

REVIEW

Clinical review: The ABC of weaning failure - a structured approach

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Abstract

About 20% to 30% of patients are difficult to wean from invasive mechanical ventilation. The pathophysiology of difficult weaning is complex. Accordingly, determining the reason for difficult weaning and subsequently developing a treatment strategy require a dedicated clinician with in-depth knowledge of the pathophysiology of weaning failure. This review presents a structural framework ('ABCDE') for the assessment and treatment of difficult-to-wean patients. Earlier recognition of the underlying causes may expedite weaning from mechanical ventilation.

Introduction and focus

In most patients, mechanical ventilation can be discontinued as soon as the underlying reason for acute respiratory failure has been resolved. However, 20% to 30% of patients are considered difficult to wean from mechanical ventilation. Weaning failure is defined as the failure to pass a spontaneous-breathing trial or the need for reintubation within 48 hours following extubation [1]. The risks associated with post-extubation distress and reintubation are considerable. Therefore, clinicians often choose to use a two-step diagnostic approach before extubation. First, weaning parameters are assessed (screening), and, second, a weaning trial is initiated. The validity of the different screening tools (for weaning), such as the rapid shallow breathing index and maximal inspiratory pressure, has been discussed in detail elsewhere [2]. Different techniques have been used for weaning and these include gradual reduction in mandatory rate during intermittent mandatory ventilation, gradual reduction in pressure support, and spontaneous breathing through a T-piece. Esteban and colleagues [3] concluded that trials of spontaneous breathing resulted in

faster liberation from mechanical ventilation compared with weaning using pressure support or intermittent mandatory ventilation. However, other studies failed to prove the superiority of spontaneous-breathing trials over pressure support ventilation as a weaning technique [4,5]. These differences in outcome most likely are related to the different designs of these studies, patient characteristics, and durations of mechanical ventilation before initiation of weaning. In-depth discussion of weaning techniques is beyond the scope of this paper and has been published earlier [2].

The pathophysiology of weaning failure is complex and often multifactorial. Accordingly, determining the reason and subsequently developing a treatment strategy require a dedicated clinician with in-depth knowledge of the pathophysiology of weaning failure. Several reviews have been published on weaning failure, but most focus on only one aspect of weaning and therefore are of limited help to clinicians. Complex clinical problems probably benefit from a structured approach. An 'ABC approach' is valuable in training juniors in trauma management [6]. In this paper, we present an opinion-based 'ABC approach' for difficult weaning. Unlike the ABC in trauma medicine ('treat first that kills first'), our 'weaning ABC' does not emphasize a specific order of assessment but is purely alphabetical and has the advantage of 'forcing' the clinician to systematically review the most likely causes for failed weaning. With the understanding of the barriers that impede successful weaning in a specific patient, a tailored treatment strategy that may reduce duration of mechanical ventilation can be designed. The following topics should be evaluated in a difficult-to-wean patient (Figure 1): airway and lung dysfunction, brain dysfunction, cardiac dysfunction, diaphragm dysfunction, and endocrine dysfunction. The algorithm presented in Figure 1 shows possible strategies to confirm the role of any of these items and options to reduce the contribution to weaning failure.

Airway and lung dysfunction

Elevated airway resistance, reduced respiratory system compliance, and impaired gas exchange increase the work of breathing and as such contribute to weaning

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	Airway / lung Compliance	Gas exchange	Brain	Cardiac	Diaphragm	Endocrine	Metabolic
Resistance							
Assessment	Flow-time loops, inspiratory occlusion	(A-a)D _{o2}	Screening: depression, anxiety, sleep pattern	12 lead ECG before at end SBT SvO ₂ before / at end SBT	Pi, max	Serial physical examination (other neuromusc disorders)	Electrolytes Blood gas Indirect calorimetry
Intervention	albuterol, steroids Repeat loops, inspiratory occlusion PEEP/Modify EIC in PSV bronchodilators	Radiology: Pleural fluid Atelectasis Ascites ↓ Diuretics Physiotherapy	Reorientation Mobilization Haloperidol	Echocardiography before & after SBT Afterload reduction Inotropes If ischemia: beta-blocker optimize hemoglobin	Early mobilization	Early mobilization	Provide adequate energy intake
Advanced assessment	Diagnostic bronchoscopy during SBT	Thoracosentesis	Neuropsychologist: depression, anxiety.	Pulmonary artery catheter	Diaphragm fluoroscopy / echography Pa,1	Examination by neurologist EMG, nerve conduction velocity	Plasma cortisol before / after 250 umol ACTH Plasma thyroid hormone
Advanced intervention				Afterload reduction Inotropes	Reduce analgetics/hypnotics	Reduce analgetics/hypnotics	Cortisol iv Thyroid hormone
Rescue assessment		Contrast echocardiography: intracardial shunt		BNP	Phrenic nerve conduction velocity Transdiaphragmatic pressure using gastric and esophageal balloon	Muscle biopsy	
Rescue intervention			Demmedetomidine	Levosimendan Bosentan	Diaphragm EMG Antioxidants (vitamin C and E) Inspiratory muscle training		

