Prolonged weaning from mechanical ventilation: who, what, when and how?

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Abstract

Weaning from invasive mechanical ventilation is an important part of the management of respiratory failure patients. Patients can be classified into those who wean on the first attempt (simple weaning), those who require up to three attempts (difficult weaning) and those who require more than three attempts (prolonged weaning). The process of weaning includes adequately treating the underlying cause of respiratory failure, assessing the readiness to wean, evaluating the response to a reduction in ventilatory support, and eventually liberation from mechanical ventilation and extubation or decannulation. Post-extubation respiratory failure is a contributor to poorer outcomes. Identifying and addressing modifiable risk factors for post-extubation respiratory failure is important; noninvasive ventilation and high-flow nasal cannulae may be useful bridging aids after extubation. Factors to consider in the pathophysiology of prolonged mechanical ventilation include increased respiratory muscle load, reduced respiratory muscle capacity and reduced respiratory drive. Management of these patients involves a multidisciplinary team, to first identify the cause of failed weaning attempts, and subsequently optimise the patient's physiology to improve the likelihood of being successfully weaned from invasive mechanical ventilation.

Educational aims

- Describe the process of weaning a patient from invasive mechanical ventilation.
- Explain the pathophysiology of weaning failure.
- Provide management strategies that should be applied when managing a patient undergoing prolonged mechanical ventilation.

Introduction

Weaning from mechanical ventilation is a key task for any critical care specialist with 3% of all hospital admissions requiring mechanical ventilation [1]. Understanding the weaning process is essential not only for critical care specialists, but all hospital physicians, as they are likely to be caring for patients after they have been weaned.

Weaning should be considered in four steps: 1) adequately treating the underlying cause of respiratory failure, 2) assessment of the readiness to wean, 3) evaluation of the response to a reduction in ventilatory support, and 4) liberation from mechanical ventilation and extubation or decannulation. Early weaning is important, and the longer a patient receives invasive ventilation the more likely they are to develop complications, such as ventilator-associated pneumonia (VAP) [2, 3] and long-term weaning failure [4], both of which are associated with a greater mortality [5, 6]. In addition, the cost of care clearly rises with each day of mechanical ventilation [7, 8]. This review will first summarise the process of weaning from mechanical ventilation. It will then explore in more detail the pathophysiology of patients requiring prolonged weaning and management strategies to improve outcomes in patients who are difficult to wean.

Weaning classification

The 2005 International Consensus Conference in Intensive Care Medicine [9] provided a classification of weaning based on the time taken to successfully wean. Weaning success is defined as being liberated from any form of invasive mechanical support. Patients may be breathing spontaneously, or they may be supported by noninvasive positive pressure therapy. Simple weaning patients (group 1) are those who proceed from initiation of weaning to successful extubation on the first attempt without difficulty. Difficult weaning patients (group 2) are those who fail initial weaning and require up to three spontaneous breathing trials (SBTs) or up to 7 days from the first SBT to achieve successful weaning. Prolonged weaning patients (group 3) are those who fail at least three weaning attempts or require >7 days of weaning after the first SBT [9]. Of all patients receiving invasive mechanical ventilation, 24% did not have a weaning attempt, 57% weaned in <24 h (group 1), 10% weaned between 1 and 7 days (group 2), while 9% required >7 days to wean from mechanical ventilation (group 3) [10]. The "Weaning according to a New Definition" (WIND) study suggested further subdividing group 3 into 3a (prolonged weaning leading to a successful wean 7 days or more after the first attempt) and 3b (prolonged weaning without success) [10, 11]. The recent WEAN SAFE study, which analysed weaning outcomes in 5869 patients across 50 countries, reported that 35% of patients remained on mechanical ventilation at 90 days. They reported that 65% of patients had a weaning time of <1 day, 10% had a weaning time of 2–6 days, 10% a weaning time of >6 days, and 15% had weaning failure [12]. A limitation of assessing the incidence of weaning failure lies in the varying definitions of failure used in the literature [13]; however, an aggregate of several studies reported a weaning failure rate of 31% [9]. Similarly, other cohort studies of patients referred to regional weaning centres reported a weaning failure rate of 30–40% [14–16]. In this review, weaning failure after endotracheal intubation is defined as either a failed SBT, reintubation and/or resumption of ventilator support following successful extubation, or death within 48 h following extubation [9]. Weaning failure after prolonged weaning is defined as death prior to discharge from hospital or the need for invasive mechanical ventilation after discharge. It is important to note that there is considerable worldwide variation in weaning practices [12, 17, 18].

Process of weaning

The process of weaning from mechanical ventilation (figure 1) can be separated into four steps:

1) Adequately treating the underlying cause of respiratory failure
2) Assessment of the readiness to wean
3) Evaluation of the response to a reduction in ventilatory support
4) Liberation from mechanical ventilation and extubation or decannulation

Exploring the management of the underlying cause of respiratory failure in patients requiring mechanical ventilation is beyond the scope of this review. Suffice to say, however, that without the underlying cause being diagnosed and managed, any attempt to wean from mechanical ventilation is unlikely to be successful.

