developing respiratory muscle fatigue even at a very modest level of ventilation [2]. The state of contraction of the muscle is a crucial determinant of its blood perfusion even with normal circulation. Muscle blood flow is impaired as the intensity of muscle contraction increases and perfusion stops completely at 70% of the maximum force [6, 33]. Thus, if during expiration the inspiratory muscles do not relax, as may well be the case in asthmatic patients [43, 49], the overall blood flow to the muscles will be limited predisposing them to fatigue. The diaphragm, however, appears to have a unique ability to increase its blood flow. Robertson et al. [55] have shown that blood perfusion increases exponentially as the work of breathing increases while Donovan et al. [18] have shown that during isometric contraction the diaphragm in dogs increases its blood flow as the intensity of contraction increases. The diaphragmatic blood flow does not appear to plateau even at very high or maximum contraction of the muscle.

The amount of energy supplied to the inspiratory muscles is largely determined by blood perfusion as well as by the oxygen content of the blood which in turn depends on the hemoglobin concentration and hemoglobin saturation. Thus hypoxemia [36, 59], low cardiac output states, and anemia should predispose the respiratory muscle to fatigue.

Other factors whose importance is less easy to predict that should determine energy supplies are the concentration of substrate in the blood, affected by nutritional factors, and the ability of the muscle to extract oxygen and other substrates.

With regard to energy demands in pathological conditions characterized by airways obstruction or stiff lungs, there is an increased work of breathing stemming from hyperventilation or by the suboptimal pattern of breathing which increases the energy demands of the working muscles. If the rate of energy consumption exceeds the $\dot{C}_{crit}$, fatigue will ensue.

Muscle efficiency is an important factor in determining the energy demands. Differences in efficiency resulting perhaps from differences in respiratory rate and depth are the most probable reasons leading various investigators in the past to observe large differences in the level of minute ventilation which normal subjects can maintain indefinitely [25, 39, 65, 68, 71]. The significance of efficiency of the respiratory muscles has also been pointed out by McGregor and Becklake [44] who found that the respiratory muscle efficiency, for the same external power produced, decreased under different conditions. When breathing through resistances, some respiratory muscles may contract only to stabilize the chest wall thus performing a quasi-isometric contraction [42]. This implies an energy expenditure without production of work. Consistent with this notion is the discrepancy between the values for critical power estimated in our laboratory [58] and those obtained by Tenney and Reese [68]. When breathing through a resistance, in our experiments the estimated critical power amounted to 15 cal/min as compared to 100 cal/min found by Tenney and Reese during voluntary isocapnic hyperventilation.

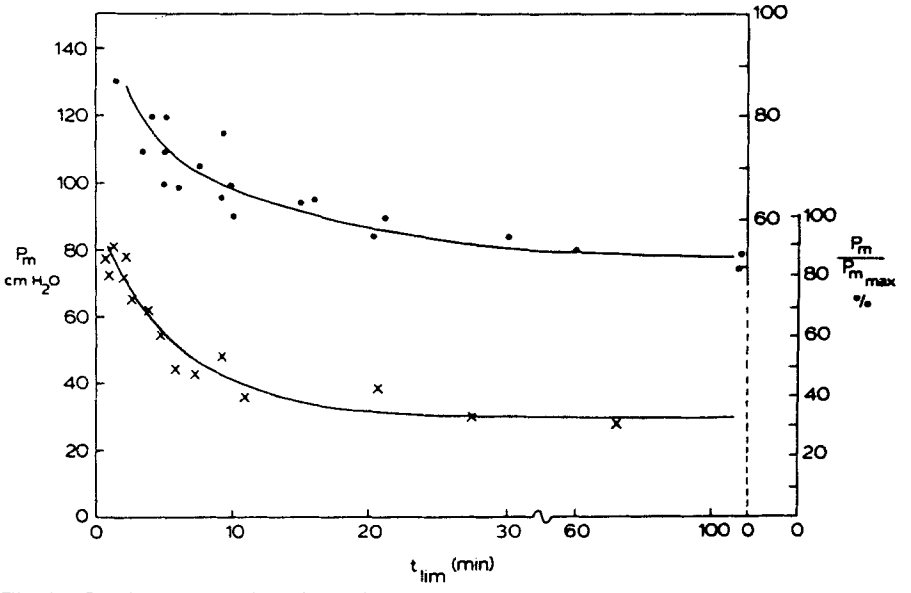

Fig. 11. Inspiratory muscle fatigue. Effect of lung volume on endurance time. Left ordinate: mouth pressure as percent of maximum (Pm/Pm_{max}) at FRC (●); right upper ordinate: Pm/Pm_{max} (%) at FRC; right lower ordinate: Pm/Pm_{max} (%) at FRC + ½ IC (×). Note difference in asymptotic value of Pm/Pm_{max} at high lung volumes (×); i.e. Pm_{crit} is substantially less at high lung volumes (after Roussos et al. [11])

