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Respiratory muscles and weaning failure

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ABSTRACT: Weaning failure is, unfortunately, a rather common phenomenon for mechanically-ventilated patients (especially those with chronic obstructive pulmonary disease (COPD)), and the respiratory muscles play a pivotal role in its development.

Weaning fails whenever an imbalance exists between the ventilatory needs and the neurocardiorespiratory capacity. This can happen if there is an increase in the energy demands of the respiratory muscles, a decrease in the energy available, a decrease in neuromuscular competence, or if the respiratory muscles pose an impediment to the heart and blood flow.

The imbalance created will lead to weaning failure through the development of respiratory muscle fatigue, hypercapnia, dyspnoea, anxiety and organ dysfunction. *Eur Respir J., 1996, 9, 2383–2400.*

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For the majority of mechanically-ventilated patients (70–80% in various series) weaning can be accomplished quickly and easily. There is, however, a smaller group of ventilated patients (20–30%) who repeatedly fail attempts at weaning and remain ventilator-dependent for prolonged periods of time. These difficult to wean patients account for a significant amount of health care costs and pose a great challenge for clinicians. The aetiology of weaning failure remains, to a large extent, in the realm of speculation. Clinicians and scientists refer to weaning as an art and/or science. In this review, we attempt to discuss, from a scientific standpoint, the pathophysiological mechanisms of weaning failure with a special focus on the role played by the respiratory muscles.

Failure to wean has been attributed either to an imbalance between the load faced by the respiratory muscles and their neuromuscular competence or to an energy supply that is inadequate to meet the energy demand of the muscles. At first glance, these factors do not seem to be directly related. However, we will try to unravel their actual intimate relationship by proposing a "mechanical model" that incorporates the various determinants of energy supply, energy demand and neuromuscular competence. These variables, by their fine interplay, create an imbalance between the ventilatory needs and the neurorespiratory capacity, which can lead to the inability to sustain spontaneous breathing, hypercapnia, and, thus, to weaning failure. Accordingly, failure to wean is usually multifactorial, with each factor contributing its own percentage. This is best exemplified by the hyperinflated chronic obstructive pulmonary disease (COPD) patient, where a combination of various factors (increased energy demands, decreased neuromuscular competence, decreased available energy) come into play, leading to ventilator dependency. This multifactorial nature of weaning failure is not usually evi-

dent in most clinical trials that, by virtue of their design, try to isolate one factor at a time and study its role.

Of course, at the other end of the spectrum, a single factor may be solely responsible, as in the postoperative cardiac surgery patient that becomes ventilator-dependent due to the development of bilateral phrenic nerve injury. Furthermore, weaning failure can occasionally be attributed to cardiovascular dysfunction that develops upon transition from mechanical ventilation to spontaneous breathing. We will explore its pathophysiology and show how this cardiovascular dysfunction is dependent upon the action of the respiratory muscles. Taking all these factors into account, our thesis will be that weaning fails whenever an imbalance exists between the ventilatory needs and the neurocardiorespiratory capacity. We will discuss in depth the various determinants of this relationship, both on theoretical grounds and from the standpoint of the experimental data available. We will then show how this imbalance may lead to the development of respiratory muscle fatigue, acute hypercapnia, dyspnoea, anxiety, organ dysfunction (fig. 1) or some combination of these conditions, and that this is, in fact, the final common pathway leading to weaning failure.

Theory: imbalance between ventilatory needs and neurocardiorespiratory capacity

To take a spontaneous breath, the inspiratory muscles must generate sufficient force to overcome the elastance of the lungs and chest wall (lung and chest wall elastic loads) as well as the airway and tissue resistance (resistive load). This requires an adequate output by the centres controlling the muscles, anatomical and functional nerve integrity, unimpaired neuromuscular transmission, an intact chest wall and adequate muscle strength.

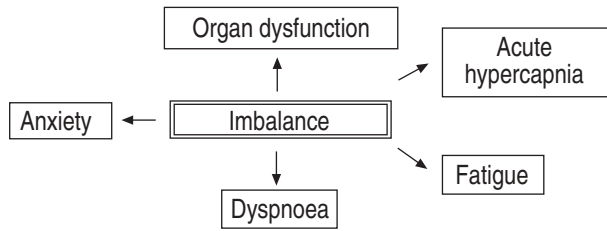


Fig. 1. — The final common pathways leading to weaning failure: fatigue, hypercapnia, dyspnoea, anxiety and organ dysfunction may develop whenever an imbalance exists between the ventilatory needs and the neurocardiorespiratory capacity.

This can be schematically represented by considering the ability to take a breath as a balance between inspiratory load and neuromuscular competence (fig. 2). Under normal conditions, this system is polarized in favour of neuromuscular competence, *i.e.* there are reserves that permit a considerable increase in load. However, for a man to breathe spontaneously, the inspiratory muscles should be able to sustain the above-mentioned load over time and also adjust the minute ventilation in such a way that there is adequate gas exchange. The ability of the respiratory muscles to sustain this load without the appearance of fatigue is called "endurance" and is determined by the balance between energy supplies (U_s) and energy demands (U_d) (fig. 3).

Energy supplies depend on the inspiratory muscle blood flow, the blood substrate (fuel) concentration and arterial oxygen content, the muscle's ability to extract and utilize energy sources, and the muscle's energy stores [1, 2]. Under normal circumstances, energy supplies are adequate to meet the demands and a large recruitable reserve exists (fig. 3). Energy demands increase proportionally with the mean tidal pressure developed by the inspiratory muscles (P_I), expressed as a fraction of

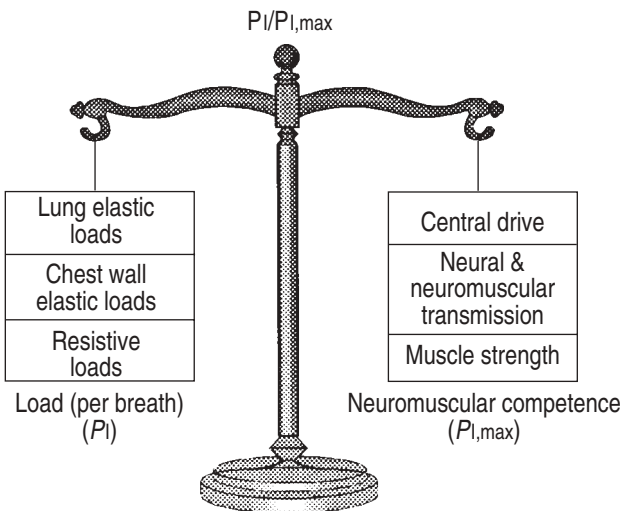


Fig. 2. — The ability to take a spontaneous breath is determined by the balance between the load imposed upon the respiratory system (pressure developed by the inspiratory muscles (P_I)) and the neuromuscular competence of the ventilatory pump (maximum inspiratory pressure ($P_{I,max}$)). Normally, this balance weighs in favour of competence, permitting significant increases in load. However, if the competence is, for whatever reason, reduced below a critical point (*e.g.* drug overdose, myasthenia gravis, *etc.*), the balance may then weigh in favour of load, rendering the ventilatory pump insufficient to inflate the lungs and chest wall.

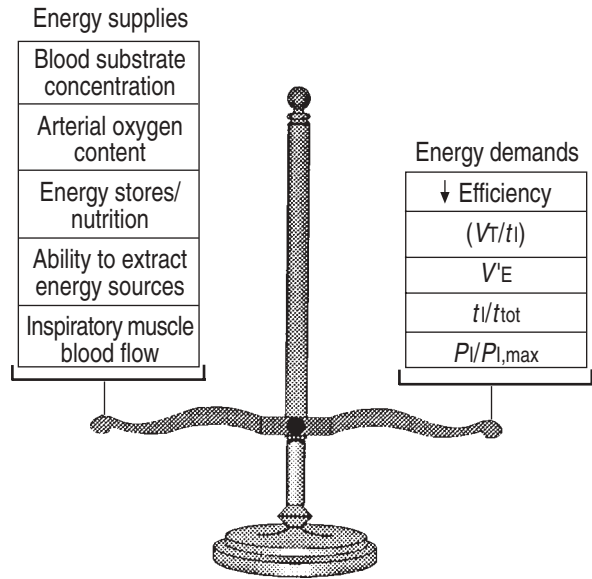


Fig. 3. — Respiratory muscle endurance is determined by the balance between energy supplies and demands. Normally, the supplies meet the demands and a large reserve exists. Whenever this balance weighs in favour of demands, the respiratory muscles ultimately become fatigued, leading to inability to sustain spontaneous breathing. ↓: decreased; V_T/t_I : mean inspiratory flow (tidal volume/inspiratory time); t_I/t_{tot} : duty cycle (fraction of inspiration to total breathing cycle duration); $P_I/P_{I,max}$: inspiratory pressure/maximum inspiratory pressure ratio; $V'E$: minute ventilation.

maximum inspiratory pressure ($P_I/P_{I,max}$), the minute ventilation ($V'E$), the inspiratory duty cycle (t_I/t_{tot}) and the mean inspiratory flow rate (V_T/t_I), and are inversely related to the efficiency of the muscles [1, 2]. "Fatigue" develops when the mean rate of energy demands (U_d) exceeds the mean rate of energy supply (U_s) [3] (*i.e.* when the balance is polarized in favour of demands) [1].

$$U_d > U_s \Rightarrow W/E > U_s \quad (1)$$

where W is the mean muscle power and E is efficiency.

BELLEMARE and GRASSINO [4] have suggested that the product of t_I/t_{tot} and the mean transdiaphragmatic pressure expressed as a fraction of maximal transdiaphragmatic pressure ($P_{di}/P_{di,max}$) defines a useful "tension time index" (TTI_{di}) that is related to the endurance time (*i.e.* the time that the diaphragm can sustain the load imposed on it). Whenever TTI_{di} is smaller than the critical value of 0.15, the load can be sustained indefinitely; but when TTI_{di} exceeds the critical zone of 0.15–0.18, the load can be sustained for only a limited time period, in other words, the endurance time. This was found to be inversely related to TTI_{di} . By analogy, a TTI was calculated for the rib cage muscles:

$$TTI_{rc} = \text{mean value } P_{pl}/P_{pl,max} \cdot t_I/t_{tot}$$

where P_{pl} is the pleural pressure and the critical value was found to be 0.30 [5]. The TTI concept is assumed to be applicable not only to the diaphragm, but to the respiratory muscles as a whole [6]:

$$TTI = \frac{P_I}{P_{I,max}} \times \frac{t_I}{t_{tot}} \quad (2)$$

Since we have stated that endurance is determined by the balance between energy supply and demand, TTI of the inspiratory muscles has to be in accordance with the energy balance view. In fact, as figure 3 demonstrates, $P_i/P_{i,max}$ and t_i/t_{tot} , which constitute the TTI, are among the determinants of energy demands; an increase in either that will increase the TTI value will also increase the demands. The energy balance may then weigh in favour of demands, leading to fatigue. Furthermore, Roussos *et al.* [7] have directly related $P_i/P_{i,max}$ with the endurance time. The critical value of $P_i/P_{i,max}$ that could be generated indefinitely at functional residual capacity (FRC) was around 0.60. Greater values of $P_i/P_{i,max}$ ratio were inversely related to the endurance time in a curvilinear fashion. When lung volume was increased from FRC to FRC + 50% inspiratory capacity (IC), the critical value of $P_i/P_{i,max}$ and the endurance time were diminished to very low values (20–25% of $P_{i,max}$).