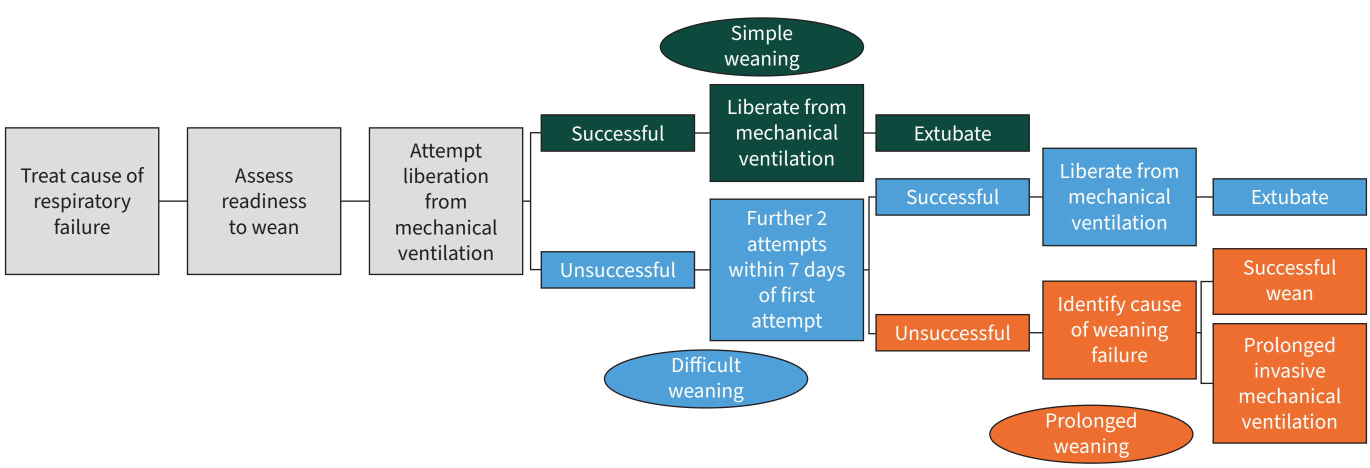

FIGURE 1 The process of weaning from invasive mechanical ventilation.

Assessing the readiness to wean

The frequent assessment of the readiness of a patient to wean is a key part of the weaning process and its importance is emphasised by the negative sequelae of delayed weaning [12]. Data suggest that clinicians frequently underestimate the ability of patients to successfully wean from mechanical ventilation; many patients are extubated on the first day of readiness assessments [19] and approximately half of self-extubations do not require reintubation [20]. This is relevant to all clinicians as a prospective cohort study reported that mortality was more than double when extubation was delayed [21]. It is essential that readiness to wean is assessed at least daily, to ensure early weaning is initiated as soon as the patient is ready to wean. A daily assessment of weaning readiness has been demonstrated to be a predictor of weaning success in itself [22]. Despite this, there is wide international variation in the practice of assessing the readiness to wean on a daily basis [18]. Assessment of the readiness to wean incorporates clinical assessment as well as measurement of objective markers. Clinical assessment includes confirming that the patient has adequate cough function and an absence of excessive tracheobronchial secretions. In addition, the clinician should ensure that the acute phase of the primary cause of respiratory failure for which the patient was intubated has resolved. Key objective markers to be assessed daily are displayed in table 1.

It is important to emphasise that these criteria are only indicators of potential successful weaning and not absolute prerequisites that must be met before weaning attempts. The clinician will need to use these criteria to guide their own clinical practice. Patients not satisfying all of the criteria can often be weaned successfully [22]. Indeed, the Weaning Task Force identified 462 weaning predictors in 65 observational studies and evaluated the ability of each variable to predict the outcome of an SBT [23]. The pooled likelihood ratios of the predictors were all found to have a low predictive power. At the time, the task force concluded that weaning predictors should be disregarded and the weaning process initiated with an SBT. Although there is now more evidence to support the use of weaning predictors (table 1), predicting successful weaning remains difficult and clinical judgement is an important element of the decision-making process.

Lung and diaphragm ultrasound have more recently been investigated as a predictive tool in weaning, as diaphragm dysfunction may play a significant role in weaning failure [24, 25]. In fact, impaired neuromechanical efficiency of the diaphragm has been demonstrated to predict weaning failure [26]. A meta-analysis and subsequent studies support the use of ultrasound to indicate those patients who are ready for a weaning trial [27–30]. However, these studies report differing ultrasound techniques and indices and so this tool needs comprehensive validation before being used in routine clinical practice.

TABLE 1 Key factors to be assessed daily when considering the readiness of a patient to wean

Clinical assessment
Adequate cough
Absence of excessive tracheobronchial secretions
Resolution of the acute phase of the disease for which the patient was intubated
Objective measurements
Stable cardiovascular status (*i.e.* heart rate $\leqslant$140 beats·min^{-1}, systolic blood pressure 90–160 mmHg, no or minimal vasopressors)
Stable metabolic status
Adequate oxygenation
Arterial oxygen saturation >90% on F_{IO_2} $\leqslant$0.4 (or P_{aO_2}/F_{IO_2} $\geqslant$150 mmHg)
PEEP $\leqslant$8 cmH$_2$O
Adequate pulmonary function
Respiratory rate $\leqslant$35 breaths·min^{-1}
Maximal inspiratory pressure $\leqslant$ −20 to −25 cmH$_2$O
Tidal volume >5 mL·kg^{-1}
Vital capacity >10 mL·kg^{-1}
Rapid shallow breathing index (respiratory rate/tidal volume) $\leqslant$105 breaths·min^{-1}·L^{-1}
No significant respiratory acidosis
Adequate mentation
No sedation or adequate mentation on sedation (or stable neurological patient)
Tympanic temperature between 36°C and 38°C
No relevant electrolyte disorder and haemoglobin level 70–80 g·L^{-1}

F_{IO_2}: inspiratory oxygen fraction; P_{aO_2}: arterial oxygen tension; PEEP: positive end-expiratory pressure. Reproduced and modified from [9] with permission.