The greater the pressure required by the inspiratory muscle, (a fraction of the maximum pressures that can be developed by these muscles) the greater are the energy demands, which, when exceeding the $\dot{C}_{crit}$, will lead to fatigue. This fraction of maximum pressure can increase not only by increasing the driving pressure required to overcome high loads but also by diminishing the maximum pleural pressure that can be generated. Three conditions applicable to the respiratory muscles are particularly pertinent: atrophy of respiratory muscles which may well be the situation after prolonged artificial ventilation or poor nutrition or neuromuscular disease; immaturity of the diaphragm as may occur in premature infants; and hyperinflation, the mechanism which was discussed previously and is a very important factor in patients with obstructive airway diseases. The effect of hyperinflation on respiratory muscle fatigue is shown in Figure 11.

With regard to the alteration of the "milieu interne" we refer to factors that are not apparently involved with a shortage of energy. Acidosis is an example. Metabolic or respiratory acidosis can impair the contractility of the myofilaments by disturbing various stages in the activation of contraction [23]. Hypophosphatemia or pharmacological agents that patients with respiratory diseases receive for other reasons may predispose the respiratory muscles to fatigue. For example antimicrobiological agents which have a curare-like effect [3, 19] or the drug dantrolene sodium [48] which is used to treat spasticity may impair the excitation contraction coupling process. Disuse of the respiratory muscles does not only produce loss of muscle mass but also an alteration in the histochemical characteristics of the muscle [60, 61]. Thus inactivity of the diaphragm during prolonged artificial ventilation may result in a decrease in the population of the oxidative fibers, which will predispose the diaphragm to fatigue.

From the preceding discussion it is easy to predict the situations in health and in disease where respiratory muscle fatigue is a potential hazard. These situations are summarized Table 3.

Table 3. Conditions likely predisposing to respiratory muscle fatigue

1) Asthma, bronchitis, emphysema
2) Severe interstitial lung disease
3) Severe respiratory distress syndrome, pulmonary edema
4) Low cardiac output state
5) Kyphoscoliosis, obesity, ankylosing spondylitis
6) Prolonged artificial ventilation
7) Catabolic states (i.e, septic shock), extreme inanition
8) Premature birth
9) Neuromuscular disorders (Guillain Barré, multiple sclerosis, poliopyelitis, amyotrophic lateral sclerosis, muscular dystrophy, rhabdomyolysis, *myasthenia gravis*)
10) Dermatomyositis, polymiositis, scleroderma
11) Acidosis, hypophosphatemia
12) Drugs (i.e., antimicrobial agents)
13) Hormonal disorders? (?hyperthyroidism)
14) Exercise

Detection of Weakness of the Ventilatory Pump

The techniques that will be briefly described are applicable to humans.

Measurement of Force

From the definition of weakness and fatigue it is implicit that techniques which measure force directly or by inference will be informative for either effort independent weakness or fatigue. However to detect whether one or the other or both conditions occur, the history of the patient will in most cases provide essential information in assessing the situation. At a given point in time in the course of a disease for example a low value of the maximum pleural pressure (Ppl), mouth pressure (Pm), and transdiaphragmatic pressure (Pdi) or a low value of Pdi developed after electrophrenic stimulation (see below) may be a result of either effort independent weakness (e.g. atrophy) or fatigue or both. However, a gradual decrease in the Ppl, Pm or Pdi from normal values, particularly in a period of hours, in a patient subjected to high inspiratory loads indicates that respiratory muscle fatigue is likely to be present.