But what determines the ratio $P_i/P_{i,max}$? The nominator, the mean inspiratory pressure, is determined by the elastic and resistive loads imposed on the inspiratory muscles. The denominator, the maximum inspiratory pressure, is determined by the neuromuscular competence, *i.e.* the maximum inspiratory muscle activation that can be achieved. It follows, then, that the value of $P_i/P_{i,max}$ is determined by the balance between load and competence (fig. 2). But $P_i/P_{i,max}$ is also one of the determinants of energy demands (fig. 3); therefore, the two balances, *i.e.* between load and competence and energy supply and demand, are in essence linked, creating a system. Schematically, when the central hinge of the system moves upwards, or is at least at the horizontal level, a balance exists between ventilatory needs

and neurorespiratory capacity, and spontaneous ventilation can be sustained indefinitely (fig. 4).

One can easily see that the ability of a subject to breathe spontaneously depends on the fine interplay of many different factors. Normally, this interplay moves the central hinge far upwards and creates a great ventilatory reserve for the healthy individual. When the central hinge of the system, for whatever reason, moves downward, an imbalance develops between ventilatory needs and neurorespiratory capacity, and spontaneous ventilation cannot be sustained. Figure 5 summarizes all possible factors that, by their fine interplay, can lead to this imbalance and then to weaning failure. However, the ventilatory pump is not only functionally linked to the cardiac pump and the vascular conduit for O_2 and CO_2 transport, but also mechanically linked because of their close apposition within the semi-rigid thorax. Therefore, the two systems must work in concert, should a patient be able to sustain spontaneous breathing. This means that the cardiovascular system must provide sufficient blood to the lung and the working respiratory muscles and, at the same time, the ventilatory pump should not pose any impediment to the heart and blood flow that could provoke either cardiac dysfunction or "steal" oxygen and blood from other tissues in favour of the respiratory muscles.

Consequently, weaning a patient from the ventilator will be successful whenever an appropriate relationship exists between ventilatory needs and neurocardiorespiratory capacity, and will ultimately fail should this relationship become inappropriate. This can happen if there is: 1) an increase in the energy demands; 2) a decrease in the energy available; 3) a decrease in neuromuscular competence; 4) an impediment to the heart

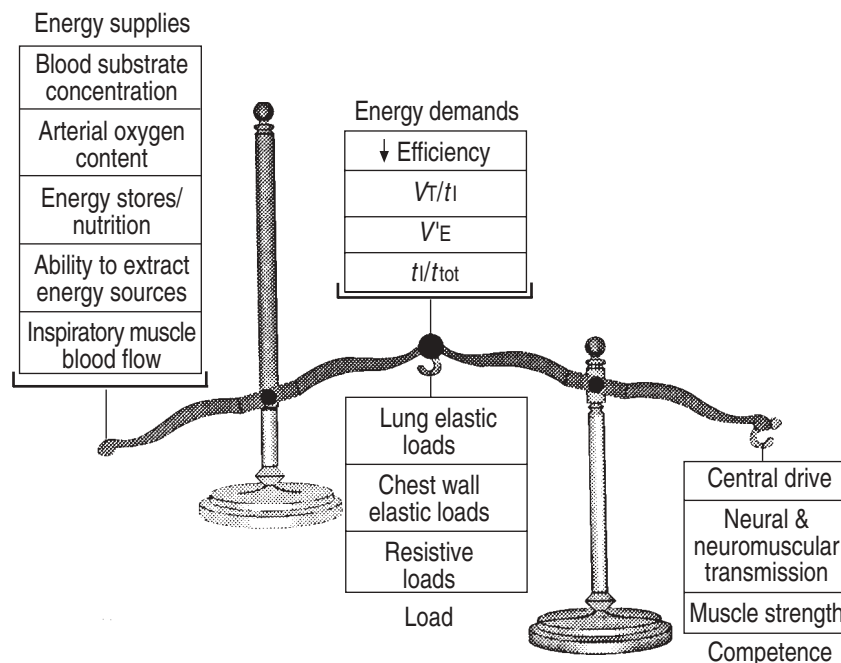


Fig. 4. – The system of two balances, incorporating the various determinants of load, competence, energy supplies and demands is represented schematically. The $P_i/P_{i,max}$, one of the determinants of energy demands (fig. 3) is replaced by its equivalent: the balance between load and neuromuscular competence (fig. 2). In fact, this is the reason why the two balances are linked. When the central hinge of the system moves upwards or is at least at the horizontal level, a balance exists between ventilatory needs and neurorespiratory capacity and spontaneous ventilation can be sustained. In healthy persons the hinge moves far upwards creating a large reserve. For definitions see legend to figure 3.

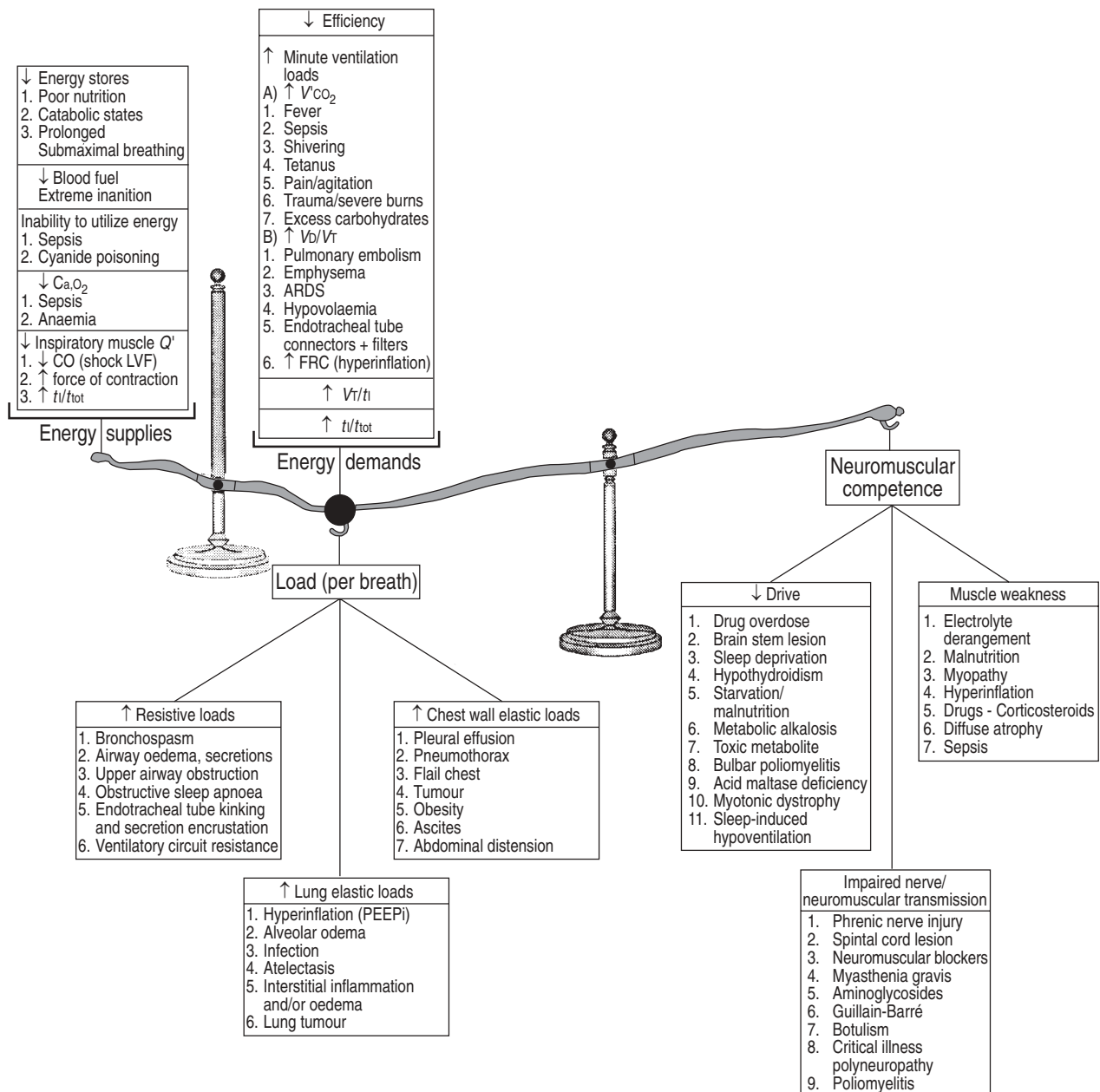


Fig. 5. – The various factors that can move the central hinge downwards by their fine interplay, leading to the inability to sustain spontaneous breathing and, thus, to weaning failure due to the imbalance between ventilatory needs and neurorespiratory capacity. C_{a,O_2} : arterial oxygen content; Q' : perfusion; CO: cardiac output; LVF: left ventricular failure; V_{CO_2} : carbon dioxide elimination; V_D/V_T : physiological dead space/tidal volume ratio; ARDS: adult respiratory distress syndrome; PEEPi: intrinsic positive end-expiratory pressure. For further definitions see legend to figure 3.

and blood flow posed by the respiratory muscles; or 5) a combination of the above-mentioned factors. Before attempting a more in-depth analysis of each factor, it is important to note that failure to wean is usually multifactorial, with each factor contributing its own percentage.

Increased energy demands

Energy demands (*i.e.* the energy required for ventilation), although easily understood qualitatively, are difficult to quantify. However, since under most conditions the respiratory muscles work aerobically, the oxygen

cost of breathing ($VO_{2,resp}$) is a good index of the energy requirements. Applying the equation regarding energy expenditure during skeletal muscle contraction to the respiratory muscles [8, 9], it follows that $VO_{2,resp}$ during breathing at a constant tidal volume is given by:

$$VO_{2,resp} = K_1A + K_2W + K_3TTI \quad (3)$$

where K_1 is a constant corresponding to the frequency of contraction; A = heat of activation; W = work rate (power); TTI = tension-time index; and K_2 and K_3 = constants. Although this equation has the presupposition of constant tidal volume that renders it insufficient to express $VO_{2,resp}$ under all possible conditions of breathing, it is

a useful approximation, which clearly denotes that energy demands ($VO_{2,resp}$) depend both on W and TTI. Whichever factor increases, either W or TTI, the result will be an increase in the energy demands.