Response to a reduction in ventilatory support

Once a patient is considered to be ready for a weaning trial, their response to a reduction in ventilatory support should be assessed. The purpose of the SBT is to determine the patient's ability to breathe spontaneously off the ventilator. It is performed either by reducing the applied airway pressure, to provide low levels of pressure support (5–10 cmH_2O), or by using a T-piece trial. A T-piece trial involves disconnecting the patient from the ventilator and attaching a T-piece to the endotracheal tube with supplemental oxygen as required. SBTs tend to last at least 30 min, increasing up to 120 min in patients considered to be at high risk of extubation failure [31, 32]. Of note, the patient's perspective about their ability to breathe unassisted has been demonstrated to improve the predictive value of the SBT [33]. Timely weaning trials are important; delay from meeting eligibility for a weaning trial to actual liberation attempt was associated with subsequent weaning failure [12, 18]. Failure of the SBT is indicated by any form of clinical instability during the trial. This can include haemodynamic compromise, cardiac arrhythmias, tachypnoea, hypoxia or hypercapnia on blood gases, increased respiratory effort, altered mental status, and agitation or anxiety. If it is not clear that the patient has passed at 120 min, the SBT should be considered a failure.

The literature indicates that there are no clear differences between pressure support and T-piece trials in their effectiveness in successfully weaning patients from mechanical ventilation. Various studies report conflicting results. A Cochrane review of nine studies with 1208 patients concluded no clear difference between pressure support and T-piece trials in achieving successful weaning (77% *versus* 73%, p=0.16), intensive care unit (ICU) mortality (9% *versus* 12%, p=0.32) or VAP (5% *versus* 8%, p=0.72) [34], albeit the evidence was judged to be of low quality. A subsequent systematic review comparing the two techniques also concluded that there was insufficient evidence to recommend one technique over the other [35]. A more recent randomised trial comparing 30-min pressure support *versus* 120-min T-piece SBT in patients deemed ready for weaning after at least 24 h of mechanical ventilation reported that the 30-min pressure support trial resulted in more successful extubations compared with the 120-min SBT group (82% *versus* 74%, p=0.001) [36]. In addition, hospital mortality was lower (10% *versus* 15%, p=0.02). There were no differences in reintubation rate or ICU and hospital length of stay [36]. However, it is difficult to draw practice-changing clinical implications from this study as the use of noninvasive ventilation (NIV) and high-flow oxygen therapy with nasal cannula (HFNC) to prevent post-extubation failure was not controlled. A large randomised study of 969 patients considered to be at high risk of extubation failure reported no difference in ventilator-free days or weaning outcome between pressure support trials and T-piece SBTs [37]. It is therefore acceptable to attempt to wean patients using either pressure support or T-piece SBTs, and the choice of strategy will largely be directed by local expertise. Once the patient has successfully completed a SBT, patients can then progress to be liberated from invasive ventilation. A recent multicentre randomised study has reported that reconnection to a ventilator for 60 min following a successful SBT reduces the risk of reintubation within 48 h [38]. Importantly, synchronised intermittent mandatory ventilation should be avoided in weaning from mechanical ventilation based on the outcomes of two landmark studies [19, 39].

Extubation

Extubation is the final step of the weaning process and involves removing the endotracheal tube. Patients who have successfully completed a SBT should be extubated if there are no contraindications. Contraindications include ongoing acute phase of the respiratory failure resulting in intubation, poor neurological status, excessive secretions, airway obstruction, cardiovascular instability or ongoing use of paralytic agents [40, 41]. Poor cough strength and excessive endotracheal secretions were associated with patients who failed extubation after a successful SBT [42]. In patients with upper airway obstruction, demonstration of air leak around the endotracheal tube after deflation of the cuff was adequate to proceed with extubation [43–45].

All patients should be reassessed for the above contraindications prior to extubation, even if they have successfully passed an SBT. When planning to extubate a patient, all equipment required to reintubate the patient should be readily available at the bedside. Patients should ideally be extubated in the upright sitting position. Immediately prior to extubation, the endotracheal tube and oral cavity should be suctioned. The patient should then be asked to take a deep breath and then exhale; as the patient exhales, the cuff should be deflated and the tube removed. After removal of the tube, the oral cavity should be suctioned and the patient asked to cough out any secretions. The patient should be provided with supplemental oxygen therapy and closely observed for several hours after extubation. Frequent airway suction is likely to be required during this time period [46].

