Intensive Care Med (1993) 19: S64–S68

Intensive Care Medicine

Respiratory muscles: working or wasting?

M. Aubier

Unité de Pneumologie, Inserm U.226, Hôpital Bichat, Paris, France

Introduction

Fatigue can be either local, affecting a single muscle, or generalised, after exhausting the whole body, as in exercise. Presumably the factors limiting performance are different with the two types of fatigue. Almost all studies of skeletal muscle fatigue are acute, fatigue having developed over the period of an hour or less in a previously normal (fresh) muscle. Virtually nothing is known about chronic fatigue, a state in which the muscle has not yet recovered from previous effort. Despite our incomplete understanding, chronic fatigue of the inspiratory muscles may be common. As with skeletal muscle fatigue, respiratory muscle fatigue can be defined as an inability of the respiratory muscles to continue to develop sufficient respiratory pressure swings to maintain normal alveolar ventilation. In contrast to skeletal muscle, respiratory muscle fatigue is characterised by two unique features: a) because the muscles are essential for life, fatigue is life-threatening; b) the respiratory muscles and particularly the diaphragm present some peculiarities among the skeletal muscles. Indeed the diaphragm must contract phasically during life and thus functionally appears to be closer to the myocardium than to limb muscles.

Mechanisms of respiratory muscle fatigue

The respiratory muscle may be considered as an engine in which fatigue occurs when the rate of energy consumption by the muscle is greater than the energy supplied by the blood (B). Under these circumstances, the muscles draw on energy stores that, when depleted, result in failure of the muscle as a force generator. The oxygen cost of breathing is defined as the ratio of the external power (W) performed by the inspiratory muscles to their efficiency (E) [1]. If $W/E < B$ (Equation 1), the muscle can continue to work indefinitely; if $W/E > B$, there will be a finite endurance time.

$W = P \times V_T \times F$, where V_T is the tidal volume, F is the frequency of breathing, and P is the pressure generated by the inspiratory muscles.

This equation becomes $W = P \times V_T \times (1/T_{tot})$, were T_{tot} represents the tidal respiratory cycle period, as $F = 1/T_{tot}$. When the numerator and the denominator are multiplied by the inspiratory time T_I, the equation becomes $W = P \times (V_T/T_I) \times (T_I/T_{tot})$. (V_T/T_I) denotes the mean inspiratory flow and T_I/T_{tot} the ratio of inspiratory time to breathing cycle total duration. The critical power or workload (W_{crit}) above which fatigue occurs is given by the equation $W_{crit} = P_{crit} \times (T_I/T_{tot}) = B.E$, where P_{crit} denotes the critical pressure above which fatigue occurs. One can deduce from the latter equation that fatigue can occur if V_T/T_I (which reflects the central respiratory drive) increases [2, 3], if T_I/T_{tot} increases, or if P_{crit} increases. Of course, the values of the two other variables depend on the value of P_{crit}. The critical pressure above which diaphragmatic fatigue occurs is 40% of the maximal transdiaphragmatic pressure (P_{dimax}) for an inspiratory flow of 0.5–1 l/s and a T_I/T_{tot} ratio of 0.4–0.5.

Bellemare and Grassino [4,5] described an index of diaphragmatic fatigue called the tension time index (T_{Tdi}) of the diaphragm. The measurement of the T_{Tdi} gives an indication of how fatiguing a breathing pattern is. T_{Tdi} can be expressed as the product of T_I/T_{tot}, and mean P_{di} can be expressed as a fraction of P_{dimax}. The cutoff level of fatigue in normal subjects [4,5] and in patients with chronic obstructive pulmonary disease [6] is between 0.15 and 0.20. Below this level, ventilation can be maintained indefinitely. Above this level, fatigue does occur; the higher the index, the faster fatigue and respiratory failure will develop. During spontaneous breathing, the T_{Tdi} of a normal subject is approximately 0.02, which is well below the fatigue level.

