Weaning from mechanical ventilation: an update

SJC Verbrugge1,2, A Kulk1,2, C van Velzen1

1 Department of Anaesthesiology, St.Franciscus Hospital, Rotterdam, The Netherlands
2 Department of Intensive Care, St. Franciscus Hospital, Rotterdam, The Netherlands

Introduction
The process of weaning covers the entire process of liberating a patient from mechanical ventilatory support and from an endotracheal tube. It is one of the more challenging aspects of intensive care management and it is estimated that about 40% of the time spent on the ventilator is dedicated to weaning [1].

In a fully sedated/paralysed, completely passive patient the ventilator totally provides the inspiratory muscle work of breathing. In contrast, the entire work of breathing is completely resumed by a patient ready for discontinuation of mechanical ventilation. In between, during the process of weaning, the breathing workload is gradually transferred back to the patient [2]. Overly aggressive and premature discontinuation of ventilatory support can precipitate ventilatory muscle fatigue, gas exchange failure and loss of airway protection [3]. On the other hand, prolonged periods of gradual withdrawal from mechanical ventilation carry the risk of ventilator-induced lung injury, nosocomial infection, airway trauma and increased cost of care [3].

Taking the weaning process into consideration as early as possible after intubation may substantially improve the success and speed of weaning [4]. In this article, we review the latest insights into the process of withdrawal from the ventilator.

Physiology
During spontaneous breathing, the work of breathing performed in any given phase of an inspiratory breath is the product of pressure and volume, and corresponds to the area enclosed under the dynamic pressure-volume curve [5]. The interplay between the compliance of the lung (C) and the resistance of the airway (R), the so-called time constant: R x C, determines the time needed to exhale [5]. It can be either increased, as in obstructive lung disease, or decreased, as in restrictive lung disease. For a constant alveolar minute ventilation in each respiratory system with a certain time constant, there is an optimal frequency resulting in the lowest overall work of breathing [6] (Figure 1).

Correspondence
SJC Verbrugge
E-mail: serge.verbrugge@gmail.com

Factors decreasing the success of weaning
Ventilator-induced diaphragmatic dysfunction
It has been established that mechanical ventilation may not only...
damage previously healthy lungs, but may also damage previously normal respiratory muscles. Studies in both humans and animals have shown that controlled mechanical ventilation may induce dysfunction of the diaphragm, resulting in decreased force generating capacity, called ventilator-induced diaphragmatic dysfunction (VIDD) [8].

In animal studies, VIDD has been shown to be an early (<12 hours) and progressive phenomenon. The development of atrophy is more pronounced in the diaphragm than in the peripheral skeletal muscles which are also inactive during controlled mechanical ventilation [8]. Direct evidence for VIDD in humans is very limited [9].

### Table 1. Ventilator-induced diaphragmatic dysfunction - critical illness polyneuropathy

#### Factors associated with ventilator-induced diaphragmatic dysfunction

<table>
<thead>
<tr>
<th>LUXATING</th>
<th>PREVENTIVE</th>
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<tbody>
<tr>
<td>Aminosteroidal neuromuscular blockers</td>
<td>Partial support modes of ventilation</td>
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<tr>
<td>Muscle stretch (PEEP)</td>
<td>Phrenic nerve stimulation</td>
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<td></td>
<td>Intermittent spontaneous breathing</td>
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<td>Antioxidant supplementation</td>
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<td>Benzylisoquinoline neuromuscular blockers</td>
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#### Factors associated with critical illness myopathy/ polyneuropathy

<table>
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<tr>
<th>LUXATING</th>
<th>PREVENTIVE</th>
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<tbody>
<tr>
<td>Severity of illness</td>
<td>Tight glucose control</td>
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<tr>
<td>Duration of organ dysfunction</td>
<td>Sepsis therapy</td>
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<tr>
<td>Renal failure</td>
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<tr>
<td>Renal replacement therapy</td>
<td>INCONSISTENT</td>
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<tr>
<td>Hypermolality</td>
<td>Hypoxia</td>
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<tr>
<td>Parenteral nutrition</td>
<td>Hypotension</td>
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<tr>
<td>Low serum albumin</td>
<td>Age</td>
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<tr>
<td>Vasopressor/catecholamine support</td>
<td>Propofol</td>
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<td>Central neurological failure</td>
<td>Aminoglycosides</td>
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<td>Corticosteroids</td>
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<td>NMBA</td>
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Several factors are known to influence the development of VIDD. These factors have only been identified under experimental conditions and not in ventilated humans, and give some indications of how to prevent VIDD (Table 1) [8].