Figure 1. Framework for the evaluation of difficult-to-wean patients. For each patient, diagnostics as described in the white box should be performed to assess the reasons(s) for difficult weaning. Endocrine dysfunction is probably relatively rare and therefore is not included in the first line of evaluation. Possible treatment/interventions are mentioned but, of course, need to be individualized. If the first-line evaluation does not improve weaning, proceed to the next level (within the affected column). For instance, if airway resistance is elevated but is not affected by albuterol and optimizing ventilator settings, diagnostic bronchoscopy should be performed to visualize the central airways. Risks and benefits should be weighed in each patient. ACTH, adrenocorticotropic hormone; BNP, brain natriuretic peptide; CAM-ICU, confusion assessment method for the intensive care unit; DO_{2i}, oxygen delivery; ECG, electrocardiogram; EIC, end inspiratory cycling; EMG, electromyography; iv, intravenous; P_{0.1}, airway occlusion pressure at 100 ms; PEEPi, intrinsic positive end-expiratory pressure; Pi, max, maximal inspiratory pressure; PSV, pressure support ventilation; SBT, spontaneous-breathing trial; SvO₂, mixed venous oxygen saturation.

Table 1. Factors affecting respiratory mechanics

Increased airway resistance	Reduced compliance
Tube (small diameter, sputum retention)	Chest wall
Central airways	Edema
Tracheostomy malposition	Elevated abdominal pressure
Sputum plug	Pleural fluid and ascites
Corpus alienum (after trauma)	Obesity
Tracheomalacia or tracheal stenosis	Lung
Small airways	Intrinsic positive end-expiratory pressure
Asthma and chronic obstructive pulmonary disease	Alveolar filling (edema, pus, and collapse)
Acute respiratory distress syndrome	Pneumonia
	Interstitial lung disease and fibrosis

failure. The most prevalent causes for impaired mechanics are summarized in Table 1.

Resistance in weaning

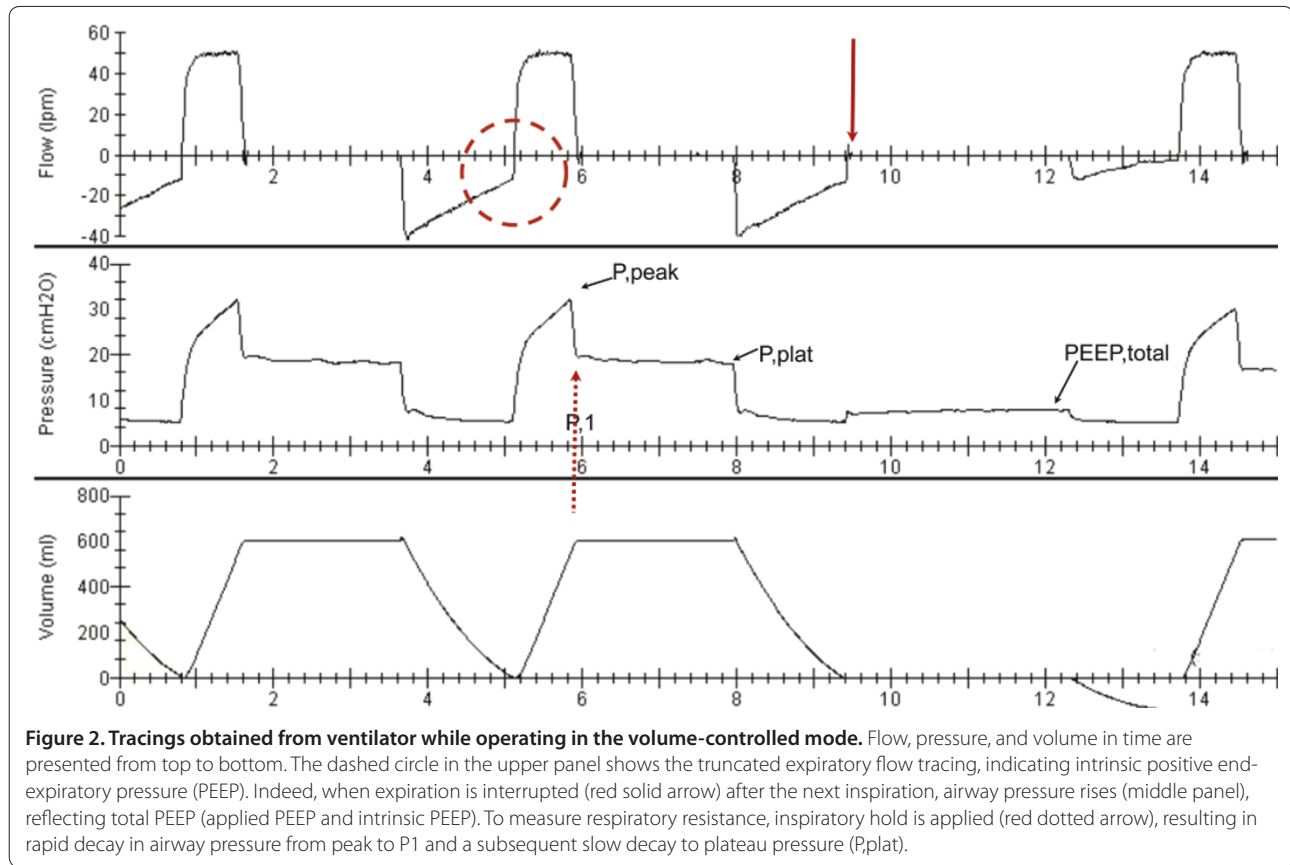
Resistance of the upper airway should be considered in difficult weaning. Rumbak and colleagues [7] found that tracheal obstruction caused by tracheal injury may contribute to weaning failure in patients who were on invasive mechanical ventilation for more than 4 weeks. Tracheal injury includes tracheal stenosis, tracheomalacia, and granulation tissue formation. In intubated patients, the endotracheal tube could increase airway resistance. Indeed, resistance of an endotracheal tube removed from a patient is significantly higher than the resistance of a new tube when tested in a laboratory setting and this is due to contamination of the tube with airway secretions [8]. No correlation between the duration intubation and the resistance of the tube was found. However, in general, it is a misconception that, after extubation, upper airway resistance decreases. In fact, the work of breathing in patients mechanically ventilated for ± 5.5 days increased after extubation, and this increase was probably due to edema of the upper airways [9].