Increased load. Increased respiratory load (elastic and/or resistive) increases energy demands because it is directly related to W (as well as to TTI). In fact:

$$W = P_I \cdot V_T \cdot f_R \quad (4)$$

where P_I = mean inspiratory pressure per breath, V_T = tidal volume, and f_R = respiratory frequency. Since P_I depends on the load imposed on the inspiratory muscles, it follows that all the factors that augment the load increase W (as well as TTI, see Equation (2)) and, consequently, the energy demands. Furthermore, since $TTI = P_I/P_{I,max} \cdot t_I/t_{tot}$, it follows that TTI and, thus, $VO_{2,resp}$ will increase not only when P_I is increased, but also when $P_{I,max}$ is reduced in relation to P_I , *i.e.* when neuromuscular competence is diminished. Thus it can be assumed that energy demands ($V'O_{2,resp}$) increase whenever the balance between load and neuromuscular competence weighs in favour of the load.

Increased lung elastic load. Intrinsic positive end-expiratory pressure (PEEPi) refers to the positive pressure present in the alveoli at the end of expiration. Normally, at end-expiration the pressure should equal zero. The existence of PEEPi mandates that during the next inspiration the inspiratory muscles have to develop an equal amount of pressure before airflow begins. Consequently, PEEPi adds an elastic threshold load [10]. The presence of PEEPi is easily understood in COPD patients. Airflow obstruction and/or decreased elastic recoil lead to the prolongation of expiration that cannot be completed before the ensuing inspiration. Expiration ends before the respiratory system reaches elastic equilibrium at FRC and, thus, a positive elastic recoil pressure (PEEPi) remains. In addition, COPD patients have increased lung elastic load, since tidal breathing occurs at a steeper portion of the pressure-volume curve due to hyperinflation. Interestingly, almost all patients with acute respiratory failure were found to have some amount of PEEPi during discontinuation from the ventilator [10]. PEEPi was detected in patients without COPD, *e.g.* cardiogenic pulmonary oedema, chest trauma or pneumonia. This finding indicates that PEEPi may play a role during acute respiratory failure even in non-COPD patients and probably during failing weaning trials, adding an elastic load to the respiratory muscles. Furthermore, inadequately resolved alveolar oedema (cardiogenic and noncardiogenic), pneumonia, atelectasis or interstitial inflammation augment the elastic load during weaning in patients mechanically-ventilated for hypoxaemic acute respiratory failure by reducing lung compliance.

Increased chest wall elastic load. Chest wall elastic load may be increased by pleural effusion, obesity that thickens the chest wall, or by ascites and abdominal distention which impede diaphragmatic descent. It may also be increased by diseases that create permanent chest wall deformity, such as kyphoscoliosis and thoracoplasty [11], or by pleural and chest wall tumours that

increase chest wall stiffness either by a mass effect or the accompanying adhesions. Neuromuscular diseases, such as bilateral diaphragmatic paralysis and tetraplegia (C5 transection), or flail chest that cause marked distortion of the chest wall during inspiration, greatly augment the chest wall elastic load.

In addition, patients with neuromuscular disorders have a chest wall compliance diminished by about two thirds the normal value [12]. This is caused by the stiffening of tendons and ligaments and ankylosis of costosternal and costovertebral articulations that develop as a consequence of chronic restriction [11].

Chest wall elastic load is also increased in patients with COPD and severe hyperinflation [13] (see Hyperinflation).

Increased resistive load. The resistive load increases whenever resistance to airflow increases. This may be caused by bronchospasm, airway oedema (due either to inflammation or cardiac failure), copious secretions, endotracheal tube kinking, or secretion encrustation. In difficult to wean patients, partial ventilatory support is used to aid the gradual transition to spontaneous ventilation. Considerable effort may then be required to inspire through ventilator circuits, raising the resistive load [14]. Once a patient is extubated, upper airway obstruction may develop due either to tracheal or laryngeal stenosis or to sleep induced reduction in pharyngeal muscle tone. Finally, both the lungs and chest wall normally exhibit tissue resistance, which is due mainly to their viscoelastic properties. This may be increased in restrictive lung and chest wall diseases, augmenting the resistive load.

Increased minute ventilation. Since minute ventilation ($V'E$) equals $V_T \cdot f_R$, Equation (4) may be transformed to:

$$W = P_I \cdot V'E \quad (5)$$

i.e. work rate and energy demands increase whenever minute ventilation is elevated. Taking into account the respiratory equation that relates the arterial carbon dioxide tension (P_{a,CO_2}) to alveolar ventilation ($V'A$):

$$P_{a,CO_2} = K \cdot \frac{V'CO_2}{V'A}$$

where K denotes the constant of proportionality and $V'CO_2$ the carbon dioxide production, respectively, and that $V'A = V'E - V'D$, where $V'D$ is dead space ventilation, f = frequency and V_D = dead space volume, it follows that:

$$P_{a,CO_2} = K \cdot \frac{V'CO_2}{V'E - V'D} = K \cdot \frac{V'CO_2}{V'E \cdot \left(1 - \frac{V'D}{V'E}\right)} = K \cdot \frac{V'CO_2}{V'E \cdot \left(1 - \frac{fV_D}{fV_T}\right)} \rightarrow$$

$$P_{a,CO_2} = K \cdot \frac{V'CO_2}{V'E \cdot \left(1 - \frac{V_D}{V_T}\right)} \rightarrow$$

$$V'E = K \cdot \frac{V'CO_2}{P_{a,CO_2} \cdot \left(1 - \frac{V_D}{V_T}\right)} \quad (6)$$

Combining Equations (5) and (6):

$$W = P_I \cdot K \cdot \frac{V'CO_2}{P_{a,CO_2} \cdot \left(1 - \frac{VD}{VT}\right)} \quad (7)$$

This equation denotes that power and energy demands increase when either $V'CO_2$ increases at constant VD/VT and P_{a,CO_2} or VD/VT increases at constant $V'CO_2$ and P_{a,CO_2} .

Carbon dioxide production may increase due to: 1) fever and/or sepsis: CO_2 production increases during hyperthermia by about 9–14% for each degree Centigrade rise in temperature [12, 15]; 2) shivering, tetanus: an increase in muscle tone, either physiological (shivering) or pathological (*e.g.* tetanus, convulsions) increases the metabolism of the muscles and, thus, CO_2 production; 3) agitation: CO_2 production is increased secondary to increased muscular activity; 4) severe burns or trauma: being catabolic states, these conditions elevate CO_2 production; 5) hyperalimentation: intravenous hyperalimentation in excess of caloric requirements augments CO_2 production, especially when a large proportion of calories is supplied as carbohydrate [16–18]. Excess carbohydrates are converted to fat for storage, a metabolic pathway that has a respiratory quotient (RQ) (*i.e.* the rate of CO_2 production *versus* oxygen consumption) of 8.0 which results in marked increase in CO_2 production. (carbohydrates and fats are metabolized to CO_2 with RQs of 1.0 and 0.7, respectively). In normal subjects, hypercapnia is prevented by an increase in alveolar ventilation. This is not possible in patients with compromised ventilatory pumps, and several patients have been reported to develop hypercapnia when given excess nutritional support during weaning. To elucidate the relative importance of excess carbohydrates *versus* excess total calories in CO_2 production, TALPERS *et al.* [18] compared three isocaloric regimens containing 40, 60 and 75% carbohydrates, and found no difference in the amount of CO_2 produced. In contrast, when carbohydrates were held constant but total calories were increased, CO_2 production proportionally increased from 181 mL·min⁻¹ when calories were equivalent to calculated resting energy expenditure (REE) to 211 mL·min⁻¹ at 1.5 × REE and 244 mL·min⁻¹ at 2.0 × REE. However, hyperalimentation *per se* is unlikely to be an important factor in determining the weaning outcome and its role seems to be contributory.

Physiological dead space is increased in virtually all the diverse processes that affect the lung parenchyma and the distribution of airflow (*e.g.* emphysema, adult respiratory distress syndrome (ARDS)). It may be due to an augmentation of either anatomical or alveolar dead space.

Certain reversible factors increasing anatomical dead space may be very important for the ventilator-dependent patient. These are: 1) endotracheal tube (especially nasotracheal or orotracheal, whilst tracheostomy tubes introduce less dead space); 2) ventilator circuit and the endotracheal tube adapter; 3) increases in end-expiratory lung volume (functional residual capacity (FRC)) caused by PEEPi.

Alveolar dead space will increase if lung perfusion is

preferentially reduced. This is caused by: 1) vascular occlusion, as in pulmonary embolism; 2) hypovolaemia and shock that reduce the perfusion in the nondependent portion of the lung; 3) alveolar wall distension and compression of the capillaries of the well-ventilated alveoli during positive pressure ventilation with high inflation pressures, mainly in patients with ARDS.

The role of CO_2 : Equation (7) denotes that P_{a,CO_2} is inversely related to W and, thus, to the energy demands. In the preceding discussion, P_{a,CO_2} was assumed to be constant. This is quite logical since maintenance of normocapnia is one of the aims of breathing. Furthermore, P_{a,CO_2} is the strongest regulator of the central nervous system (CNS) output to the respiratory system. Whenever P_{a,CO_2} rises, it stimulates the chemoreceptors, increasing $V'E$ so that P_{a,CO_2} returns to normal. However, if this regulatory mechanism fails, for whatever reason, P_{a,CO_2} will rise. This diminishes the work rate and energy demands. In fact, this may be a protective strategy adopted by the CNS to prevent respiratory muscle fatigue [19, 20]: by allowing P_{a,CO_2} to rise, energy demands are reduced so that energy supplies can meet these demands, and the consequent development of fatigue is prevented or postponed.

Increased mean inspiratory flow and duty cycle. The role of inspiratory flow (VT/tI) and duty cycle (tI/t_{tot}) in determining work rate and energy demands are revealed by an arrangement of Equation (4):

$$\begin{aligned} W &= P_I \cdot VT \cdot fR \\ &= P_I \cdot \frac{VT}{tI} \cdot tI \cdot fR \quad (\text{substituting } \frac{60}{t_{tot}} \text{ for } fR) \\ &= P_I \cdot \frac{VT}{tI} \cdot \frac{tI}{t_{tot}} \cdot 60 \quad (8) \end{aligned}$$

Any increase in VT/tI and/or tI/t_{tot} will obviously increase the energy demands. In addition, tI/t_{tot} is implicated in TTI determination, Equation (2), that is a well-known index of $V'O_{2,resp}$ [21].