**Critical illness polyneuropathy and critical illness myopathy**

Difficult weaning from the ventilator has an historical value, since it was this clinical problem that permitted the identification and characterization of critical illness polyneuropathy (CIP) [10]. There are more human data available on factors related to CIP than on factors related to VIDD. Weaning problems due to CIP and critical illness myopathy (CIM) are attributed to involvement of the phrenic nerves and accessory muscles of ventilation [10]. The incidence of CIP varies, but may be as high as 100% in multiple organ failure [11]. CIP/CIM may prolong the need for ventilatory support; the duration of weaning in these patients may be increased 2 to 7 times and is associated with longer intensive care stay, hospital stay and higher mortality [11].

A number of independent risk factors for the occurrence of CIP/CIM have been identified [11] (Table 1). A recent meta-analysis suggests that tight glucose regulation using intensive insulin therapy significantly reduces the incidence and duration of CIP/CIM [12]. Sepsis, systemic inflammatory response syndrome and multiple organ failure have been identified as crucial risk factors, and most authors agree on aggressive treatment of sepsis in the prevention of CIP/CIM [11]. In addition, corticosteroids and neuromuscular blocking agents (NMBA) should be used in selected situations only, at minimal dosages and for as short a period as possible [11]. Daily interruption of NMBA administration has been suggested [10]. Nutritional schemes and supplements, antioxidant therapies, testosterone derivates, growth hormone and immunoglobulins appear to have no beneficial effects on CIP/CIM in patients on the intensive care unit (ICU) [11].

Both VIDD and CIP/CIM will result in decreased diaphragmatic strength and endurance. Increased inspiratory resistance (tracheal tube, heat and moisture exchange devices, ventilator tubing and valves) and increased elastance/decreased compliance from hyperdynamic inflation or restrictive lung disease for example, may lead to further imbalance of respiratory load and capacity [3].

**Dyschronicity or asynchronicity**

The basic mechanism of patient-ventilator asynchrony commonly associated with all conventional modes of assisted mechanical ventilation is a mismatch between the patient’s neural inspiratory time and the mechanical inspiratory time [2]. It may occur in the form of wasted inspiratory triggering efforts (inspiratory trigger asynchrony), ineffective termination of mechanical breaths (expiratory trigger asynchrony), or inadequate ventilator flow delivery despite a matched inspiratory time (flow asynchrony) [2]. Patient-ventilator asynchrony imposes an additional burden on the respiratory system and may increase morbidity in critically-ill patients [13]. Monitoring of pressure, flow and volume waveforms is a valuable tool in helping physicians recognize patient-ventilator synchrony and to take appropriate action to improve this situation [14]. For example, if the respiratory system fails to
reach equilibrium volume at end-expiration passive functional residual capacity (FRC), the inspiratory muscles are forced to start contracting at volumes above passive FRC where alveolar pressure is positive, a phenomenon referred to as dynamic hyperinflation. This can be detected by a flow versus time curve, which will show that end-expiratory flow does not reach zero. This, in turn, increases the amount of inspiratory effort needed to trigger the ventilator and hence the work of breathing or even the inability to trigger the ventilator (ineffective effort). Thus, in chronic obstructive pulmonary disease (COPD) patients, ventilator settings should allow enough time for the lungs to exhale to reach passive FRC [14].

An abrupt decrease in expiratory flow from the previously established flow trajectory indicates the beginning of the triggering phase. The time lag between this point and the point at which the airway pressure and/or the volume begins to increase is called the triggering delay. If too long, it signifies inadequate efforts which will increase the work of breathing. A decrease in airway pressure may also be used to identify contraction of inspiratory muscles, but is usually less sensitive [14].