Prevention of post-extubation respiratory failure

Post-extubation respiratory failure (PERF) is defined as the need for reintubation within 7 days of extubation. It is associated with considerably higher mortality compared with successfully extubated patients [47–49]. In addition, preventing PERF is likely to result in a lower likelihood of prolonged weaning, although reintubation after extubation has not been investigated widely as a risk factor for prolonged weaning. The cause of PERF is often excessive secretion load, fatigue, respiratory muscle weakness or fluid overload, and the patient should receive regular clinical review and be closely monitored. Factors that increase the risk of PERF include increasing age (age >65 years), pre-existing left ventricular dysfunction, anaemia, higher Acute Physiology and Chronic Health Evaluation (APACHE) II score and longer duration of mechanical ventilation [50]. The management of patients who are at high risk of PERF is not clearly defined. NIV and HFNC have been investigated as potential "bridging" support to reduce the risk of PERF in selected patients.

Noninvasive ventilation

NIV may be an effective tool to facilitate extubation. In patients with COPD who failed an SBT, extubation onto NIV compared with continued invasive ventilation with further SBTs resulted in a shorter time on mechanical ventilation (10 *versus* 17 days, p=0.021), shorter length of ICU stay (15 *versus* 24 days p=0.005) and a higher rate of weaning success (p=0.002) [51]. The evidence for the use of NIV in patients with conditions other than COPD is less clear. A randomised study in all-cause patients who had failed SBTs on three or more days demonstrated that when compared with continued invasive ventilation with SBTs, NIV resulted in shorter duration of invasive mechanical ventilation (10 *versus* 20 days, p=0.003), shorter ICU (14 *versus* 25 days, p=0.002) and hospital (28 *versus* 41 days, p=0.026) length of stay and higher ICU survival (90% *versus* 59%, p=0.045) [52]. A randomised trial comparing NIV with oxygen immediately post extubation in simple weaning patients who received mechanical ventilation for >3 days reported that NIV reduced the 48-h re-extubation rate (5% *versus* 39%, p=0.016) and the in-hospital mortality rate (0% *versus* 22%, p=0.041), without any difference in length of ICU stay [53]. A randomised study investigating chronic respiratory failure patients who had failed a SBT reported that when compared with invasive mechanical ventilation with SBTs, extubation onto NIV resulted in shorter duration of mechanical ventilation (5 *versus* 8 days, p=0.004) but without any difference in length of ICU or hospital stay, or in-hospital mortality [54]. Contrary to these studies, two large multicentre randomised studies have failed to demonstrate additional benefit of NIV. Esteban *et al*. [55] reported a trial that was stopped early, as it was found that extubation onto NIV compared with standard medical therapy in simple weaning patients with PERF resulted in a higher ICU mortality (25% *versus* 14%, p=0.048). The recent UK BREATHE trial compared protocolised weaning with early extubation to NIV against invasive ventilation in patients who had failed a SBT. The authors reported that NIV did not shorten the time to liberation from mechanical ventilation or improve mortality [56], but there was a reduction in invasive ventilator days and ICU length of stay with similar tracheostomy rate and mortality. A non-randomised prospective study in prolonged weaning patients with respiratory failure due to various causes reported that the addition of NIV as an adjunct to the weaning process had no effect on mechanical ventilation days, ICU length of stay or 1-year mortality, compared with weaning without NIV [57]. Clinicians must remember to carefully review the target population enrolled in these trials (*e.g.* under 65 years, non-obese and only moderate APACHE II scores) as this will guide the clinician as to which patients may benefit from early extubation using NIV if developing local protocols. Both of these trials contained a broad spectrum of conditions causing respiratory failure without preference to COPD and these trials are more reflective of the general ICU population. NIV has an important role in prolonged weaning patients and can facilitate decannulation onto long-term NIV [58]. Two meta-analyses, 10 years apart, comparing early extubation onto NIV with continued invasive ventilation have demonstrated that NIV decreases hospital mortality, incidence of VAP and ICU length of stay [59, 60]. The benefit of NIV was most pronounced in patients with chronic respiratory disease. Therefore, it appears that in patients with chronic respiratory disease, particularly those who are difficult-to-wean, the value of NIV in facilitating weaning is clear. It is less clear in patients without chronic respiratory disease and in these patients, NIV use should be limited to those units with a multidisciplinary weaning team with clinical expertise and established clinical protocols.

High-flow oxygen therapy with nasal cannula

HFNC is a more recent addition to the armoury in the management of respiratory failure. Two recent large studies have reported on the value of HFNC in preventing PERF. A randomised study comparing HFNC and conventional oxygen therapy in low-risk patients reported that HFNC reduced the risk of reintubation at 72 h (5% *versus* 12%, p=0.004) and PERF (8% *versus* 14%, p=0.03) [61]. A randomised study comparing HFNC with NIV in patients at high risk of PERF demonstrated non-inferiority of HFNC compared with NIV in preventing reintubation (23% *versus* 19%) and PERF (27% *versus* 40%) [62]. As there are potential patient comfort benefits of HFNC over NIV, this is a useful study to consider in clinical practice. Finally, the addition of HFNC to NIV in high-risk patients, when compared with HFNC alone, has also been demonstrated to reduce the risk of reintubation by day seven (12% *versus* 18%, p=0.02), PERF by day seven (21% *versus* 29%, p=0.01) and PERF until ICU discharge (12% *versus* 20%, p=0.009) [63].