One can deduce from equation 1 that the factors predisposing to inspiratory muscle fatigue ($W < B.E$) are either an increase in energy demand of the muscles, or a decrease in energy stores; i.e. fatigue occurs when energy falls or efficiency is reduced.

Factors determining inspiratory muscle energy demand

The work of breathing: The level of minute ventilation, the frequency of breathing, a decrease in lung compliance, or an increase in airway resistance increase the work of breathing and energy demands of the muscle. A hyperstimulated central respiratory drive likewise imposes an increased inspiratory muscle work of breathing.

Muscle strength: The greater the fraction of the maximum pressure that can be developed by the inspiratory muscles, the greater their energy demands. This fraction can be increased either by increasing the pressure necessary to breathe (e.g., increased airway resistance) or by reducing the maximum force that the muscle can develop (hyperinflation, muscle atrophy). Hyperinflation [7,8], which is usual in patients with chronic obstructive pulmonary disease (COPD), shortens the diaphragmatic fibres and thus reduces the maximal force of the diaphragm (maximal force being a function of initial fibre length).

Efficiency: For a given workload, the energy demands and oxygen cost of breathing increase as efficiency decreases. Efficiency decreases as airway resistance increases [9]. In this condition, there is hyperinflation leading to a flatness of the diaphragm, which in turn acts as a fixator and not as an agonist (quasi isometric contraction). This requires energy expenditure without useful work.

Factors determining available inspiratory muscle energy

The energy supply: A decrease in energy supplies to a muscle can be observed when muscle blood flow decreases (low cardiac output [10] and increased force of diaphragmatic contraction); when the O_2 content of arterial blood decreases (anaemia, hypoxaemia) [11], and when the ability to extract sources of energy decreases.

The energy stores: Poor nutritional status, catabolic states (sepsis), and depletion of glycogen by prolonged hyperventilation may all facilitate the occurrence of muscular fatigue.

Muscle blood flow and fatigue

The fact that the diaphragm fatigues beyond a critical rate of tension-time strongly suggests an association between the rate of work, a limitation on the diaphragmatic capacity to extract or consume oxygen, and the blood flow to the diaphragm. This association implies as well that peripheral muscle fatigue is a consequence of the same mechanism.

Lind and McNicol [12] found that the circulation to the isometrically contracting forearm increased as a function of the tension developed, up to 30% of maximal tension. At tensions below 15% of maximum, flow increased to a plateau in less than 1 min, and, when contraction stopped, flow decreased to control levels. However, at tensions higher than 15% of maximum, flow increased progressively for over 5 min, and, when the exercise was interrupted, blood flow increased even further (postexercise hyperaemia). This was interpreted as indicating that, in isometric contractions held at 15–20% or more of the maximum force, the blood supply was insufficient for the requirements of the muscles: the resulting blood deficit or "debt" accumulated during the contraction had to be repaid during the postexercise hyperaemia. In addition to the energy supply aspect, the extra flow may be required to wash out catabolites accumulated during the contractions.

In intermittent strong contractions, blood flow decreased considerably during the contraction and increased during the resting period. Bellemare et al. [6] measured blood flow in the diaphragm of the dog during bilateral phrenic stimulation (the diaphragm was stimulated with various intensities and contraction/relaxation intervals (duty-cycle) and found a postexercise hyperaemia when tension increased beyond 15–20% of maximum. In addition, they observed that at any given tension the blood flow to the diaphragm decreased with increased duty-cycle. By plotting diaphragmatic flow as a function of T_{Tdi}, they found an unique relationship: flow increased in contraction patterns held up to a T_{Tdi} of about 0.20, then decreased. Postcontraction hyperaemia became evident at a T_{Tdi} of about 0.15 and increased progressively with high T_{Tdi}. This was interpreted as indicating that a "fatiguing" contraction may result from insufficient blood flow to meet the energetic demand or to wash out catabolites even though blood flow increases. With increases in T_{Tdi}, the blood flow deficit grows and the period during which contraction can be sustained becomes shorter. The validity of this dog model in relation to human subjects breathing naturally remains to be tested.