With termination of mechanical inspiration prior to neural termination, the patient will continue to generate inspiratory muscle pressure and the passive expiratory flow pattern will show no or low expiratory flow for some time after opening the exhalation valve. Opening of the expiration valve after termination of the neural drive of the patient results in a sharp decrease in inspiratory flow followed by an exponential decline in inspiratory flow towards the end of inspiration [14].

Cardiovascular dysfunction
Cardiopulmonary dysfunction may be the primary pathophysiological mechanism of failure to wean in the patient requiring prolonged mechanical ventilation [15,16]. Abrupt transfer from mechanical ventilation to spontaneous breathing may result in acute cardiopulmonary oedema in patients with pre-existing heart disease. The shift from positive to negative intrathoracic pressure results in a marked increase in central blood volume and eventually lung filtration pressure [17]. Secondly, extubation may enhance venous return and hence increase preload [15]. In addition, weaning may result in right ventricular enlargement due to an increase in right ventricular afterload and, through diastolic biventricular interdependence, in an increase in left ventricular end-diastolic pressure [17]. Finally, weaning may increase the work of breathing and the adrenergic state, increasing cardiac work and the myocardial oxygen demand [17]. This explains the occurrence of acute cardiopulmonary oedema and myocardial ischaemia in patients with pre-existing cardiac disease [17]. The analysis of cardiovascular and tissue-oxygenation variables such as mixed venous saturation, B-type natriuretic peptide and the positive cumulative fluid balance before and during weaning has been proposed for characterizing weaning-outcome profiles [17]. If failure to wean is suspected of being of cardiac origin, specific treatment based on diuretics, vasodilators and inotropic drugs should be proposed.

Analgo-sedation
Treatment of anxiety, provision of adequate analgesia and (if necessary) amnesia in critically-ill patients is humane. Additionally, it optimizes patient ventilator synchrony by preventing patients from ‘fighting’ against the ventilation pattern imposed upon them by the ventilator [18]. Treatment of delirium also seems pivotal as it has been shown to be an independent predictor of mortality in mechanically-ventilated patients on the ICU [19]. Injudicious use of analgo-sedative medication to produce a passive and motionless patient may, however, prolong weaning and length of stay on the ICU [20].

Promising new agents may be dexmedetomidine [21] and remifentanil [22], as on comparison with older agents, both may permit a significant reduction in weaning and extubation times. However, instead of seeking the ideal analgo-sedative agent [18], frequent evaluation and monitoring of analgesia and sedation with escalation/de-escalation of drugs [23] or daily interruptions in sedative infusions [23], are pivotal in avoiding oversedation and eliminating pain and agitation [24]. Effective structured protocolized approaches to sedation will result in a shorter time on mechanical ventilation and faster weaning, with faster discharge from the ICU [24].

Combining daily spontaneous awakening trials with daily spontaneous breathing trials results in even better outcomes for mechanically ventilated patients in intensive care [25].

Metabolic factors
Metabolic disturbances need to be evaluated if a patient fails to wean from mechanical ventilatory support. Hypophosphataemia and hypomagnesaemia have been associated with diminished diaphragmatic function, although the effects of replacement therapy on weaning outcome are not known [26]. Additionally, hypothyroidism with accompanying respiratory muscle weakness, diaphragmatic dysfunction and decreased respiratory drive is known but uncommon cause of ventilator-dependent respiratory failure [26]. Finally, treating adrenal insufficiency with stress doses of hydrocortisone increases the success of ventilator weaning [3].

Other issues
Weaning is associated with mental depression and treatment of this may be helpful. An important element of the care of patients during weaning is to devise methods of psychological support [3].

Critically-ill cancer patients with acute kidney injury have also been shown to have a longer duration of mechanical ventilation and weaning, with a longer ICU stay and higher ICU mortality compared with patients without acute kidney injury [27].

Organized tube secretions can significantly increase resistance and may affect tolerance to weaning [28]. The authors feel that suctioning the airway should be performed using a closed circuit which avoids disconnecting the patient from the ventilator and the risk of alveolar collapse [29]. In addition, we question whether the potential advantage of bag and valve ventilation to mobilize secretions outweighs the possible risks of high airway pressures which may be detrimental to the lungs [29].
Finally, it should be realised that weaning failure often results from persistent low-grade (pulmonary) infection, subclinical myocardial failure, anaemia and systemic disease such as subclinical adrenal insufficiency. Therefore, the underlying medical disease may be a more prominent reason for weaning failure than ‘incorrect’ weaning strategies.