A good index of respiratory muscle strength is the maximal inspiratory or expiratory mouth pressure (Pm_{max}). A decrease in Pm_{max} may indicate fatigue or effort independent weakness e.g. hyperinflation. Thus, in assessing respiratory muscle strength, it is important to know the lung volume. Simultaneous recording of

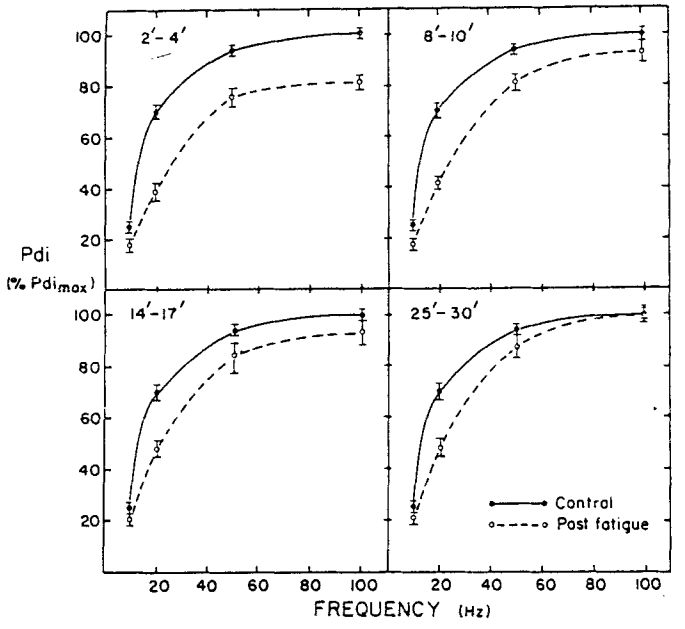

Fig. 12. Transdiaphragmatic pressure (Pdi) at different frequencies of supramaximal transcutaneous stimulation of phrenic nerve in man. Solid line shows the relationship obtained with fresh muscle. Broken line shows the relationship obtained at different intervals during the recovery period following a breathing task against very high inspiratory resistance (see text). (After Aubier et al. [1])

esophageal and gastric pressure provides information about diaphragmatic function. However both Pm_{max} and Pdi_{max} require good cooperation.

In our laboratory Aubier et al. [1] have recently described a new test for detecting diaphragmatic strength and fatigue at FRC. This test measures the Pdi during supramaximal stimulation applied to one phrenic nerve transcutaneously in the supraclavicular area at different frequencies (f). In Fig. 12 the solid line indicates the Pdi–f obtained in normal subjects. The broken line shows the evolution of Pdi–f after the subject breathed through resistances until exhaustion. It appears that immediately after the test the Pdi diminishes at all f. However at 30 min the Pdi at high f is back to normal while it remains low at low f. This behaviour appears also in other skeletal muscles and has been interpreted by Edwards et al. [20] to indicate different sites of fatigue. According to them the loss of pressure at high f (high frequency fatigue) is due to the impairment of function at the neuromuscular junction while the long lasting element of fatigue at low f (low frequency fatigue) is due to impairment of the excitation concentration coupling process.

In the measurement of lung volumes (provided that the elastic recoil of the lung and chest wall are within the normal range and that the patients perform maximally), a decrease in TLC or an increase in RV and thus a decrease in VC is suggestive of respiratory muscle weakness. This reasoning follows from the fact that the two extreme volumes are determined by two opposing forces, the elastic recoil of the chest wall and lung and the forces exerted by the inspiratory (TLC) or expiratory (RV) muscles.

Fluoroscopy may be a useful technique in the evaluation of diaphragmatic function. The paralysed diaphragm is usually immobile during quiet breathing and in some cases it moves paradoxically. The sniff test is used to diagnose diaphragmatic paralysis and theoretically may be used to diagnose any kind of diaphragmatic weakness. The diaphragm is observed fluoroscopically during a sudden sniff. When the diaphragm is weak, the other respiratory muscles produce a decrease in the intrapleural pressure, which draws the paralyzed diaphragm into the chest. However a small percentage of normal persons show unilateral paradoxical movement. Furthermore contraction of abdominal muscles with upward displacement of the weak diaphragm followed by abrupt cessation of abdominal activity in early inspiration results in passive descent of the diaphragm which can be interpreted as normal diaphragmatic motion.

Electromyographic Studies

The EMG of the diaphragm and intercostal muscles may help in distinguishing between neuropathic and myopathic diaphragmatic dysfunction as well as in detecting fatigue [27, 50, 63]. Absent or minimal EMG activity during a maximum inspiratory effort strongly suggests disturbance of the nerve and/or the muscle. A promising technique still under experimental investigation is the frequency spectrum analyses of the EMG for detecting fatigue of the inspiratory muscles [27, 50, 63]. It has been shown that with the development of fatigue in a skeletal muscle, the low frequency components (L) of the EMG increase in amplitude, whereas the high frequency components (H) decrease for the same tension developed. Thus the ratio of H/L decreased in the course of fatigue.