Accordingly, CLANTON *et al.* [22] have shown a decrease in threshold TTI of the global inspiratory muscles from 0.31 to 0.16 when inspiratory flow increased from 0.5 to 2 L·s⁻¹. Furthermore, McCool *et al.* [23] measured the oesophageal pressure-time index (PT_{oes}) as a measure of inspiratory muscle pressure output, and showed that for a given PT_{oes} and constant tI/t_{tot} (*i.e.* for a given P_{oes}) endurance time was inversely related to VT/tI over a wide range of flows. The critical value of the PT_{oes} was also found to be inversely related to the inspiratory flow. It can, thus, be assumed that inspiratory flow is an independent determinant of the endurance and energy demands of the respiratory muscles.

The role of the duty cycle (tI/t_{tot}) is clearly shown in the work of BELLEMARE and GRASSINO [4] and ZOCCHI *et al.* [5] already presented in the previous discussion.

Reduced efficiency. Efficiency (E) is defined as the ratio of the mechanical work rate (W) to the oxygen cost of breathing ($V'O_{2,resp}$): $E = W/V'O_{2,resp}$ [1]. By rearrangement: $V'O_{2,resp} = W/E$. It follows that energy demands ($V'O_{2,resp}$) increase when the efficiency is reduced (for

the same work output). This happens during resistive breathing, breathing against elastic loads or breathing at high lung volumes [1] (*i.e.* elastic and resistive loads increase the energy demands, not only by increasing the work rate but also by reducing the efficiency).

It is important to note that a single value of efficiency does not exist; it varies as a result of numerous factors [1] (elastic and resistive load, velocity of shortening, muscle fibre composition, intrinsic rate of adenosine triphosphate (ATP) hydrolysis) from a value of zero (*i.e.* inspiratory effort with closed airways) to a maximum value which appears to be 20–25% (*i.e.* breathing through external dead space in the supine position). In this regard, TENNEY and REESE [24] found that the critical power (W_{crit}), above which fatigue occurs, during hyper-ventilation is at least four times greater, corresponding to 55% of maximum breathing capacity, than the W_{crit} (and UsE) of 6–8 kg·min⁻¹ found during resistive breathing in normal subjects [7]. Similar arguments may account for the smaller critical P_{di} , if the diaphragm operates at shorter lengths during acute hyperinflation, when a given force requires much greater excitation [25]. At half inspiratory capacity, E can be reduced by as much as 50% [26]. To our knowledge, the efficiency of respiratory muscles has never been measured in patients who fail to wean. However, MANTHOUS *et al.* [27] have recently estimated E in eight mechanically-ventilated, critically ill patients, and found values as low as $3.7 \pm 2.9\%$ that clearly contributed to the increased energy demands ($V'O_{2,resp}$) observed.

Decreased neuromuscular competence

Decreased respiratory drive. Although the majority of patients appear to have normal or increased drive to breathe during weaning, as evidenced by indices of drive, such as airway occlusion pressure at 0.1 s ($P_{0.1}$) or mean inspiratory flow (V_T/t_I) that are usually above the normal range, occasional patients may fail to wean due to their inability to properly stimulate their ventilatory pump [28, 29]. CNS depression, caused by neurological damage, toxic-metabolic encephalopathy or drug overdose (sedatives, narcotics), is the main reason for decreased drive. Metabolic alkalosis is another potential factor. Furthermore, occult hypothyroidism, sleep deprivation and starvation are now recognized as potential aetiologies of a decreased drive [28]. Dysfunction of the respiratory centre may be caused by bulbar poliomyelitis, myotonic dystrophy or acid maltase deficiency [12]. Alterations in central respiratory control may also develop in patients with neuromuscular disorders that do not produce specific dysfunction of the respiratory centre. These alterations might be related to sleep-induced hypoventilation [12, 30].

Decreased neural and neuromuscular transmission. Neural transmission to the respiratory muscles may be interrupted in phrenic nerve or spinal cord transection. It may also be impaired in phrenic nerve injury (thermal, hypoxic, or traction injury during cardiac surgery), demyelinating diseases, either immunological (Guillain-Barré [29, 31], multiple sclerosis) or toxin-induced

(diphtheria), or in diseases affecting the lower motor neurons, either infectious (poliomyelitis) or degenerative (amyotrophic lateral sclerosis). A variety of other neuropathies could also be included, but are rare enough not to merit special mention in this context.

Neuromuscular transmission, in turn, may be impaired by toxins (*e.g.* botulism that inhibits presynaptic acetylcholine release), an episode of myasthenia gravis, and drugs (organophosphate poisoning, aminoglycosides and, especially, neuromuscular blockers) [29, 32]. Sometimes, mechanically-ventilated patients develop prolonged neurogenic weakness, leading to failure of weaning trials that cannot be attributed to a specific aetiological factor despite thorough investigation [33].

Two groups of patients have been reported as particularly susceptible to developing weaning difficulties due to failure of neural transmission: 1) patients undergoing coronary artery bypass grafting commonly (up to 40–50%) develop phrenic nerve injury postoperatively as documented by electrophysiological studies. The usually ensuing unilateral diaphragmatic paralysis may make weaning difficult in the first 2–3 days following surgery. Fortunately, only a small number of patients develop bilateral diaphragmatic paralysis resulting in prolonged ventilatory dependency [34]. 2) Critical illness polyneuropathy (CIP) is a syndrome of prolonged muscle weakness or paralysis also presenting as failure to wean [29, 35]. Aetiology is unknown, although sepsis, multiple organ failure, shock, hypoxia, medications and prolonged use of neuromuscular blocking agents have been implicated [36]. Electrophysiological studies have revealed abnormalities of primarily axonal degeneration type [29, 36, 37]. Although CIP is usually improved in parallel with the underlying disease, weaning is difficult and the mortality rate is high in these patients [29, 35].

Muscle weakness. There are a variety of reasons for muscles weakness, a condition in which the capacity of a rested muscle to generate force is impaired: 1) inflammatory, alcohol and thyroid myopathies; 2) muscular dystrophies; 3) drug-induced myopathies (especially corticosteroids [38, 39], antibiotics (aminoglycosides) and relaxants); 4) malnutrition [40–42] and muscle atrophy (especially important in the critically ill patient); 5. obesity [43]; 6) electrolyte imbalances: hypocalcaemia [44], hypokalaemia [45], hypophosphataemia [46, 47] and both hypo- [48] and hypermagnesaemia [45]; 7) hypercapnia (acute) [49] and acidosis [50, 51] may be important superimposing factors, since most patients who fail to wean increase their carbon dioxide tension (PCO_2) and this reduces muscle strength [49]; ventilatory failure is worsened increasing PCO_2 further and creating a vicious circle.

8) Mechanical disadvantage: respiratory muscles, like other skeletal muscles, obey the length-tension relationship. At any given level of activation, changes in muscle fibre length alter active and passive tension modifying actin-myosin interaction. At a specific fibre length (L_0), active tension is maximal, whereas below or above this it declines. Respiratory muscle length depends largely upon lung volume and to a lesser extent, on thoracoabdominal configuration [52–54]. The exact *in vivo* relationships have not been defined in detail yet.

However, it is believed (based on animal experiments) [55, 56] that L_0 for inspiratory muscles (diaphragm and intercostals) is near residual volume (RV). In addition, a relationship between lung volume and diaphragmatic fibre length in humans has recently been confirmed [57] and could entirely explain the decreases in pressure with increasing lung volume by corresponding decreases in contractility. Hyperinflation then causes a decrease in the length of the respiratory muscles and a change in their geometry that clearly decreases $P_{I,max}$. However, an important distinction should be made between the chronic, slowly developing static hyperinflation due to loss of lung elastic recoil and the acute, rapidly developing dynamic hyperinflation due to bronchoconstriction and/or respiratory tract infection, or to an abnormally increased frequency of breathing.

In fact, it has been shown that changes in the inspiratory muscle characteristics can compensate for the decrease in the operating length caused by hyperinflation. In emphysematous hamsters, there is a reduction in the number of sarcomeres per cell in the diaphragm, resulting in a leftward shift of the whole length-tension curve, so that the muscle adapts to the shorter operating length [58]. These alterations in muscle fibre length-tension characteristics may help to restore the mechanical advantage of the diaphragm in chronically hyperinflated states, though the extent to which this adaptation occurs in humans remains unclear. Indirect evidence for the existence of such an adaptation in humans comes from the work of SIMIŁOWSKI *et al.* [59], who studied the contractile properties of the human diaphragm of well-nourished, stable, chronically hyperinflated COPD patients. Interestingly, they have shown that at comparable lung volumes the twitch transdiaphragmatic pressure (*i.e.* the P_{di} developed in response to supramaximal bilateral phrenic nerve stimulation) was higher in the patients than in the normal controls, whereas the reverse was true when P_{di} twitch was measured at the corresponding FRCs. Thus, in chronically hyperinflated COPD patients some form of adaptation (length adaptation being the most probable) must have accounted for the better contractile performance of the diaphragm at the same lung volumes compared to normals. This adaptation may partially counterbalance the deleterious effects of hyperinflation on the contractility and inspiratory action of the diaphragm in patients with COPD.

Furthermore, changes in thoracoabdominal configuration also alter the fibre length and the pressure generated independently of changes in lung volume. In fact, GRASSINO *et al.* [52] found that transdiaphragmatic pressure (P_{di}) at the same lung (isolung) volume and a given level of excitation depended on the thoracoabdominal configuration. Interestingly, P_{di} decreased when ribcage volume decreased. Thus, it can be assumed that at any given lung volume an inward paradoxical ribcage movement would decrease $P_{I,max}$ since it would lower ribcage volume. This is observed either in patients with neuromyopathies (*e.g.* tetraplegia) or COPD (Hoover's sign). Changes in thoracoabdominal configuration can also explain the decrease in $P_{I,max}$ observed in patients with kyphoscoliosis [60].

9) Sepsis and endotoxic shock: pose a potentially great threat to respiratory muscle contractility, as is convincingly evident from animal models [61–64]. This is

especially important for mechanically-ventilated patients, since mechanical ventilation, *per se*, greatly increases the risk of infection and/or sepsis, thus potentially initiating a vicious circle. 10) Disuse atrophy: artificial ventilation may be followed by respiratory muscle weakness due to atrophy (secondary to disuse). This is likely, since muscles that are used most often, such as the inspiratory muscles (particularly the diaphragm), atrophy the fastest [12, 65].