Pathophysiology of difficult and prolonged weaning

The longer a patient spends on mechanical ventilation, the more likely they are to suffer adverse outcomes [8, 64]. Worldwide observational studies indicate that of patients who experience weaning failure, approximately 50% remain dependent on invasive ventilation at 1 year [65, 66] and that they have a 40–75% 1-year mortality [65–69]. Of patients who were successfully liberated after prolonged weaning, 42% required reinstitution of mechanical ventilation, and the longer the time spent on ventilation, the more likely they were to require reinstitution [70]. In addition, prolonged mechanical ventilation attracts increased healthcare-related costs. The in-hospital cost for patients who required >3 weeks of mechanical ventilation is three-fold greater than those who did not [8, 71, 72], and uses more than one third of the intensive care budget [73]. It is therefore imperative that difficult-to-wean patients are offered the highest probability of weaning from invasive ventilation to improve their outcome. As the literature tends to consider groups 2 and 3 of the 2005 International Consensus Conference in Intensive Care Medicine classification [9] together, they are also discussed together in this section. The two groups can be considered a spectrum of pathophysiological states that result in a failure to wean successfully after the first attempt. These difficult-to-wean patients comprise ∼20% of all patients weaning from mechanical ventilation, and therefore a sizable and important subgroup of patients whose management is far more complex, challenging and expensive than their small proportion would suggest [10].

The pathophysiology leading to difficult weaning can be best understood by considering the factors that contribute to adequate alveolar ventilation. In difficult-to-wean patients, the interaction between respiratory muscle load, drive and capacity should be considered, in relation to impairment of the neural respiratory pathway (figure 2). The resolution of the initial insult leading to the need for mechanical ventilation is the overriding contributor to successful weaning, and so consideration of the pathophysiology of difficult weaning assumes resolution of this initial insult.

Respiratory muscle load

Respiratory muscle load is the combination of resistive load, elastic load and threshold load [74]. Excessive secretions or bronchospasm can cause airway obstruction leading to increased resistive load. Elastic load is increased by atelectasis, pulmonary fibrosis, alveolar oedema and chest wall dysfunction. As a result of airflow limitation in severe exacerbations of asthma and COPD, gas-trapping will lead to increased intrinsic positive end-expiratory pressure (PEEP), resulting in increased threshold load [75, 76].

Respiratory muscle capacity

Respiratory muscle capacity is a measure of inspiratory muscle strength and endurance [74]. Thus, any condition causing respiratory muscle dysfunction will result in reduced respiratory capacity. In the critical care environment, most frequently this will be observed in patients suffering from critical care neuromyopathy and electrolyte disturbances such as hypokalaemia [77].

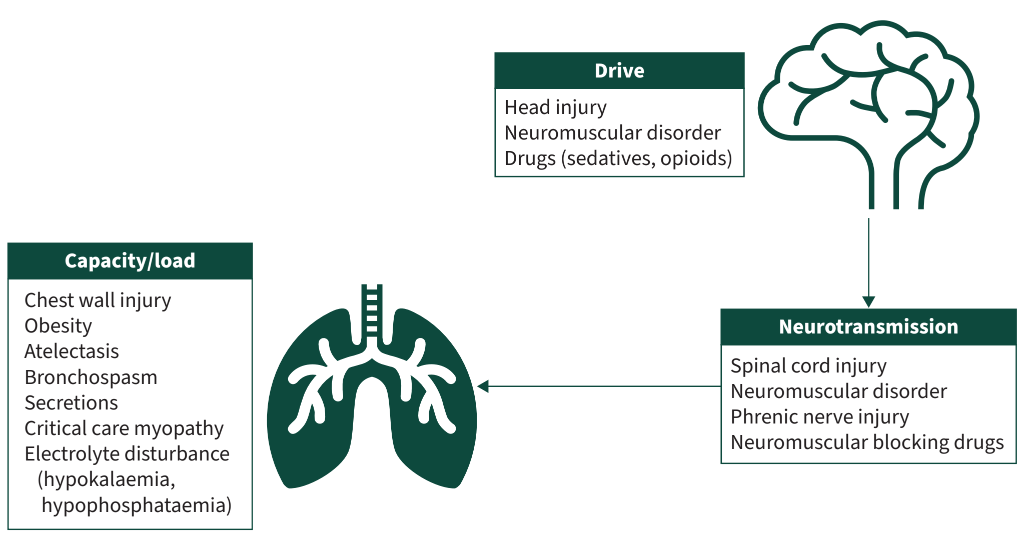

FIGURE 2 Potential causes of weaning failure that should be considered and addressed when managing an individual requiring prolonged weaning.

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Respiratory muscle drive

Respiratory muscle drive is the transfer of neural signals from the respiratory centre in the medulla through the spinal cord and on to the respiratory muscles, and is required to control the respiratory rate and tidal volume in response to changes in H^+ ion concentration in the cerebrospinal fluid [74]. Ongoing neurological dysfunction secondary to the initial insult or use of sedation, opioids and antiepileptic medication can lead to a depression of neural respiratory drive. In addition, metabolic alkalosis (*e.g.* caused by loop diuretics) can also result in reduced respiratory drive [78]. Interruption in the transmission of neural drive signals, such as observed in spinal cord injury (above C3), phrenic nerve injury or the use of neuromuscular blocking agents or aminoglycosides [79, 80], will also result in reduced drive. It is important for the clinician to assess respiratory muscle load, drive and capacity in all difficult-to-wean patients and adequately address and treat reversible conditions.