**Increasing the success of weaning**

Apart from avoiding complications and treating factors that reduce the success of weaning where and when possible, a number of factors have been shown to increase the success of weaning.

**Protocol-driven weaning**

It has been shown that, compared with care guided by the individual practices of clinicians, use of weaning protocols to guide the weaning of patients from ventilatory support leads to shorter ventilation time, an increased rate of successful extubations and reduced costs [3,16,30,31]. To increase the efficacy, such protocols may be driven by non-physician healthcare providers, such as nurses [3,32]. A meta-analysis on the efficiency of protocol-driven weaning is currently in progress [33].

**Corticosteroids for laryngeal oedema**

Endotracheal intubation is associated with the development of glottic and subglottic oedema resulting in stridor upon extubation. Steroids could offer protection or treatment by virtue of their anti-inflammatory actions and reduce the need for subsequent reintubation. Recent meta analyses suggest that multiple-dose steroids (as opposed to a single dose) initiated 12-24 h prior to planned extubation decrease the global incidence of laryngeal oedema after intubation, and the need for subsequent reintubation in critically-ill adults [34-36]. No significant side-effects were identified in the studies included in the meta analyses. Based on this information, the use of routine prophylactic corticosteroid therapy should be considered in mechanically ventilated patients at risk for postextubation laryngeal oedema. A dosage schedule could be prophylactic methylprednisolone 20-40 mg every 4-6 h, initiated 12-24 h prior to a planned extubation in patients at high risk for postextubation laryngeal oedema [35].

**Early tracheostomy**

A major advantage of tracheostomy is facilitated weaning from mechanical ventilation through proposed mechanisms of lower resistance to breathing, less dead space, better removal of secretions and improved patient comfort with less need for sedation [37]. The timing of tracheostomy has been shown to correlate significantly with the duration of mechanical ventilation [38] and has been the subject of debate. Several authors were able to show a weaning benefit and a shortening in the duration of mechanical ventilation by early tracheostomy in selected patient groups (trauma patients, patients with brain injury, patients expected to require prolonged ventilation) [37,39-41]. However, other studies have failed to show any major benefits of early tracheostomy in a general population of intensive care patients [37,42,43]. Strong consideration should be give to early tracheostomy in patients who are likely to need mechanical ventilation for > 2 weeks [16].

**Nutritional support**

Malnutrition reduces respiratory muscle mass and can contribute to failure to wean and ventilatory dependency [26]. Although guidelines now support the use of enteral formulation characterized by its anti-inflammatory lipid profile, antioxidants and trace minerals in patients with acute lung injury and acute respiratory distress syndrome, no recommendations are made for weaning patients [44]. Specially high-lipid, low-carbohydrate formulations designed to manipulate the respiratory quotient and reduce carbon dioxide production are not recommended for routine use [44].

**Other issues**

The process of weaning patients from mechanical ventilation may be facilitated by the appropriate selection and use of bronchodilators, mucolytics and steroids. Sputum clearance may also be improved by postural drainage [45]. Additionally, proper humidification of inspired gases during mechanical ventilation remains a standard of care.

Intensive physiotherapy may help patients with weaning failure to be get off the ventilator. However, evidence supporting physiotherapy is scarce and larger studies with better methodology are needed to prove its effectiveness [10,46].

**Liberation from mechanical ventilation**

Of the adequately studied weaning predictors, only five (negative inspiratory force, minute ventilation, respiratory frequency, tidal volume and the rapid shallow breathing index) were associated with clinically significant changes in the probability of weaning success or failure [3]. Of the weaning indices, the rapid shallow

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**Figure 2.**

Simplified overview of a protocolized weaning process. After (52), see text for details. SBT = spontaneous breathing trial.
breathing index (ventilatory frequency/tidal volume) is the most frequently used, most accurate, reliable [47] and well-studied test in clinical practice [48]. Recent studies suggest that incorporating indices that measure ventilatory endurance and determine whether inspiratory muscle force is placed above the threshold of diaphragm fatigue may improve sensitivity and specificity to predict the long-term outcome of weaning [49,50]. Nevertheless, the predictive capacity of weaning indices is modest at best [51,52]. Furthermore, reliance on a single weaning parameter actually may only delay discontinuation of ventilation [4].