Decreased available energy. Energy supplies may be diminished due to: 1) low blood substrate concentration, as in extreme inanition; 2) low oxygen content of arterial blood (Ca,O_2) caused by decreased haemoglobin concentration (anaemia), decreased haemoglobin oxygen binding or carrying capacity (CO poisoning), and decreased haemoglobin saturation (hypoxaemia); 3) inability to extract and utilize energy from the blood, as in sepsis and cyanide poisoning. In these cases, increases in respiratory muscle oxygen consumption out of proportion to load suggest that the processes of oxygenation and phosphorylation are uncoupled [64]. Furthermore, depletion of oxidative enzymes in the respiratory muscles begins within the first 72 h of complete mechanical ventilation, thus diminishing their ability to utilize energy efficiently [66]; 4) depletion of glycogen and other energy stores observed in catabolic states, prolonged submaximal breathing and poor nutritional status [1]; 5) insufficient inspiratory muscle blood flow.

During strenuous inspiratory efforts, the intramuscular vessels are compressed by the contracting respiratory muscles, thus limiting their nutrient flow. The magnitude of this compressive effect is a function of TTI [67, 68]. Increases in $P_I/P_{I,max}$ obviously augment this effect, since a greater pressure development requires a more forceful contraction and this compresses the intramuscular vessels more. Increases in t_I/t_{tot} increase the time spent on contraction. Since blood flow is in essence unimpeded only during muscle relaxation, *i.e.* expiration for the inspiratory muscles, the increased duty cycle fraction increases the time that the compressive effect is exerted, thus diminishing the blood flow. During states of decreased cardiac output in animal models with cardiogenic [69] or septic shock [62, 63], blood flow to the inspiratory muscles remained relatively high representing a substantial percentage of cardiac output. However, the amount of blood flow was smaller than that required, leading eventually to fatigue of the respiratory muscles and inability to sustain spontaneous breathing.

Hyperinflation

A highly illustrative example of how the fine interplay of many different factors may drive the central hinge of the proposed mechanical model downwards and lead to imbalance between ventilatory needs and neurocardiorespiratory capability, and thus to the inability to sustain spontaneous ventilation, is provided by acutely hyperinflated patients.

In these patients, the load of the inspiratory muscles

is increased for a variety of reasons. Firstly, airway obstruction and/or decreased elastic recoil lead to prolongation of expiration that cannot be completed before the ensuing inspiration. Expiration ends before the respiratory system reaches elastic equilibrium at FRC, and thus a positive elastic recoil pressure (PEEPi) remains. During the next inspiration, the inspiratory muscles have to develop an equal amount of pressure before airflow begins. Secondly, due to hyperinflation tidal breathing occurs at a steeper portion of the pressure-volume curve of the lung, further increasing the load. Thirdly, as FRC increases, tidal breathing may take place at that portion of the chest wall static pressure-volume curve where either positive recoil pressure exists, *i.e.* the chest wall tends to move inwards, or its expanding tendency is reduced. This is contrasted to the expanding tendency of the chest wall when tidal breathing begins from normal FRC. Furthermore, with severe hyperinflation, the marked flattening of the diaphragm causes its costal and crural fibres to be arranged in series and perpendicularly to the chest wall. Contraction of these perpendicularly oriented fibres results in paradoxical inward movement of the lower rib cage (Hoover's sign). This distortion of the chest wall during inspiration elevates the elastic load [2, 13]. Finally, the resistive load is also increased due to the obstruction of the airways, the copious secretions, mucous plugging, *etc.*

At the same time that the load is severely increased, the neuromuscular competence is decreased due to muscle weakness. Multiple factors are again responsible. Hyperinflation forces the inspiratory muscles to operate at an unfavourable position of their length-tension curve. The costal and crural fibres of the diaphragm are arranged rather in series, and this diminishes the force that can be generated compared to that achieved when they are arranged in parallel [2, 13]. The zone of opposition of the diaphragm is reduced, rendering it less efficient in expanding the lower portion of the thorax [2, 13]. The resultant flattening of the diaphragm increases its radius of curvature (R_{di}) and, according to Laplace's law $P_{di} = 2T_{di}/R_{di}$, diminishes its pressure generating capacity (P_{di}) for the same tension development (T_{di}). Apart from the above-mentioned mechanical disadvantage, the frequently coexisting hypercapnia, acidosis, malnutrition and even drug therapy (steroids) work in concert to further compromise the force that can be generated.

Obviously, the energy demands are significantly increased. Concurrently, the available energy is diminished due to a combination of hypoxaemia and insufficient muscle blood flow caused by the increased $P_i/P_{i,max}$ ratio (increased load, decreased strength). Thus, many different factors come into play in the hyperinflated patient, interact and push the central hinge of the model downwards, leading to an imbalance between ventilatory needs and neurocardiorespiratory capacity, and then to weaning failure.

Accordingly, it has recently been shown that elevated static compliance of the total respiratory system (due to hyperinflation in COPD patients) measured non-invasively in the first 24 h after intubation was a predictor of weaning failure [70], a finding that highlights the detrimental role of hyperinflation in the weaning outcome.

The respiratory muscles as an impediment to the heart and blood flow

Cardiovascular dysfunction

Patients with underlying ventricular dysfunction may develop increases in pulmonary capillary wedge pressure (PCWP) and sometimes, ultimately, decreases in cardiac output (CO) upon removal from positive-pressure mechanical ventilation [71]. Several factors may be responsible [72, 73] (table 1). The mechanism leading to weaning failure in these patients might be considered as follows: during spontaneous or diminished support ventilation, the increase in respiratory muscle workload as well as anxiety and sympathetic discharge result in an abrupt increase in oxygen and cardiac demands. The failing left ventricle is then unable to respond normally and left ventricular end-diastolic pressure (LVEDP) rises, causing interstitial, peribronchiolar and alveolar oedema. This reduces lung compliance, increases airway resistance and worsens ventilation/perfusion mismatching, leading to hypoxaemia. The energy demands of the respiratory muscles are increased, whilst energy supplies are either diminished or not sufficiently increased (inadequate CO, hypoxaemia). This eventually leads to the inability to sustain spontaneous ventilation at a

Table 1. – Factors increasing PCWP during unsuccessful weaning from mechanical ventilation

1. Increased preload
a) Increased venous return
Decreased pleural pressure
Sympathetic discharge (stress, hypercapnia)
Increased abdominal pressure
b) Reduced LV compliance (diastolic stiffness)
Myocardial ischaemia
↓ O_2 supply
↓ P_{a,O_2}
↑ LVEDP and ↑ HR, reducing coronary blood flow
↓ Mean arterial pressure
↑ O_2 demands
↑ Catecholamines
↑ HR
↑ Systolic blood pressure
LV enlargement
RV enlargement (ventricular interdependence)
↑ Venous return
↑ Pulmonary artery pressure (acute)
RV ischaemia leading to reduced RV contractility
Compression of heart chambers by regionally hyperinflated lung
2. Reduced contractility
Myocardial ischaemia
Myocardial hypoxia
Myocardial acidosis, especially due to hypercapnia
Ionized hypocalcaemia
Drugs
3. Increased afterload
↑ Systolic blood pressure (hypercapnia, catecholamine discharge)
↓ Pleural pressure

PCWP: pulmonary capillary wedge pressure; LV: left ventricle; RV: right ventricle; ↓: reduced; ↑: increased; LVEDP: left ventricular end-diastolic pressure; P_{a,O_2} : arterial oxygen tension; HR: heart rate. (From [72], after modification).

level adequate to achieve normocapnia, and PCO_2 rises. The abnormal blood gas values depress cardiac contractility and, at the same time, respiratory muscle function. This further worsens blood gas values and creates a vicious circle that may culminate in failure to wean.

The pivotal role played by the respiratory muscles in the development of left ventricular dysfunction is mediated through the effects of muscle activation on pleural and abdominal pressures. Normally, spontaneous inspiration increases abdominal pressure at the same time that it decreases pleural pressure due to diaphragmatic contraction and descent. The importance of the decreased pleural pressure for augmentation of venous return is easily understood. Furthermore, the negative intrathoracic pressure increases the afterload of both ventricles and this, combined with the increased venous return, may lead to right ventricular distension. Because the two ventricles are constrained by a common pericardial sac and share the interventricular septum, changes in the volume of one ventricle may affect the function of the other; thus, right ventricular distension impedes the filling of the left ventricle [74]. This occurs both through a generalized increase in pericardial pressure and also because of a shift of the interventricular septum toward the left. Impediment of left ventricular filling increases its diastolic stiffness at the same time that its afterload is elevated due to the decreased pleural pressure. This combined effect leads to the elevation of LVEDP with the above-mentioned sequence of events culminating in weaning failure.

In contrast, the role of abdominal pressure is not usually considered significant, and yet abdominal pressure surrounds the abdominal venous system through which two thirds of the venous return passes [75]. Therefore, an increase in abdominal pressure could theoretically compress the abdominal veins and increase the amount of blood returning to the heart [76]. In order to explain the contradictory results in the literature regarding the effects of diaphragmatic descent on venous return, TAKATA and co-workers [77, 78] recently expanded the concept of zones of the lung to the abdominal vasculature. According to their model, an increase in abdominal pressure would increase inferior vena cava (IVC) venous return when the transmural IVC pressure at the thoracic inlet ($P_{IVC}-P_{ab}$) significantly exceeds the critical closing transmural pressure (P_c), *i.e.*:

$$P_{IVC}-P_{ab} \geq P_c \text{ (Zone III condition)}$$

where P_{IVC} = IVC pressure at the level of the diaphragm, P_{ab} = abdominal pressure, and P_c = critical closing transmural pressure. On the contrary, an increase in abdominal pressure would reduce IVC venous return when the transmural IVC pressure at the thoracic inlet is below the critical closing transmural pressure:

$$P_{IVC}-P_{ab} \leq P_c \text{ (Zone II condition)}$$

because of the development of vascular waterfall.

This concept was successfully tested in animal models [77, 78], and can adequately explain the results of LEMAIRE *et al.* [71]. In this study, the haemodynamic effects of changing from positive pressure to spontaneous ventilation in 15 patients with combined COPD

and coronary artery disease were measured. Spontaneous breathing increased CO and right and left ventricular filling pressures rapidly leading to respiratory failure, while weaning indices had predicted a successful weaning. The increase in venous return and CO was an expected finding, since the decrease in pleural pressure associated with spontaneous breathing would increase venous return by lowering right atrial pressure (the downstream pressure for venous return). However, in these patients the right atrial pressure actually rose relative to atmospheric pressure despite the lower pressure surrounding the heart. The increase in venous return could only have been due to either a greater increase in the upstream pressure (P_{ab}) or a reduction in the resistance to venous return. Only the first probability, however, was applicable under those circumstances. Although no patient had clinical evidence of volume overload, all were subsequently forced into diuresis for 1 week, losing an average of 5 kg. After that, 8 of the 15 patients were successfully weaned. These patients now had CO and filling pressures during spontaneous breathing essentially unaltered from their values during mechanical ventilation.