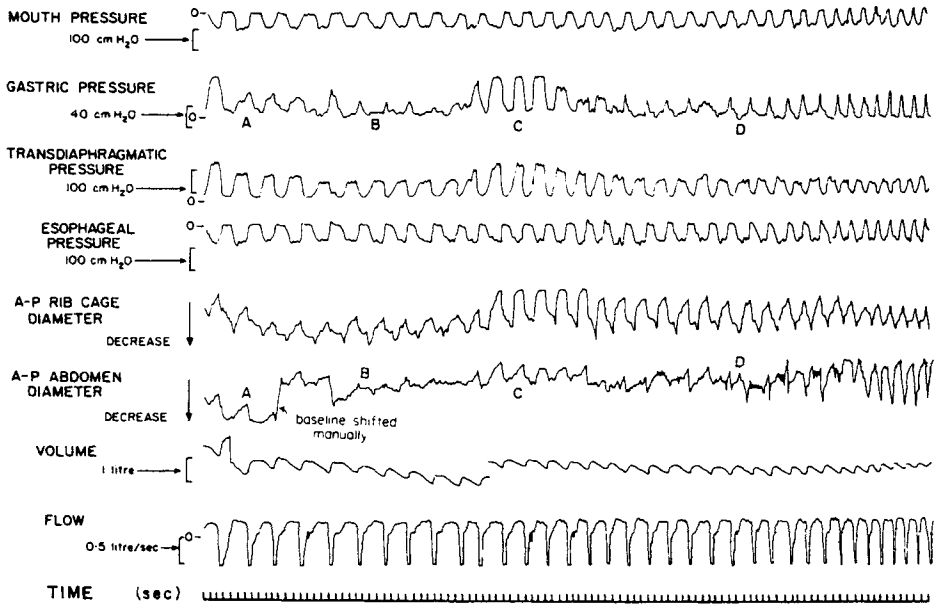

Fig. 13. Typical tracing from normal subject breathing through high inspiratory resistance. Swings in mouth and esophageal pressure remained constant; those in gastric pressure (Pg) and Pdi varied. Increase in Pg during inspiration was associated with an increase of anteroposterior (AP) diameter of the abdomen (Periods A and C); where Pg did not change, AP diameter of abdomen did not change much (Period B); when Pg decreased, AP diameter also decreased (Period D). Note the cycling variation of Pdi. (After Roussos et al. [58])

Clinical Signs of the Failing Ventilatory Pump

With a paralyzed diaphragm, during inspiration the abdominal wall, particularly in the supine position, moves inward. This is an important clinical sign. This paradoxical movement is not only easy to quantitate with magnetometers and by measurements of gastric pressure, but is also easy to detect by simple inspection.

In normal subjects and in patients with respiratory muscle fatigue chest wall discoordination is a common finding. Figure 13 characterizes subjects breathing through a resistance until exhaustion [58]. It is to be noted that the respiratory frequency increases. One also notes that although the mouth pressure is kept constant there are cyclic variations in abdominal pressure, which are followed by outward or inward displacement of the abdominal motion. The fact that mouth pressure remains constant, while the Pdi shows cyclic variation, indicates that for some breaths the diaphragm contracts more forcefully than other muscles. Finally, the tracing shows a fall in abdominal pressures during inspiration towards the end of the run, followed by an inward inspiratory abdominal displacement, which can also be observed during bilateral diaphragmatic paralysis.

The above clinical manifestation of respiratory muscle fatigue was studied in patients being weaned from artificial ventilation whose inspiratory muscles had become fatigued, as assessed by the spectrum analysis of the EMG (Fig. 14). Thus from our studies in normal subjects and in patients, three clinical manifestations