The more clinically relevant question is whether weaning predictors facilitate decision making on weaning [52]. New consensus guidelines do not recommend the routine use of weaning predictors [16], but rather suggest that patients are ready for weaning when lung injury is stable/resolving, oxygenation (using liberal criteria) is adequate, haemodynamics are stable and spontaneous breathing efforts are present [52] (Table 2). If so, a spontaneous breathing trial (SBT) on low-level pressure-support ventilation or unassisted breathing through a T-piece is indicated. An optimal SBT should last 30 min and may perhaps be extended to as long as 120 min in certain patient categories, such as those with COPD [52]. Assessment for extubation [53] should follow the successful completion of an SBT (Figure 2).

If SBT fails (Table 2), this should prompt the clinician to conduct a systematic search for reversible factors that may be responsible for weaning failure. In proceeding, the clinician must decide whether to perform daily SBTS or to more gradually reduce ventilatory support (progressive withdrawal) [52] (Figure 2).

Concerning SBTS, if clinical evidence for respiratory muscle fatigue is absent, multiple daily SBTS are well tolerated. If fatigue is evident during the SBT then clinicians should consider providing supported ventilation until signs of fatigue have resolved before proceeding with the next SBT [52].

Concerning progressive withdrawal, studies on the use of progressive withdrawal modes of weaning are conflicting [54]. Two randomized controlled trials compared progressive withdrawal techniques in patients satisfying readiness criteria but intolerant of a 2-h SBT [55,56]. One study showed a T-piece to be superior, while another preferred the use of pressure-support ventilation [55,56]. It is generally agreed that the use of synchronized intermittent mandatory ventilation should be discouraged as it leads to a longer weaning process [55,56]. Whether progressive withdrawal actually trains the respiratory muscles or whether it simply provides more time for recovery of the respiratory muscles and thus improves weaning is unknown [52].

**Extubation readiness**

Multiple weaning indices have been investigated as possible predictors of extubation outcome [53]. Assessment for extubation follows successful completion of an SBT. Even with the success of an SBT, the possibility of extubation failure is 10-20% [3]. Accurate prediction of post-extubation respiratory failure remains challenging and the integration of several parameters to predict post-extubation respiratory failure is most useful. These parameters include the cuff leak test, and an assessment that integrates cough strength, the volume of respiratory secretions and mental status/alertness [52].

**Alternative ventilation modes that improve weaning**

**Non-invasive ventilation**

Patients with COPD who are being weaned from mechanical ventilation are at increased risk of intubation-associated complications and mortality. Several randomized controlled studies have shown that the use of non-invasive ventilation (NIV) to advance extubation in this patient group may result in reduced periods of weaning, endotracheal intubation, and lower morbidity and mortality [57,58].

The use of non-invasive ventilation in the management of respiratory failure in unselected patients with post-extubation respiratory failure did not show clinical benefits [57,58]. However, in a subcategory of stable patients at risk for the occurrence of post-extubation failure (particularly those with chronic respiratory disease and hypercapnic failure) NIV instituted immediately after extubation may reduce the rate of re-intubation, the duration of ventilatory assistance and stay on ICU [57,58].

**Newer ventilation modes that improve weaning**

New modes of assisted mechanical ventilation have been introduced that aim to improve patient-ventilator asynchrony and increase the success of weaning [16]. With proportional assist...
ventilation (PAV), the support pressure provided is proportional to the pressure generated by the inspiratory muscles [16]. Automated tube compensation (ATC) compensates for the drop in pressure across an endotracheal tube during inspiration and expiration and compensates for the tube-related additional work of breathing [16], and has been shown to enhance patient ventilator synchronization. Additionally, other new ventilation modes for triggering utilize the diaphragmatic pressure [59] and the electrical activity of the diaphragm (neurally adjusted ventilatory assist, NAVA) as triggering signal [60]. Triggering delay and ineffective efforts do not occur in either method as mechanical inflation occurs almost immediately after the initiation of the patient’s effort. Although researchers have postulated a potential role for these new methods of weaning, they have not been thoroughly investigated in weaning trials for difficult-to-wean patients [3, 16].