An interesting explanation for these findings is offered by the above-mentioned model [79]. Prior to diuresis, the abdomens of these patients were in Zone III condition. When they began spontaneous breathing, their mean abdominal pressure rose and led to increased venous return; this sudden increase in venous return coupled with elevation of the left ventricular afterload caused by the lowered pleural pressure precipitated heart failure and, in turn, respiratory failure. After diuresis, the abdomens of many patients were in Zone II condition; increased abdominal pressure did not now increase venous return as much, due to the development of vascular waterfall. Although respiratory work and left ventricular afterload initially increased as much as they had the prior week, deterioration of heart function was prevented and these patients were successfully weaned.

The increased left ventricular preload and afterload resulting from the activation of the respiratory muscles upon resumption of spontaneous breathing, may also lead to altered myocardial perfusion and ischaemia [80, 81], and thus to the inability to wean successfully. Accordingly, RÄSÄNEN *et al.* [80] found electrocardiographic (ECG) evidence of myocardial ischaemia in 6 of their 12 patients with myocardial infarction complicated by respiratory failure upon withdrawal of ventilator support. Furthermore, HURFORD *et al.* [81] observed new regions of decreased myocardial thallium 201 (^{201}Tl) uptake and transient left ventricular dilation in 7 of their 15 patients assessed by ^{201}Tl myocardial scintigraphy during discontinuation of mechanical ventilation. Their results suggest that the haemodynamic and ventilatory changes associated with resumption of spontaneous breathing were sufficient to increase myocardial oxygen demands (as evidenced by the increased heart rate, arterial blood pressure and left ventricular (LV) cavity size during spontaneous ventilation (SV)) to an extent that the coronary oxygen supply available could not meet, probably due to coronary atherosclerosis or spasm, thus leading to ischaemia. Interestingly, the authors were unable to detect any electrocardiographic changes diagnostic of myocardial ischaemia,

implying that ECG criteria are relatively insensitive and that myocardial ischaemia should be suspected in the patient who fails to wean even in the absence of ECG changes.

Stealing effect

In normal subjects who are breathing quietly, the oxygen cost of breathing ($\dot{V}O_{2,\text{resp}}$) is a small proportion of the total oxygen requirement ($\dot{V}O_{2,\text{tot}}$). However, this may not be the case for the patient who fails to wean, whose $\dot{V}O_{2,\text{resp}}$ may be significantly elevated at the same time that the energy available may be decreased. In an elegant theoretical analysis, RILEY [20] has suggested that patients like these (*i.e.* who have imbalance between ventilatory needs and neurocardiorespiratory capacity) may be severely limited in the extent to which their ventilation may be increased. As ventilation increases, an ever greater proportion of the additional oxygen taken up will have to be diverted to the respiratory muscles at the expense of the oxygen available for nonrespiratory work. A point will then be reached beyond which the increase in $\dot{V}O_{2,\text{resp}}$ becomes greater than the increase in $\dot{V}O_{2,\text{tot}}$, so that oxygen available for nonrespiratory work begins to decrease and further increases in ventilation are detrimental. This theoretical analysis may be applicable to some patients who fail to wean. In such cases $\dot{V}O_{2,\text{resp}}$ may increase to such an extent that the working respiratory muscles may "steal" oxygen and blood from other tissues.

Animal studies provide strong support in favour of this "stealing effect" theory. When dogs with cardiogenic or septic shock [62, 63, 69, 82] were mechanically ventilated, only 3% of their CO was directed to their respiratory muscles. On the contrary, when these dogs were allowed to breathe spontaneously their respiratory muscles received up to 20% of the CO, stealing blood from other organs, such as the brain, liver or other muscles. It has also been shown in animal models that activation of small afferent neural fibres from intensely working respiratory muscles results in active vasoconstriction of vessels supplying other organs [83], further diminishing their nutrient flow, which is probably diverted to the respiratory muscles. This decrease in the blood flow supplying other organs could theoretically predispose them to dysfunction. Furthermore, at least for the brain, this could also have an impact on the function of the respiratory muscles *per se* by affecting the output of the respiratory centre. In fact, in an elegant animal model, NAVA and BELLEMARE [84] have shown that when dogs were subjected to shock, thus reducing their carotid blood flow, they gradually developed (after an initial increase) a decline both in P_{di} and the electrical activity of the diaphragm (E_{di}), followed by development of respiratory arrest (apnoea). Interestingly, the values of P_{di} measured in response to phrenic nerve stimulation before shock and soon after apnoea were not different, suggesting that respiratory failure and apnoea resulted from a decrease in central neural output to the respiratory muscles (central fatigue) and not from peripheral contractile failure.

Various studies have tried to address the issue of $\dot{V}O_{2,\text{resp}}$ in patients during weaning [85–88]. Their results do not seem, at a first glance, to provide strong evidence that

the respiratory muscles were creating a stealing effect despite the relatively high $\dot{V}O_{2,\text{resp}}$ values obtained. However, this holds true as far as the mean values of $\dot{V}O_{2,\text{resp}}$ are considered in the patients studied. When the results are being analysed on a patient-by-patient basis, the conclusions drawn can be quite different. Accordingly, FIELD *et al.* [85] measured the $\dot{V}O_{2,\text{resp}}$ in 13 patients with cardiopulmonary disease being weaned from artificial ventilation and found it to be on average 75 mL $O_2 \cdot \text{min}^{-1}$, representing 24% of $\dot{V}O_{2,\text{tot}}$. However, there were two patients in whom the $\dot{V}O_{2,\text{resp}}$ amounted to 286 and 157 mL $O_2 \cdot \text{min}^{-1}$, representing 55 and 44% of $\dot{V}O_{2,\text{tot}}$, respectively. It can be speculated that in these two patients, at least, the respiratory muscles were stealing energy from other tissues. Furthermore, BROCHARD *et al.* [86] measured the $\dot{V}O_{2,\text{resp}}$ in six patients during weaning and found similar values: mean $\dot{V}O_{2,\text{resp}}$ was 78 mL $O_2 \cdot \text{min}^{-1}$, representing 27% of the $\dot{V}O_{2,\text{tot}}$; but again, there was a patient whose $\dot{V}O_{2,\text{resp}}$ was 59% of his $\dot{V}O_{2,\text{tot}}$.

Similarly, OH *et al.* [87] and SHIKORA *et al.* [88] have studied occasional patients with $\dot{V}O_{2,\text{resp}}$ amounting to over 40% of their $\dot{V}O_{2,\text{tot}}$. Consequently, it can be assumed that there are patients whose respiratory muscles create a stealing effect during weaning, depriving other organs of oxygen and blood, and thus leading to weaning failure.

The final pathway to weaning failure: fatigue/hypercapnia/dyspnoea/anxiety/organ dysfunction

Up to this point, we have discussed the various factors that, by their interplay, may create an imbalance between ventilatory needs and neurocardiorespiratory capacity. We will now address the issue of how this imbalance may lead to weaning failure. Our thesis is that there are five pathways, not mutually exclusive, which may culminate in weaning failure, *i.e.*: fatigue; hypercapnia; dyspnoea; anxiety; and organ dysfunction. We will consider each one, presenting the available experimental data whenever possible.

The consideration of the imbalance between energy supply and demand of the respiratory muscles suggests that inspiratory muscle fatigue is frequently a final common pathway leading to inability to sustain spontaneous breathing and, thus, to weaning failure. Few data exist in this area. In a very influential study, COHEN *et al.* [89] studied 12 patients with various disorders leading to hypercapnic respiratory failure after discontinuation of mechanical ventilation. To detect diaphragmatic fatigue, the power spectrum of diaphragmatic surface electromyographic activity was analysed. A sustained reduction of the ratio of high to low frequencies of the electromyograph (H/L) below 80% of the initial value was taken as indicative that diaphragmatic fatigue would ensue. Seven patients showed electromyographic evidence of inspiratory muscle fatigue. Electrical fatigue was followed by respiratory alternans and/or paradoxical inward movement of the abdominal wall during inspiration (abdominal paradox). However, it is possible that these changes may reflect alternations in central drive due to excessive loading response rather than inspiratory muscle fatigue *per se* [90]. Nevertheless, such high inspiratory loads observed during

weaning failure will eventually lead the ventilatory pump to exhaustion and overt fatigue which is, undoubtedly, a 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 failure of the forthcoming task.

Some of the controversy regarding the exact role of inspiratory muscle fatigue during weaning failure stems 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 [91]. 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 objective physiological or clinical test (or set of tests) that are unique indicators of fatigue [92]. However, recent data offer significant support in favour of fatigue. Respiratory muscle maximum relaxation rate (MRR) has been measured during the weaning process and a decline has been demonstrated in those patients failing to wean. It has also been shown to remain

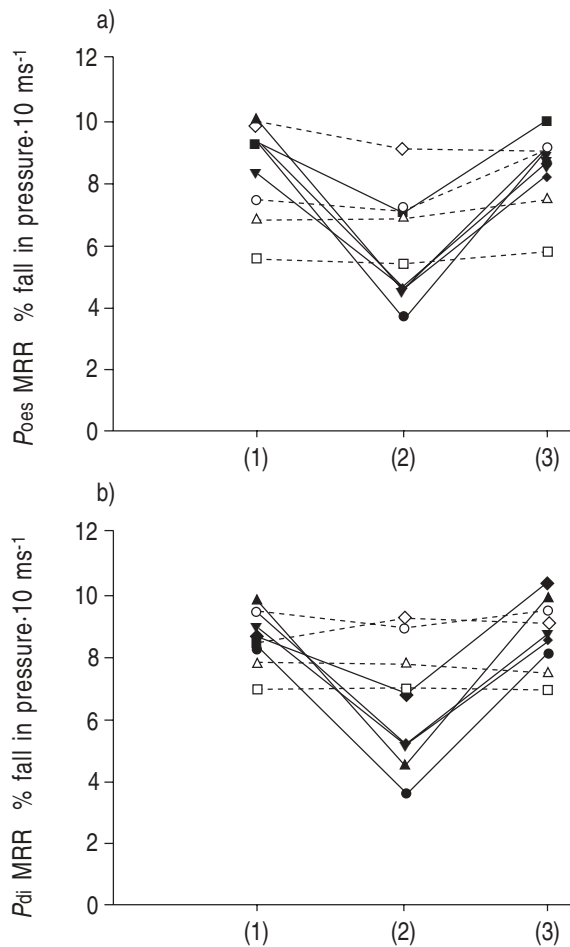


Fig. 6. — a) Sniff oesophageal pressure (P_{oes}); and b) transdiaphragmatic pressure (P_{di}) maximum relaxation rates (MRR) in nine patients undergoing a weaning trial. MRR was measured before (1); during (2); and after (3) the weaning trial. MRR slowed in the five patients who failed to wean, returning to normal when mechanically ventilated. In the four patients who weaned successfully, MRR remained unchanged. Open symbols/dashed line: weaned; closed symbols/solid line: failed. Modified from [93], with permission.

unchanged in those weaning successfully [93] (fig. 6). This suggests that, during failing weaning trials, a fatigue process is initiated peripherally into the respiratory muscles. When associated with the slowing of MRR, it is likely that the central drive is modulated [94].