Management strategies for prolonged weaning

The management of patients requiring prolonged weaning requires input from a multidisciplinary team (figure 3), to maximise the likelihood of being liberated from invasive ventilation. Of patients who require prolonged mechanical ventilation, 55–65% are successfully weaned [14, 81]. A systematic approach should be adopted to address each factor influencing the efficacy of weaning efforts (figure 4), albeit there are limited data on difficult-to-wean patient cohorts. Patients requiring prolonged weaning are ideally cared for in specialised weaning units. Care provided at these units is significantly less costly than care provided by acute ICUs [82, 83].

Predicting weaning success

Predicting weaning success in prolonged weaning patients is even more difficult than in simple weaning patients. Indeed, a successful SBT may not be a useful marker of weaning success [53] and ICU admission severity scores are not predictive of weaning success [54, 55] in difficult-to-wean patients. A single centre observational cohort study of all-cause critically unwell patients reported on their weaning practice. All patients underwent a trial of pressure support ventilation once preset screening criteria were met (arterial oxygen tension to inspiratory oxygen fraction ratio >26.3 kPa, PEEP $\leqslant$5 cmH_2O, Richmond Agitation–

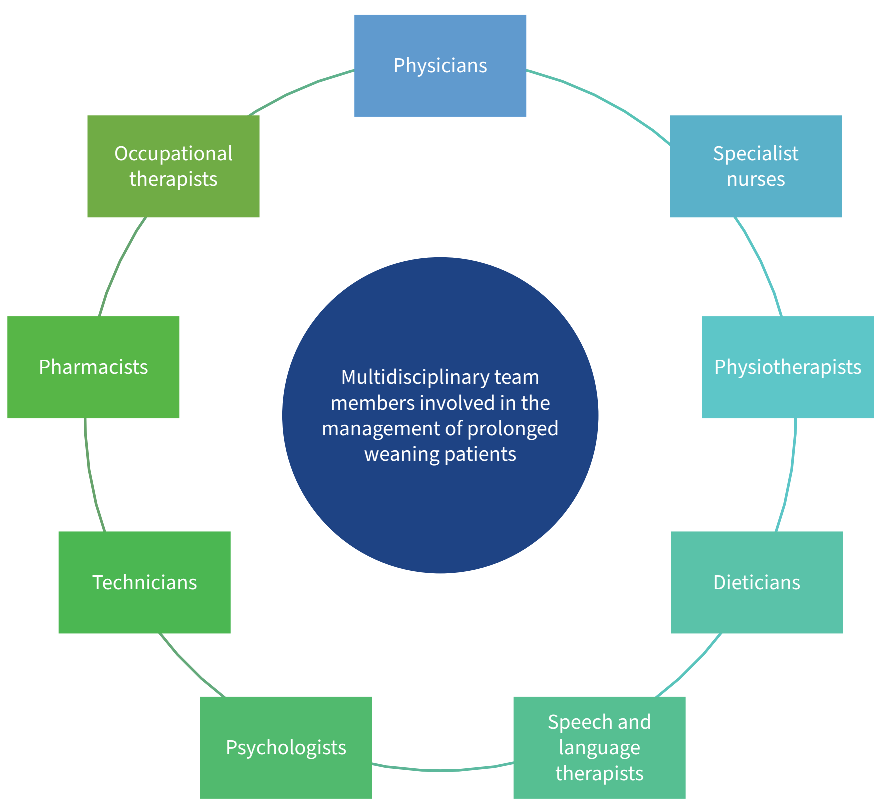

FIGURE 3 Members of the multidisciplinary team who are involved in the management of prolonged weaning patients.

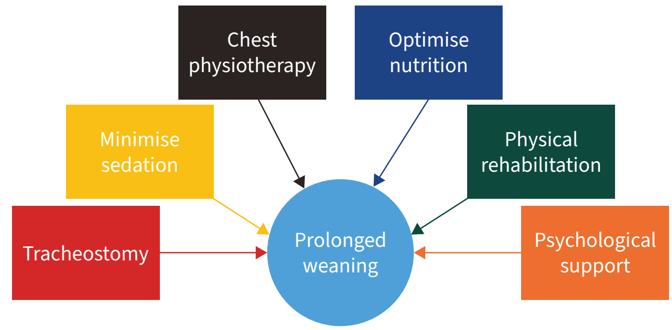

FIGURE 4 Management strategies to improve the likelihood of weaning from prolonged mechanical ventilation.

Sedation Scale $\geqslant 3$ (more awake than "moderate sedation") and cardiovascular stability). They reported that the failure to sustain pressure support for 24 h (due to hypoventilation, rapid shallow breathing unresponsive to titration of pressure support, or deterioration in pulmonary gas exchange) was associated with a two-fold increase in the requirement for mechanical ventilation for greater than 7 days (risk ratio 2.12, p=0.002) and a three-fold increase in ICU mortality (risk ratio 2.94, p=0.002). Multivariate regression demonstrated that only preweaning arterial pH (risk ratio 0.996, p=0.002) was associated with failure of a pressure support trial [84]. These data suggest that patients with lower arterial pH and those who are unable to tolerate early pressure support trials should be highlighted early in the course of their critical illness as possible difficult-to-wean patients, and a more cautious approach to weaning be taken.