The importance of inadequate blood flow as a cause of respiratory muscle fatigue was emphasised by Aubier et al. [10] in another dog model in which breathing was unloaded and blood flow was limited by cardiogenic shock. Under these conditions, all spontaneously breathing animals died of respiratory arrest when the respiratory muscles failed to generate sufficient pressure to maintain alveolar ventilation despite an increase in phrenic nerve output. This was an example of fatigue due not to an increase in energy demand but to a decrease in energy supply alone.

All of the above seem to contrast with previous observations made by Rochester and Bettini [13], who failed to see limitation in blood flow to the diaphragm in anaesthetised dogs breathing spontaneously with inspiratory resistances. However, Bellemare et al. [6] observed that the T_{Tdi} at which maximal diaphragmatic flow was measured by Rochester and Bettini [13], was below the level expected to produce blood flow limitation.

Respiratory muscle blood flow is not easy to evaluate in human subjects. However, O_2 consumption by the respiratory muscles is easily measured and represents a good index of their metabolic needs. The O_2 cost of breathing was found to be high in COPD patients, in sepsis and in shock [14]. These patients are at high risk of developing respiratory muscle fatigue and failure. Recently, Pardy et al. (personal communication) found good evidence of diaphragmatic fatigue at the end of exhaustive exercise in normal subjects at 80% of maximum workload. This occured at a T_{Tdi} of less than 0.15. The authors suggested that under these circumstances there was "competition" between the exercising muscles and the inspiratory muscles for the available cardiac output. As a result, the energy supply to the diaphragm was presumably less than it would have been had it been performing the same work while the subject was not exercising.

Surprisingly, the situations during cardiogenic shock and exercise at 80% maximum workload appeared to be analogous. Both are characterised by a cardiac output inadequate to meet the needs of the body tissues. In both, this results in lactic acidosis. As a result of the "competition" between the various body tissues for the available sources of energy, the diaphragm may become fatigued at levels of activity below the fatigue threshold under conditions of normal perfusion.

Acute respiratory failure and respiratory muscle fatigue

Respiratory failure may result from either a failure of the lungs due to airway obstruction and parenchymal disease, or a failure

of the respiratory muscle pump; the former leads to hypocapnia or normocapnia, the latter to alveolar hypoventilation with hypercapnia and hypoxaemia. The failure of the respiratory muscles can itself generate an acute respiratory failure [15]. Nevertheless, the muscle failure is most often a consequence of lung failure [16]. Secondary failure of the respiratory muscles may occur as a result of CNS respiratory centre depression, as, for example, in drug overdose.

Does respiratory muscle fatigue really exist during acute respiratory failure? This point will be discussed by reviewing some clinical conditions of acute respiratory failure.

Chronic obstructive pulmonary disease

In patients with COPD in acute respiratory failure, some factors predispose to the occurrence of respiratory muscle fatigue. The respiratory centres are hyperstimulated, which increases the workload of the respiratory muscles [2]. This workload is also increased by the high airway resistances. The efficiency of the respiratory muscles is impaired by hyperinflation [7] and by airway resistances. In the extreme case, the diaphragm contracts isometrically, i.e., with energy demand without production of work. Furthermore, the acute respiratory acidosis itself decreases the contractility and endurance time of the diaphragm in humans and thus could lead to respiratory muscle fatigue.

The oxygen cost of breathing is increased in COPD patients [14], but it is unclear whether muscle blood flow is maintained at an adequate level in relation to muscle workload. It is known that muscle blood flow increases when contractile activity increases. However, beyond a critical level [6], mechanical compression of diaphragmatic vessels decreases blood flow. When one adds to this factor the effect of cor pulmonale and right heart failure, which may impair cardiac output, respiratory blood flow may decrease below levels required to adequately supply substrates and oxygen.