Furthermore, using electrical criteria similar to COHEN *et al.* [89] to predict diaphragmatic fatigue, BROCHARD *et al.* [86] found that seven out of eight patients who met the usual criteria for weaning but who failed to wean exhibited electromyographic signs of fatigue during spontaneous breathing, followed by a decreased V_T , an increased f_R and the development of hypercapnia. Interestingly, all of these patients had increased energy demands as evidenced by the oxygen consumption ($V'O_{2,resp}$) of the respiratory muscles and the work of breathing per unit of time (W). W was always above 8–10 L·min⁻¹. When pressure support was applied, thus reducing the work performed by the muscles, diaphragmatic fatigue was prevented (fig. 7).

Impaired diaphragmatic function during weaning was also implicated by POURRIAT *et al.* [95], who studied diaphragmatic function and the pattern of breathing in patients with COPD being weaned from mechanical ventilation after acute respiratory failure. They noted that when P_{di} was expressed as a fraction of the maximal P_{di} ($P_{di,max}$) this value reached a mean of 46% in the group failing to wean. According to ROUSSOS and MACKLEM [96] a $P_{di}/P_{di,max}$ ratio greater than 40% cannot be tolerated for long periods without fatigue of the diaphragm. It has also been possible, in these patients, to measure the load imposed on the respiratory muscles and their capacity. When the ratio of load to capacity (*i.e.* $P_i/P_{i,max}$ ratio) is high, weaning fails [10, 97]. In fact, $P_i/P_{i,max}$ had an excessively high mean value amounting to 0.42 ± 0.11 in patients failing at discontinuation from mechanical ventilation [10] as did the ratio of P_{peak} to $P_{i,max}$ (fig. 8b). Additionally, dynamic

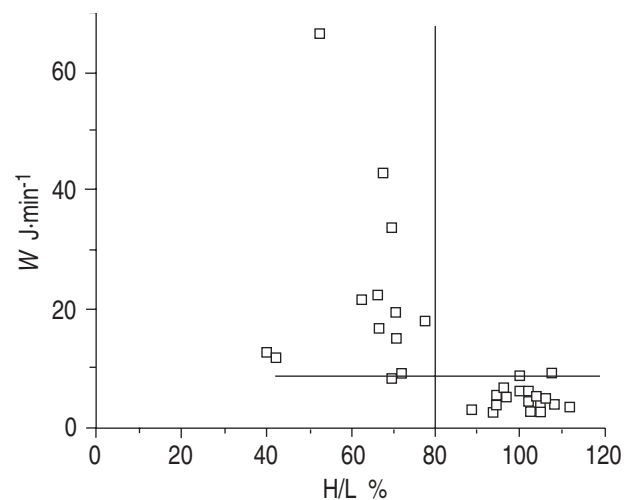


Fig. 7. — Plot of individual values of the respiratory muscles power (W) against H/L of the diaphragm during weaning trials. H/L was expressed as a fraction of its initial value in each period. Two regions can be distinguished: 1) above a certain level of W (horizontal line), values of H/L were in the zone of fatigue (left of vertical line) and patients were failing at weaning; 2) below this level of W , no evidence of fatigue occurred and patients were weaned successfully. H/L: ratio of high to low frequencies of the electromyogram. (From [86] with permission).

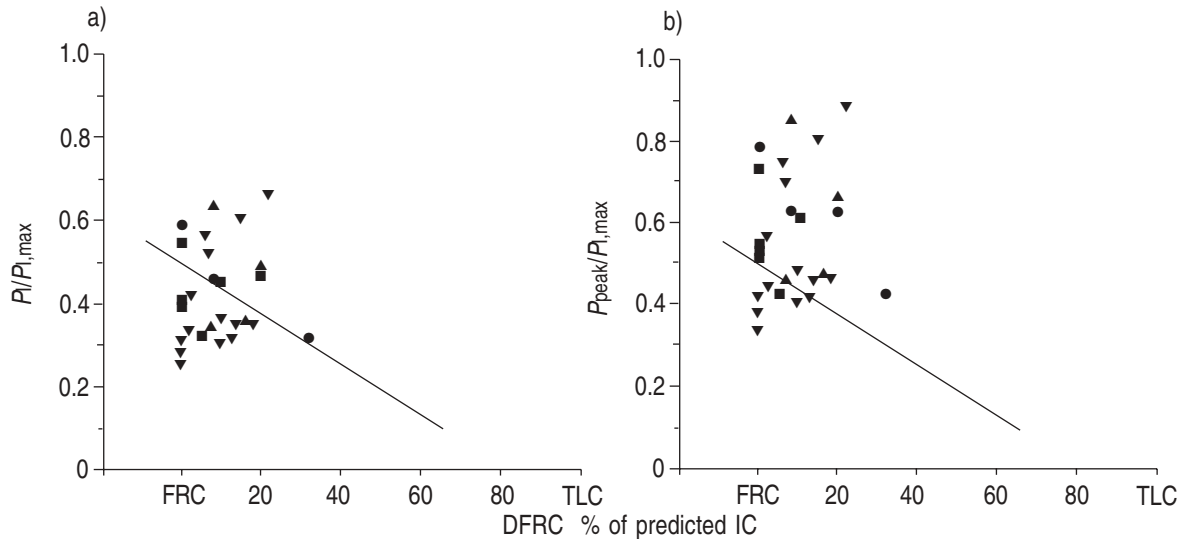


Fig. 8. – Pressure-volume diagram similar to that of Roussos *et al.* [7] plotting the ratio: a) $P_i/P_{i,max}$; and b) $P_{peak}/P_{i,max}$ against DFRC expressed as percentage of predicted inspiratory capacity (IC). The solid line was constructed from data in normal subjects and represents the critical inspiratory pressures above which fatigue may occur. At normal FRC, the critical inspiratory pressure per breath above which fatigue may occur in normal subjects is about 50% of maximum inspiratory pressure, whereas at FRC +50% 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 remaining away from it, as happens in normal subjects. $P_i/P_{i,max}$ and $P_{peak}/P_{i,max}$: mean and peak inspiratory pressure per breath, respectively, expressed as a fraction of maximum inspiratory pressure in 10 normal subjects. DFRC: dynamic hyperinflation; FRC: functional residual capacity; TLC: total lung capacity; ● : chronic obstructive pulmonary disease; ■ : adult respiratory distress syndrome; ▼ : other pulmonary disease; ▲ : extrapulmonary disease. (From [10] with permission).

hyperinflation amounting to 0.25 ± 0.19 L was present in almost all patients. When the ratio $P_i/P_{i,max}$ was plotted against the dynamic increase in FRC to account for the effect of hyperinflation, 13 out of 31 patients (42%) were placed above a hypothetical critical line representing the critical inspiratory pressure above which fatigue may occur. In addition, all patients were gathered around the critical line [10] (fig. 8). Furthermore,

the combination of a decrease in inspiratory load and an increase in neuromuscular competence (as indicated by an increase in MIP) is adequate to make weaning successful in patients previously unable to wean [10, 97] (fig. 9). In conclusion, fatigue of the inspiratory muscles frequently seems to be a final common pathway, leading to the inability to sustain spontaneous ventilation and, thus, to weaning failure.

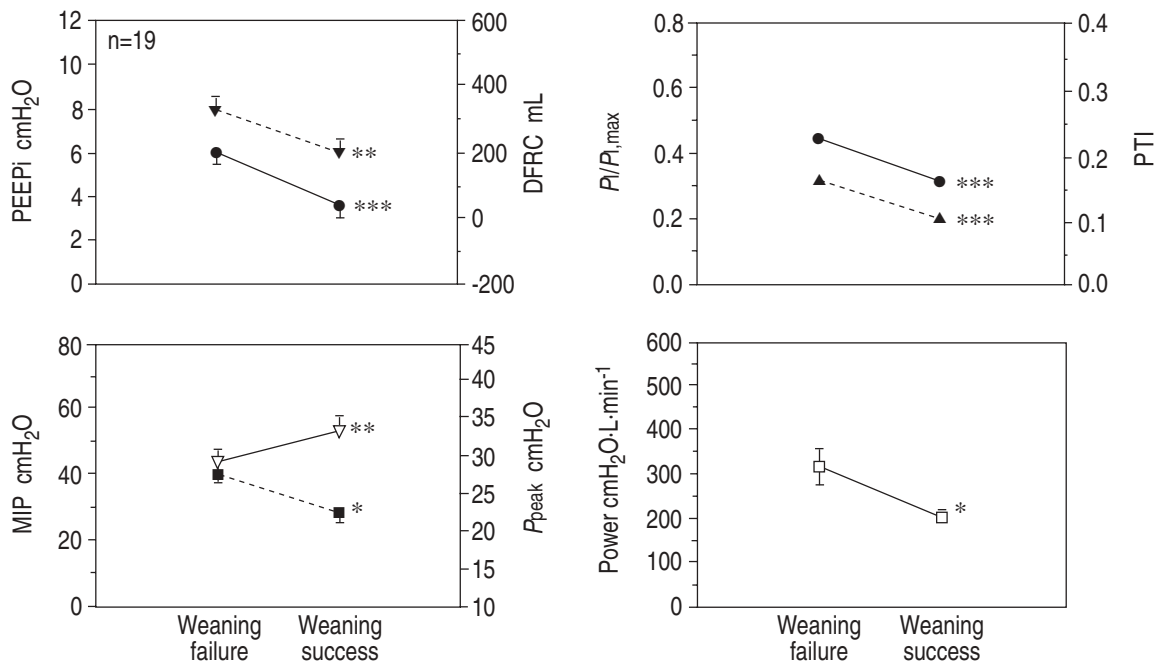


Fig. 9. – Various determinants of load (PEEPi, P_{peak} and $P_i/P_{i,max}$), capacity (MIP), and energy demands (PTI and Power) in 19 patients during weaning failure trials (Weaning failure), and 5–18 days later when the patients were able to wean successfully (Weaning success). Power = total power of the respiratory system. These data suggest that in patients unable to wean the combination of a decrease in inspiratory load and an increase in ventilatory capacity is adequate to make the weaning successful. PTI: pressure time index; MIP: maximal inspiratory pressure; ***,****: $p < 0.05$, < 0.01 , < 0.001 vs weaning failure. ● : PEEPi; ▼ : DFRC; ▽ : MIP; ■ : P_{peak} ; ○ : $P_i/P_{i,max}$; ▲ : PTI; □ : power. For further definitions see legends to figures 5 and 8.