Tracheostomy management

If a patient has not been successfully weaned, they should be considered for tracheostomy. Conversion from endotracheal intubation to tracheostomy results in improved physiology (increased tidal volume and maximum inspiratory and expiratory pressure, and decreased airway resistance and respiratory frequency to tidal volume ratio) [85]. The timing of tracheostomy remains controversial. Although the complications of prolonged endotracheal intubation are clear, tracheostomy insertion itself poses risk. Various observational studies have demonstrated that early tracheostomy can hasten liberation from invasive ventilation and improve weaning success, but not necessarily survival [86–89]. A large randomised study that compared early and late tracheostomy investigated a primary outcome of VAP incidence, and reported no difference. Secondary outcomes demonstrated that early tracheostomy when compared with late tracheostomy resulted in more ventilator-free days (11 days *versus* 6 days, p=0.02), and weaning success (77% *versus* 68%, p0.002) [90]. A Cochrane review demonstrated that although early tracheostomy was associated with lower mortality, the evidence was of insufficient quality to make a definitive conclusion [91]. A potential reason for this lack of clarity about timing of tracheostomy is the definition of "early" tracheostomy. The literature has defined early tracheostomy as anything from within 10 days [87–89, 91] to up to 21 days [87, 89] of endotracheal intubation. Despite this, the majority of units in the UK and Europe perform tracheostomies in difficult-to-wean patients within the first 14 days post-intubation [92, 93].

Once a patient has been tracheostomised, the goal is eventual decannulation. There is limited evidence to guide the development of protocols to advise on the method of decannulation and care tends to be personalised [94]. Tracheostomy tubes should be downsized, and patients should receive pressure support ventilation. As clinical stability is achieved, cuff deflation trials should be performed, with increasing duration and frequency. If successful, a one-way speaking valve can be introduced [95]. If cuff deflation trials are successful on a regular basis, the tube can be changed to a cuffless tube. In parallel, daytime self-ventilation periods should be increased aiming to achieve self-ventilation throughout the daytime. Once this is achieved, the tracheostomy tube can be capped, with overnight pressure support ventilation. Once this is achieved, the tracheostomy tube can be capped overnight, and NIV delivered at higher pressure support than required invasively. Once the patient can tolerate both daytime spontaneous ventilation and overnight NIV without any cardiorespiratory instability, decannulation can be performed, with continuation of NIV as required [96–98].

Minimise risk of VAP

VAP is one the most common causes of prolonged weaning, and is associated with prolonged length of stay and increased mortality [5]. An evidence synthesis of several guidelines on VAP prevention (European Task Force on VAP, the US Centers for Disease Control and Prevention, the Canadian Critical Care

Society, and the American Thoracic Society and Infectious Diseases Society of America) reported that the following factors may be useful to reduce the risk of VAP: 1) reducing the risk of PERF, 2) early tracheostomy, 3) use of subglottic secretion drainage, 4) nursing the patient in the semi-recumbent position, 5) minimising sedation use, and 6) oral care combining chlorhexidine rinse and mechanical cleaning [99]. Respiratory muscle weakness as a result of prolonged mechanical ventilation can result in inadequate secretion clearance, further increasing the risk of VAP. Respiratory physiotherapy is important for the optimisation of secretion clearance, but very little objective data exist to demonstrate the impact this has on weaning outcome.

Optimise nutrition

Although the importance of adequate nutrition in the critical care population is clear, an optimal nutritional strategy for patients requiring prolonged mechanical ventilation remains elusive. It appears that adequate early feeding is particularly important in those who go on to require prolonged ventilation [100]. A randomised study that compared permissive underfeeding with target feeding in patients admitted to critical care for more than 48 h demonstrated no difference in 28-day all-cause mortality (18% *versus* 23%, p=0.34), mechanical ventilation duration (11 days *versus* 13 days, p=0.1) or hospital length of stay (70 days *versus* 67 days, p=0.8). However, in-hospital mortality was less in the permissive underfeeding group (30% *versus* 42%, p=0.04) [101]. Similarly, although optimising trace elements such as magnesium enhances respiratory muscle function [102], there does not appear to be any clinical impact of this on the weaning population [103].

Physical rehabilitation

As a consequence of the catabolic phase-induced skeletal muscle loss in critical care [104], critical care-acquired weakness is highly prevalent in the prolonged weaning cohort [105] and a risk factor for the requirement for prolonged weaning [106]. Physical rehabilitation, particularly of the respiratory muscles, is therefore a crucial part of the weaning process [107, 108]. A randomised study compared a multimodal physical rehabilitation programme with usual care in prolonged mechanical ventilation patients. They demonstrated that the physical rehabilitation programme resulted in shorter time on ventilation compared with usual care (median: 17 *versus* 56 days, p=0.07) and a higher rate of successful weaning (87% *versus* 41%, p<0.01) [109]. A retrospective cohort study reported on prolonged weaning patients who underwent an incremental intensive physiotherapy programme. Weaning success was higher in patients who progressed further in the incremental programme, compared with those who did not (72% *versus* 56%, p<0.001). Logistic regression also demonstrated that further progression through the incremental programme was an independent predictor of successful weaning (odds ratio 2.2, p<0.001) [110]. A recent study demonstrated that the implementation of a protocolised physical therapy programme in prolonged weaning patients resulted in shorter time on mechanical ventilation and improved survival, although no effect on weaning success rate [111]. Similarly, a randomised study reported that inspiratory muscle training in prolonged weaning patients resulted in improved weaning success and survival [112]. Despite limited strong evidence for the inclusion of physical therapy in the management of prolonged weaning [113], there are no negative data and therefore, given the potential for benefit, this is a worthwhile intervention.