In the literature, there is some evidence for the existence of respiratory muscle fatigue in acute respiratory failure in COPD patients. In these patients, signs such as paradoxic motion of the abdominal wall during the breathing cycle, or thoracic alternans are frequently observed.

Bellemare and Grassino [5] measured the T_{Tdi} of resting ventilation in 20 patients with COPD. T_{Tdi} ranged between 1% and 12% of maximum P_{di}, even though the fatigue threshold of the human diaphragm in normal subjects is 15% of maximum P_{di}. In COPD patients, the T_{Tdi} was significantly related to total airway resistance. When the subjects were asked to modify T_I/T_{tot} by increasing inspiratory time, the fatigue threshold was easily exceeded with a reduction in the high to low ratio of the diaphragmatic EMG. It was concluded that the force reserve of the diaphragm of COPD patients is decreased because of a decrease in maximum P_{di} and that the diaphragm is exhausted by minor modifications of the breathing pattern, the fatigue threshold being easily reached in these patients.

Esau et al. [17] demonstrated that the relaxation rate of the diaphragm was increased in the case of diaphragmatic fatigue and was closely correlated with the modifications of the high to low ratio of the diaphragmatic EMG. Mal et al. [18] have also shown in 14 COPD patients, intubated and ventilated for acute respiratory failure, that the relaxation rate of the diaphragm measured just after intubation significantly decreased toward the range of normal values before extubation. This attests to the fact that respiratory muscle fatigue probably exists in these patients at the onset of acute respiratory failure and that it is reversed by mechanical ventilation.

In another study on the same type of patients, who were intubated and ventilated for acute respiratory failure, Murciano et al. [19] showed that, at the onset of acute respiratory failure, the patients had high occlusion pressure ($P_{0.1}$) values (Fig. 1) (hyperstimulated respiratory centers) associated with a decreased high to low ratio of the diaphragmatic electromyogram (EMG) (Fig. 2), an index closely related to diaphragmatic fatigue. After a few days of mechanical ventilation, most of the patients were successfully weaned from the respirator, with a significant decrease in $P_{0.1}$ and a significant increase in the high to low ratio. Nevertheless, some patients had to be reventilated within 48 h of extubation. In these patients, the high to low ratio did not increase and $P_{0.1}$ did not decrease. These patients probably had persistent fatigue of the respiratory muscles, requiring a longer period of artificial ventilation.

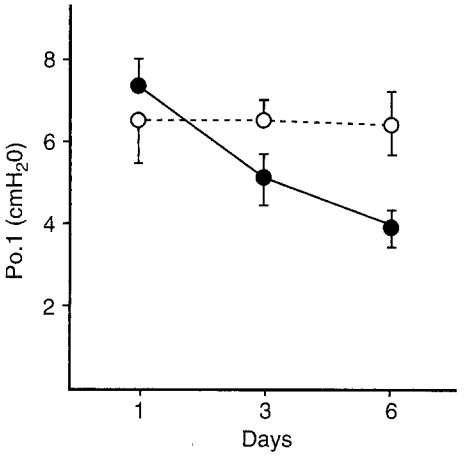

Fig. 1. Tracheal occlusion pressure ($P_{0.1}$) from the onset to the end of the acute respiratory failure. ●——●, mean values for 11 patients who were successfully weaned; ○- - -○, mean values for 5 patients who had to be reintubated. Bars indicate 1 standard error. BE – before extubation.