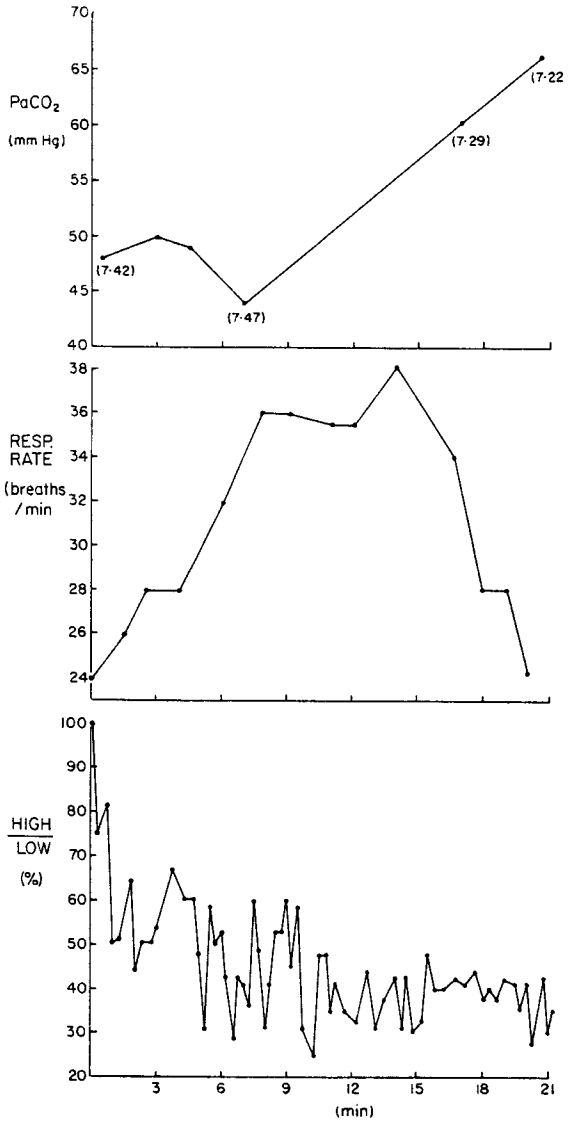

Fig. 14. Measurements obtained from a patient with respiratory failure during the weaning period. $PaCO_2$ for short period of time remained unchanged as well as pH (values in brackets), while subsequently PCO_2 increased and pH decreased. Respiratory rate started to increase very early simultaneously with the drop of the high/low ratio (an index of shift of the power spectrum of the electromyogram during fatigue). Note that respiratory rate towards the end decreased; patient at that time returned back to respirator

may predict inspiratory muscle fatigue: 1) Rapid shallow breathing followed by bradypnea, 2) alternation between predominantly abdominal and predominantly rib cage displacements during inspiration, and 3) abdominal paradoxical motion. Given these findings it is possible that the "discoordination" of the chest wall in patients with respiratory failure reported by Ashutosh et al. [4], Sharp et al. [64] and Pontoppidan et al. [54] may well have been a sign of respiratory muscle fatigue. Teleologically this discoordination may protect the inspiratory muscles from exhaustion. Thus, patients breathing against high loads may alternate the contribution of the various muscles to the breathing task, so that when the diaphragm works predominantly, the intercostals/accessories rest and vice versa.

Therapeutic Implications

How can the physician prevent or treat failure of the ventilatory pump? Certainly, mechanical ventilation is, in many cases, a viable option. According to the animal experiments described earlier [2], in patients with low cardiac output the mortality rate should be reduced by artificial ventilation. In this situation, artificial ventilation will markedly decrease the O_2 consumption of the respiratory muscles, making it available to other organs. Artificial ventilation also decreases the energy demands of the working muscles, anaerobic metabolism is decreased and lactic acid production is reduced.

The only known treatment for muscle fatigue is to rest the fatigued muscles which can be accomplished either by unloading the respiratory muscles, with bronchodilators, for example, or by correction of pulmonary edema, or by instituting artificial ventilation. In Fig. 11 it appears that a long lasting element of fatigue (low frequency fatigue) persists for a long time. It is therefore possible that patients subjected to high respiratory loads for a long time develop a state of chronic fatigue; in this case intermittent assistance may be indicated.

Skeletal muscles, including the respiratory muscles can be trained to increase their endurance and strength [28, 39]. Although little is known, as yet, about this approach, it is unquestionably most promising and deserves the full attention of future physiotherapeutic approaches so that we may learn more about the efficacy of the various training techniques.

Finally, respiratory muscle failure may be treated with appropriate medication, as for heart failure. Our recent findings regarding the effect of xanthines and catecholamines on the fatigued diaphragms are encouraging (unpublished observation). We have found that aminophylline rapidly restores the Pdi of the fatigued diaphragm either in animals or in humans.

Epilogue

The only synopsis of a review confronting a topic as vast and as challenging as respiratory failure is Whitehead's aphorism: "seek simplicity and then distrust it". Indeed, the rapidly accumulating research on the topic points towards what seems to be the simplest and most logical options; however, it has been my hope that this brief review suggests that further probing of the critical mind will surpass the simplistic notions which lie at the threshold of the more tantalizing complexities of respiratory muscle fatigue. Respiratory muscle fatigue unquestionably exists and it can be responsible for the development of respiratory failure. However, it seems that it is not just an isolated event limited to the muscle; it is probably the result of an interplay between the respiratory muscles and the nervous system in the chain of events leading to respiratory failure.

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Accepted for publication: 27 March 1981