The development of acute hypercapnia is another potential pathway leading to weaning failure. For instance, a patient with decreased central drive, for whatever reason [29], will develop respiratory acidosis upon withdrawal from ventilatory support due to development of alveolar hypoventilation, and thus will fail to wean. Patients with Guillain-Barré [31] or myasthenia gravis, who have decreased pressure generating capacity ($\downarrow P_{I,max}$) due to their disease process, may develop acute hypercapnia even though the tension-time index of the diaphragm (TTIdi) does not exceed the fatigue threshold [98], suggesting that fatigue is not responsible for the failure to wean. Since we feel that this issue is easily understood, we will not go into it in detail; however, the closely associated pathways of dyspnoea and anxiety are more complex and deserve thorough discussion.

The fact that weaning may fail due to psychological factors has been repeatedly reported [28, 66]. However, no reliable explanation has been provided. The true physiology is very difficult to explore, since one has to combine the psyche with the body functions, something that we are far from being able to do. However, a few comments can be made. During weaning trials, patients experience a substantial degree of dyspnoea [99–101], which is frequently underestimated by their physicians [99]. However, this should not be unexpected since dyspnoea (discomfort experienced and associated with breathing) is closely associated with the sense of effort. More specifically, small interneurons high in the CNS are thought to transduce the firing frequency of a complex motor programme to the respiratory muscles by collateral discharge to the sensory cortex, acting conceptually as "central receptors" for the sense of effort. The actual anatomical location of these pathways, however, remains uncertain [102]. The perceived effort (Ψ) during breathing is related to the pressure generated by the inspiratory muscles (P_I) and the inspiratory duration (t_I) [103].

$$\Psi = k \cdot P_I^{1.3} \cdot t_I^{0.56} \quad (9)$$

Furthermore, for the same pressure generation (P_I) the perceived effort increases when the maximal inspiratory pressure (MIP) that can be generated decreases and when the inspiratory flow and the inspired volume increase [104]. Finally, the magnitude of perceived effort and dyspnoea increases significantly when fatigue of the respiratory muscles develops [105].

All these factors that participate in the generation of the sense of effort and the closely associated sense of dyspnoea usually coexist in the patient who fails to wean (as is evident from the previous discussion). Accordingly, PETROF *et al.* [98] measured dyspnoea in seven COPD patients during weaning trials before and after the application of continuous positive airway pressure (CPAP). They found that CPAP reduced the sense of dyspnoea in all of them and attributed this beneficial effect to the reduction of the inspiratory mechanical load, especially that due to PEEP_i, mediated by the application of CPAP. Furthermore, KNEBEL *et al.* [99] found substantial degrees of dyspnoea in the 21 patients they studied, both before weaning and during weaning trials using partial ventilator support, either in the form

of synchronized intermittent mandatory ventilation (SIMV) or in the form of pressure support ventilation (PSV). Interestingly, dyspnoea levels during the SIMV weaning trials predicted the ability to wean. Finally, convincing data for the role of dyspnoea in weaning failure are provided in a recent work by STROETZ and HUBMAYR [101], in which seven of the 14 patients that failed did so because of intense dyspnoea.

The question now arises: how could dyspnoea, a purely sensory modality, contribute to weaning failure? Although no definite answer can be given, some speculations could find scientific support. Most patients with chronic pulmonary disease have eliminated strenuous activities and behaviour that are associated with increased shortness of breath from their daily routine, even before they need mechanical ventilation. These patients typically develop a systematic decrease in tolerance for dyspnoea, and they often exhibit anxiety and avoidance in anticipation of any physical exertion. When starting trials of weaning from mechanical ventilation, many patients display fearfulness and apprehension related to the anticipation of dyspnoea rather than the stress of the activity *per se*; a response analogous to that observed when these "dyspnoea intolerant" patients initiate an exercise programme [106].

One could speculate that dyspnoea may be the limiting factor during weaning trials, as is quite often the case during exercise testing. Furthermore, dyspnoea seems closely associated with anxiety [107], and this is supported by the results of KNEBEL *et al.* [99], where both dyspnoea and anxiety were measured using a Visual Analogue Scale and were found to be highly correlated. In fact, it seems that in addition to motor output, sensory feedback from peripheral respiratory mechanoreceptors contributes markedly to respiratory sensation. When the relationship between effort (motor output) and the anticipated ventilatory consequence (instantaneous change in respired volume) is seriously disturbed, neuroventilatory dissociation (NVD) ensues, implying awareness of disproportionate or unsatisfied inspiratory effort.

The psychophysical basis of NVD probably resides in the complex central processing of integrated sensory information, originating from the collateral of the motor command output (*i.e.* the "central receptors" for the sense of effort) and the abundant respiratory mechanoreceptors. At a cognitive level, NVD may be recognized as a disparity between expectations (whether genetically programmed or learned) and current perceptions of the internal environment. This disparity may elicit patterned psychological and neurohumoral responses, among which anxiety is almost invariably present [108]. Anxiety potentially has four physiological consequences:

- 1) Muscle tone is increased and this leads to increased $V'O_2$ at the same time that the respiratory muscles also increase their $V'O_{2,resp}$. Increased muscle tone also elevates the chest wall elastic load *via* its effect on the intercostals [109]. Increased tension in the internal intercostal muscles makes inspiration more difficult, since they are expiratory muscles. On the other hand, increased tension in the external intercostals that are inspiratory muscles opposes expiration. Either effect renders the respiratory muscles less efficient.

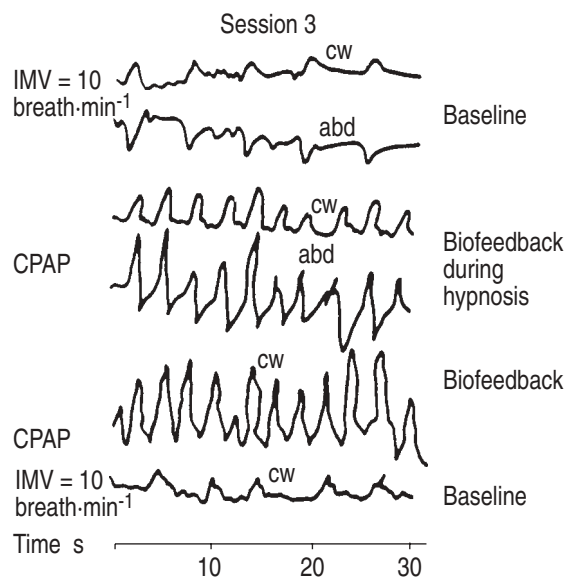


Fig. 10. — A typical session of biofeedback and/or hypnosis in a patient unable to wean from the ventilator. The patient was given visual feedback of the movements of the chest wall *via* an oscilloscope. Hypnosis was combined with biofeedback for a portion of each training period. The patient was hypnotized using an eye-fixation method, and under hypnosis was instructed to visualize herself breathing normally as she had 5 yrs before and to visualize herself breathing normally during the training session. She was then asked to open her eyes and view the biofeedback monitor. Intermittent mandatory ventilation (IMV) and continuous positive airway pressure (CPAP) was used to wean the patient. The session included initial and final baseline recordings. Upward deflections of the chest wall (cw) tracings indicate chest wall expansion. Abdominal wall (abd) movements were initially opposite to chest wall movements; however, this paradoxical pattern was normalized in part during biofeedback, and even more with biofeedback during hypnosis. (From [110], with permission).

2) Anxiety causes muscle deconditioning and this leads to disco-ordinate breathing, again increasing the load. Indirect proof for the above-mentioned effects comes from a recent study by HOLLIDAY and HYERS [109], in which relaxation biofeedback decreased intercostal muscle tension and improved breathing patterns that became more co-ordinated (fig. 10). The respiratory muscle efficiency was increased and the weaning time was reduced.

3) Anxiety increases the concentration of circulating catecholamines. This increases the heart's afterload (by increasing systemic vascular resistance), its preload (by constricting the great veins and forcing blood towards the heart) and the myocardial oxygen demands. In the "borderline" failing heart, this could contribute to the development of acute left ventricular dysfunction.

4) Breathing frequency may increase, which in turn, would increase the energy demands of the respiratory muscles, with obvious consequences.

Indirect evidence for the detrimental role of anxiety in the weaning outcome has been provided by various studies [110–112], where biofeedback and/or hypnosis were used to successfully wean patients who had previously failed at weaning. The beneficial effect of either intervention was attributed mainly to the achievement of a reduction in the anxiety experienced by the patients during the weaning trials.

In conclusion, the excess effort associated with the activation of the respiratory muscles of patients during weaning trials generates considerable dyspnoea and anxiety. This in turn increases the load of the inspiratory muscles and decreases their efficiency, thus necessitating even greater effort to achieve the required inspiratory pressure. But the greater effort increases dyspnoea and anxiety and in this way a vicious circle is established that may finally culminate in weaning failure.

The last pathway leading to weaning failure is the development of organ dysfunction. This is easily understood as far as the heart is concerned. The work of LEMAIRE *et al.* [71] and HURFORD *et al.* [81] provided sound scientific support and have already been presented in detail (see 'The respiratory muscles as an impediment to the heart and blood flow' section in this article). Recent work [101, 113] lends further credence to the role of cardiac dysfunction in weaning failure. As many as one third of failures in the study by EPSTEIN [113] resulted solely or in part from congestive heart failure, whereas 21% of the patients of STROETZ and HUBMAYR [101] failed due to the development of cardiovascular dysfunction (7% developed ventricular ectopy and 14% blood pressure changes).

Weaning may occasionally fail, however, due to organ dysfunction other than the heart. In the work of EPSTEIN [113], development of encephalopathy was recognized as the aetiological factor, and altered mental status appears to be a common cause for delayed weaning from mechanical ventilation [114]. Based on animal models [84] and theoretical considerations, one could speculate that the respiratory muscles were "stealing" blood and oxygen from the brain and that this was the reason for altered mental function.

Certainly, the pathways presented that lead to weaning failure are not mutually exclusive. For instance, a patient who develops fatigue will also develop dyspnoea [105] and probably anxiety; under these circumstances it is very difficult to separate each effect. However, keeping these in mind helps the clinician to understand the underlying physiology and plan therapeutic strategies.

Epilogue

In 1986, MILIC-EMILI [6] considered the question "Is weaning an art or a science?" A dedicated clinician might state that it is certainly an art, whereas a research physiologist may say that it is an applied science. However, this dichotomy is, in our opinion, inappropriate and can be rejected by an analogy: some years ago one could in no way think that computers had any relationship to art. People working with computers were considered as technocrats and were, in fact, contrasted to artists in the prevalent way of thinking. However, the time came when computers acquired capabilities that are nowadays serving art, something beyond the imagination of previous years. In weaning research, an analogous trend has to be followed in the future: put the science to work in the art of weaning. This paper will, hopefully, be a small contribution towards this perspective.

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