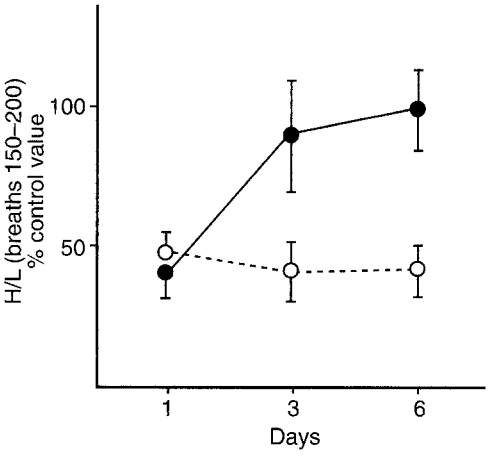

Fig. 2. High-to-low ratio (H/L) of the diaphragmatic EMG from the onset to the end of the acute respiratory failure. Each point represents the average value of the ratio for 50 breaths (between breath 150 and 200 after the patients have been taken off the ventilator). Symbols as in Fig. 1.

Cardiogenic shock

During cardiogenic shock with or without pulmonay oedema, factors predisposing to respiratory muscle fatigue are present [15]. The work of breathing is increased in pulmonary oedema (hyperventilation, stiff lungs resulting in an increased O_2 demand by respiratory muscles). Concomitantly, there is an inadequate O_2 delivery to the respiratory muscles [20] secondary to hypoxia and decreased cardiac output. The lactic acidosis resulting from the inadequate O_2 delivery to the tissues will, in turn, further increase ventilation and respiration and thus the work of breathing, which could lead to respiratory muscle fatigue. The latter could be an explanation for hypercapnia, sometimes observed during acute pulmonary oedema. Aubier et al. [10] and Viires et al. [21] provided evidence that the development of an imbalance between diaphragmatic metabolic demands and blood flow may result in diaphragmatic fatigue in this situation.

Septic shock

During sepsis, a sustained increase in protein catabolism has been reported in skeletal muscles, with skeletal muscle contractile proteins being used or consumed to provide amino acids. Furthermore, hyperventilation increases pulmonary resistance and decreases lung compliance while increasing the work of breathing and the energy demand of the respiratory muscles. Decreases in blood pressure and cardiac output, which may occur in septic shock, decrease the energy supply to the respiratory muscles. In addition, muscle oxygen extraction is impaired. Thus, fatigue of respiratory muscle is expected in septic shock. In a model of endotoxic shock in spontaneously breathing dogs, Hussain et al. [22] provided evidence of respiratory muscle fatigue. Boczkowski et al. [23] studied the effects of a 3-day pneumococcal infection on diaphragmatic strength and endurance capacity in an in vivo rat model, the inoculated rats being compared with control rats. The diaphragmatic strength was assessed by measuring P_{di} generated during electrical stimulation of the phrenic nerves at different frequencies. It was found that acute sepsis produced a decrease in diaphragmatic strength related to both an impaired contractility and a reduction in diaphragmatic endurance capacity.

Status asthmaticus

In status asthmaticus, the work of breathing is increased because respiration is rapid and airway resistance is high [24]. Hyperinflation is usually severe and will thus reduce respiratory muscle efficiency. Blood supply may also become impaired as respiratory muscle contraction increases in order to develop adequate inspiratory pressures. This blood supply impairment may persist during expiration because of the need to maintain higher end-expiratory lung volumes. Furthermore, hypoxaemia will reduce the amount of energy available for the respiratory muscles.

Although many factors predisposing to respiratory muscle fatigue are present in status asthmaticus, respiratory muscle fatigue, which has been clinically suspected, has not yet been confirmed in this situation.

Therapeutic considerations

Restoring the balance between energy supply and demand

If fatigue results from the imbalance between energy supply and demand, the objectives of therapy must be to restore this balance. Energy supplies may be increased by treating hypoxaemia and improving cardiac output, and the demands for energy may be decreased by treating bronchospasm or pulmonary oedema. If the usual methods of restoring the balance between energy supply and demand fail, the clinical manifestations of inspiratory muscle fatigue persist, one must seriously consider putting the muscles to rest by the use of artificial ventilation. Just how much rest is required is unknown. Total rest in normal subjects is obviously not required: otherwise, one would not recover from experimental fatigue. However, a body respirator, which does indeed put the diaphragm at rest, may be useful in some patients [25]. If these patients are in a chronic state of fatigue during quiet breathing, complete rest may restore their respiratory muscle function.