Psychological support

Critical care patients suffer from high levels of psychological morbidity [114]. A prospective cohort study of patients requiring prolonged ventilation reported that patients who failed weaning attempts had a particularly high prevalence of psychological symptoms, such as anxiety and fear [115] and delirium [116]. The presence of psychological morbidity can impact on the patient's ability to engage with the weaning process [117, 118]. Despite this, there are limited studies demonstrating the benefit of psychological interventions on outcome in critical care. A single interventional study was identified which demonstrated the value of intervention from a clinical psychologist on long-term psychological sequelae following critical care admission [119]. A recent randomised study failed to demonstrate any benefit of cognitive behavioural therapy on post-traumatic stress outcomes following critical care admission [120]. There are no studies investigating psychological interventions in the prolonged weaning population. Historical data have demonstrated that biofeedback techniques may have some benefit in difficult and prolonged weaning patients [121, 122].

Outstanding challenges to prolonged weaning

Early predictors for the readiness to wean in difficult-to-wean patients are required and this will become an increasingly important research priority. Although the use of diaphragm ultrasound is a potential clinical tool, comprehensive validation is required for this to be adopted into wider clinical practice. The use of NIV, outside of chronic respiratory disease, and HFNC in preventing post-extubation failure need further investigation to determine their safety, clinical efficacy and cost-effectiveness. In difficult-to-wean patients, the most appropriate timing of tracheostomy remains elusive, whilst the implementation of physical rehabilitation and psychological interventions needs to be further investigated. Poor sleep quality and architecture have been demonstrated in patients receiving prolonged mechanical ventilation [123]. Although this is not particularly surprising given that poor sleep quality has been widely reported in critical care patients [124–126], the impact of this specifically on weaning outcomes remains to be elucidated. Interventions aiming to improve sleep quality may result in shorter time to liberation from invasive mechanical ventilation. Finally, with the advent of artificial intelligence, the utility of machine learning in weaning needs to be further explored. It may have a role in predicting readiness to wean, but this is a relatively new technology with unclear results [127, 128].

Summary

Weaning from invasive mechanical ventilation is a key part of the management of the critical care patient and its early implementation has direct impact on outcomes. It remains difficult to predict accurately when a patient is ready to undergo a weaning attempt, and a combination of objective parameters and clinical judgement should be employed. SBTs can be conducted using either pressure support ventilation or a T-piece, depending on local expertise. To reduce the risk of PERF, extubation onto NIV in COPD has a clear benefit; less so in conditions other than COPD. HFNC has the potential to be useful in preventing PERF, but its safety and efficacy need further evaluation. Patients requiring prolonged mechanical ventilation suffer from profound and complex pathophysiology and require a multidisciplinary approach to prepare them for weaning attempts. As well as correcting the initial insult leading to the respiratory failure and daily assessment of the readiness to wean, these patients will require intensive input from physiotherapy, dietetics, occupational therapy and psychological services. Several specifics of weaning patients from invasive mechanical ventilation remain elusive, leaving many questions for future research.

Key points

- Weaning from invasive mechanical ventilation is an important task in the management of a patient with respiratory failure. Weaning can be split into simple, difficult and prolonged, based on the number of attempts taken to liberate the patient from mechanical ventilation.
- Early and frequent assessments of the readiness to wean, and early weaning attempts when the patient is ready, are important to improve overall outcomes.
- The risk of PERF may be reduced with the use of NIV or HFNC after extubation.
- Factors to be considered in the pathophysiology of prolonged mechanical ventilation include increased respiratory muscle load, reduced respiratory muscle capacity and reduced respiratory drive.
- The management of a prolonged weaning patient requires a comprehensive multidisciplinary assessment to 1) identify the cause of failed weaning attempts and 2) optimise the patient's physiology to improve their likelihood of successfully weaning from invasive mechanical ventilation.

Self-evaluation questions

1. The definition of prolonged weaning is:
   a) Liberation from invasive mechanical ventilation after first attempt.
   b) Liberation from invasive mechanical ventilation after up to three attempts within 7 days of the first attempt.
   c) The requirement for invasive mechanical ventilation for >7 days after first weaning attempt, or more than three weaning attempts.
2. Risk factors for the development of PERF include all of the following <u>except</u>:
   a) Pre-existing left ventricular dysfunction
   b) Anaemia
   c) Lower APACHE II score
   d) Longer duration of mechanical ventilation
   e) Increasing age
3. For which of the following methods to assess readiness to wean is there a stronger evidence base?
   a) A reduction in pressure support
   b) T-piece trial
   c) Neither

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Suggested answers

1. c.
2. c.
3. c.