**Closed-loop protocols in weaning**

There is conflicting evidence regarding the role of computerized weaning as opposed to ‘manual paper-based’ protocol weaning [61]. Closed-loop systems (e.g. adaptive support ventilation, mandatory minute ventilation and smart care) modify ventilatory parameters by predetermined algorithms and adapt ventilator output by comparing measured and actual values of specific parameters with target (i.e. ideal) values [61, 62]. While some systems were developed to support patients requiring controlled or assisted ventilation, other systems were specifically designed to guide selected aspects of mechanical ventilation such as weaning. Up to now, these systems have not been fully tested in specific patient populations which often prove challenging to wean from mechanical ventilation. Therefore, their impact on important clinical outcomes, and their value in comparison with other weaning techniques needs to be further elucidated [16, 61, 62].

Rather than instigating the need for computerized weaning procedures, the results of studies showing the benefits of computerized protocols may draw attention to the fact that clinicians are too slow to initiate weaning and that weaning is substantially shortened if started at the earliest possible time [63].

**Failure to wean**

It is estimated that 10-20% of patients who need ventilatory support will require prolonged mechanical ventilation >21 days, with substantial costs to health care [16, 26, 52]. However, a patient requiring prolonged mechanical ventilation for respiratory failure should not be considered permanently ventilator-dependent until three months of weaning attempts have failed [30]. The causes of failure to wean and prolonged mechanical ventilation are numerous and the first step is to address such causes in patients who are difficult to wean [3, 16, 26, 52, 64]. It should be realised that weaning failure often results from persistent low-grade (pulmonary) infection, subclinical myocardial failure, anaemia and systemic disease such as subclinical adrenal insufficiency. Therefore, underlying medical disease may be a more prominent reason for weaning failure than ‘incorrect weaning strategies. Weaning strategies in patients on prolonged mechanical ventilation should be slow-paced and should include gradually lengthening SBTs [30].

The demand for ICU beds has led to the development of facilities specializing in weaning, which tend to admit patients with single organ failure who do not require complex organ support. International data show that by concentrating effort in a specialist area, it is possible to decrease costs by decreasing the time spent on mechanical ventilation [64] and in the ICU [65]. Eventually, 50% of patients transferred to long-term facilities could be successfully weaned from mechanical ventilation [66, 67]. Such data would support the set up of a centre specialized in long-term weaning in the Netherlands.

Decisions to eventually withhold or withdraw mechanical ventilatory support should reflect a shared decision-making model. A full disclosure of prognostic data is necessary and the decision to withhold should be based on patient-centred interests and values [16].
Conclusion

Often, weaning is started too late after intubation and if factors that decrease the success of weaning are focused on soon after intubation, the weaning process may be more successful. Weaning should start from the moment the patient is put on the ventilator, by attempting to avoid factors that precipitate VIDD and CIP (Figure 3). With the patient on mechanical ventilatory support, patient-ventilator interaction should be optimally synchronized, avoiding overzealous analgo-sedation (Figure 3). Newer weaning strategies and ventilation modes that improve synchrony, avoiding overzealous analgo-sedation (Figure 3). While the cause of failure of spontaneous ventilation is being resolved, one should constantly correct precipitating factors and optimize supporting factors for the weaning process (Figure 3).

Each institution should develop its own protocol for liberation from mechanical ventilation (Figure 3). It should be based on sound scientific data, taking into consideration the level of personal and technical support in the ICU (e.g. Figure 2). The exact role of automated closed-loop protocols needs further investigation (Figure 3). Patients who are expected to be on mechanical ventilation for a prolonged period of time may benefit from early tracheostomy and corticosteroids administered in advance of a planned extubation (Figure 3). Patients with COPD who show signs of post-extubation failure may benefit from early instituted trials of NIV (Figure 3).

Acknowledgments

The authors thank Mrs Laraine Visser-Isles for English language editing.

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