However, difficulties in weaning patients after prolonged controlled ventilation have been reported to occur in as many as 20% of ventilated patients [26].

During mechanical ventilation, respiratory muscle activity stops, as demonstrated by the absence of diaphragmatic electrical activity [27]. This inactivity could be involved, at least in part, in the difficulties of weaning after prolonged controlled ventilation. Indeed, diaphragmatic disuse may induce muscular atrophy and changes in contractile properties, as described after peripheral skeletal muscle immobilisation [28]. However, few data are available concening the effects of disuse on respiratory muscle mass and contractile properties. Anzueto et al. [29] have demonstrated that 11 days of mechanical ventilation in baboons produced a decrease in maximal diaphragmatic strength and in diaphragmatic endurance capacity. However, these authors studied only 3 animals and they did not measure diaphragmatic mass, contractile properties, or enzymatic profile.

We have recently been examining diaphragmatic mass, contractile properties, and enzymatic profile after 48 h of mechanical ventilation in rats, and have compared these changes with those observed on peripheral muscles soleus and extensor digitorium longus (EDL) after 48 h of rest in the same mechanically ventilated animals.

The weight of the diaphragm, soleus and EDL was significantly reduced in the mechanically ventilated (MV) group compared with the control group. This was accompanied in the diaphragm by a reduction in the normalised force generated for all the frequencies of stimulation except 20 Hz. By contrast, diaphragmatic twitch contraction time and time constant of the relaxation (t) were not modified after 48 h of mechanical ventilation. The force generated by the soleus and EDL after 48 h rest was not significantly reduced in the MV group as compared with the controls. However, t for the soleus was significantly increased in the MV group. The activities of citrate synthase and lactate dehydrogenase (enzyme markers of oxidative and glycolytic capacity, respectively) in the diaphragm, soleus and EDL were not significantly different in the MV group as compared with controls. We conclude that 48 h of mechanical ventilation in rats produced an atrophy of the diaphragm accompanied by a reduction in its force-generating capacity. By contrast, 48 h rest of the soleus and the EDL in the same animals resulted in muscle atrophy without reduction in force generation.

The main result of this study was therefore that 48 h of mechanical ventilation in rats produced an atrophy of the diaphragm accompanied by a reduction in the muscle force-generating capacity. Although the soleus and the EDL in the same mechanically ventilated animals were also atrophied, no

reduction in force generation was observed. Therefore, a balance should be found between the rest needed and its duration in treating respiratory muscle fatigue with mechanical ventilation.

References

1. Roussos C, Macklem PT (1982) The respiratory muscles. N Engl J Med 307:786–797
2. Aubier M, Murciano D, Fournier M et al (1980) Central respiratory drive in acute respiratory failure of patients with chronic obstructive pulmonary disease. Am Rev Respir Dis 122:191–200
3. Derenne J Ph, Couture J, Isocoe S et al (1976) Occlusion pressure in man rebreathing CO_2, under methoxyflurane anesthesia. J Appl Physiol 40: 805–814
4. Bellemare F, Grassino A (1982) Effects of pressure and timing of contraction of human diaphragm fatigue. J Appl Physiol 53:1190–1195
5. Bellemare F, Grassino A (1983) Force reserve of the diaphragm in patients with chronic obstructive pulmonary disease. J Appl Physiol 55:8–15
6. Bellemare F, Wight C, Lavigne M et al (1983) Effect of tension and timing of contraction of the blood flow of the canine diaphragm. J Appl Physiol 54:1597–1606
7. Roussos Ch, Fixley M, Gross D et al (1979) Fatigue of respiratory muscles and their synergic behaviour. J Appl Physiol 46:867–904
8. Macklem PT (1984) Hyperinflation. Am Rev Respir Dis 129:1–2
9. McGregor M, Becklade MR (1961) The relationship of oxygen cost of breathing to respiratory mechanical work and respiratory force. J Clin Invest 40:917–980
10. Aubier M, Trippenbach T, Roussos Ch (1981) Respiratory muscle fatigue during cardiogenic shock. J Appl Physiol 51:499–508
11. Jardim J, Farkas G, Prefaut C et al (1981) The failing inspiratory muscle under normoxic and hypoxic conditions. Am Rev Respir Dis 124:279
12. Lind AR, McNicol GW (1967) Local and central circulatory responses to sustained contractions and the effect of free or restricted arterial inflow on post exercise hyperaemia. J Phyiol (London) 192:575–593
13. Rochester DF, Bettini G (1976) Diaphragmatic blood flow and energy expenditure in the dog. Effects of inspiratory airflow resistance and hypercapnea. J Clin Invest 57:661–672
14. Field S, Kelly S, Macklem PT (1982) The oxygen cost of breathing in patients with cardio-respiratory disease. Am Rev Respir Dis 126:9–13
15. Macklem PT (1980) Respiratory muscle. The vital pump. Chest 78: 753–758
16. Aubier M (1987) What is failing in respiratory failure. Hospital Practice January 30:6–9
17. Esau SA, Bellemare F, Grassino A et al (1983) Changes in relaxation rate with diaphragmatic fatigue in humans. J Appl Physiol 54:1353–1360
18. Mal H, Aubier M, Pamela F et al (1987) Evaluation of the transdiaphragmatic pressure (Pdi) relaxation rate in COPD patients during respiratory failure. Bull Eur Physiopathol Respir 23 (suppl 12):3595
19. Murciano D, Boczkowski J, Lecucguic Y et al (1988) Tracheal occlusion pressure: A simple index to monitor respiratory muscle fatigue during acute respiratory failure in COPD patients. Ann Intern Med 108:800–805
20. Roussos C (1985) Ventilatory failure and respiratory muscles. In: Roussos C, Macklem PT (eds): The thorax, Part B. Marcel Dekker, New York, pp 1373–1405
21. Viires N, Syllie G, Aubier M et al (1983) Regional blood flow distribution in dog during induced hypotension and low cardiac output, spontaneous breathing vs arterial ventilation. J Clin Invest 72:935–947
22. Hussain SNA, Simkus G, Roussos C (1985) Respiratory muscle fatigue. A cause of ventilatory failure in septic shock. J Appl Physiol 58: 2033–2040
23. Boczkowski J, Dureuil B, Branger C et al (1988) Effects of sepsis on diaphragmatic function in rats. Am Rev Respir Dis 138:260–265
24. Freedman AR, Lavietes MH (1986) Energy requirements of the respiratory musculature in asthma. Am J Med 80:215–222
25. Rochester DF, Braun NMT, Larne S (1977) Diaphragmatic energy expenditure in chronic respiratory failure: the effect of assisted ventilation with body respirators. Am J Med 63:223
26. Tahvanainen J, Salmenpera M, Nikki P (1983) Extubation criteria after weaning from intermittent mandatory ventilation and continuous positive airway pressure. Crit Care Med 11:702–707
27. Flick GR, Bellamy PE, Simmons DH (1989) Diaphragmatic contraction during assisted mechanical ventilation. Chest 96:130–135
28. Booth FW (1982) Effect of limb immobilization on skeletal muscle. J Appl Physiol 52(5):1113–1118
29. Anzueto A, Tobin MJ, Moore G, Peters JL, Siedenfeld JJ, Coalson JJ (1987) Effect of prolonged ventilation on diaphragmatic function: a preliminary study. Am Rev Respir Dis 137:180–183

Dr. M. Aubier
Unité de Pneumologie
Inserm U. 226
Hôpital Bichat
Paris
France