Increased resistance of the small airways is a characteristic of chronic obstructive pulmonary disease (COPD) and asthma but has been demonstrated in acute respiratory distress syndrome (ARDS), and this latter increase was due to edema of bronchial walls. Vassilakopoulos and colleagues [10] showed, in a heterogeneous group of patients, that airway resistance is significantly higher when failing a weaning trial compared with a successful trial in these same patients. Jubran and Tobin [11] found that, in COPD patients failing a spontaneous-breathing trial, airway resistance significantly increases during this trial (9 ± 2 cm H₂O up to 15 ± 2 cm H₂O; $P < 0.05$), whereas in weaning-success patients, airway resistance did not increase significantly. These studies show that increased airway resistance may contribute to weaning failure.

Increased airway resistance is associated with the development of intrinsic positive end-expiratory pressure (PEEPi). PEEPi develops if expiratory time is shorter than the time needed to empty the lungs to the elastic equilibrium volume of the total respiratory system. Accordingly, PEEPi may develop because of increased flow resistance, expiratory flow limitation, high breathing frequency, and loss of elastic recoil of the lung. Indeed, in COPD patients with weaning failure, PEEPi is higher compared with those successfully weaned [11]. PEEPi acts as an inspiratory threshold before inspiratory flow can be generated and result in elevated work of breathing. In addition, pulmonary hyperinflation resulting from PEEPi places the diaphragm at a suboptimal position on the length-tension curve, impairing the ability to generate negative pressure. Moreover, PEEPi is associated with patient-ventilator asynchrony and, in particular, with ineffective triggering (inspiratory effort without ventilator support). Recently, de Wit and colleagues [12] showed that, in patients with a high incidence of ineffective triggering (>10% of all breaths) (as derived from ventilator waveform tracings), duration of mechanical ventilation is significantly longer compared with patients with a lower incidence of ineffective triggering. Although the causes for ineffective triggering are unknown in this study, it demonstrates the clinical relevance of patient-ventilator asynchrony. Measurement of airway resistance and PEEPi may help clinicians to understand the reason for failed weaning.

Resistance: diagnostic approach

Flexible bronchoscopy is the gold standard for diagnosing upper airway disease. Patients should be disconnected from the ventilator during bronchoscopy so that the presence of tracheomalacia can be assessed. Tracheomalacia may be treated with (nocturnal) non-invasive ventilation or placement of endotracheal stents [7]. Management of the other causes for central airways obstruction is usually evident but is complex in nature.



The flow-time and pressure-time loops provide a qualitative assessment of the presence of increased airway resistance and PEEP_i (Figure 2). When ventilating with a constant flow, a more quantitative assessment of total airway resistance can be obtained by measuring peak pressure, plateau pressure, and inspiratory flow:

$$R_{aw} = (P_{peak} - P_{plat}) / \text{flow}$$

(normal is less than 5 cm H₂O/L per second).

PEEP_i is obtained by subtracting PEEP_{appl} from PEEP_{tot}. Unfortunately, this technique is seldom satisfactory in spontaneously breathing patients. In those patients, the only way that PEEP_i can be measured adequately is by using an esophageal balloon.

Resistance: therapeutic strategies

In COPD patients being weaned with pressure support ventilation, appropriate setting of the cycle-off criterion is of importance to limit PEEP_i and the work of breathing, as demonstrated by Chiumello and colleagues [13]. Changing the cycling-off criterion from 5% to 40% significantly reduced PEEP_i and the work of breathing. These effects were most prominent at low levels of pressure support [13]. Applied PEEP may reduce

inspiratory work of breathing imposed by PEEP_i [14]. Applied PEEP should match the level of PEEP_i, as estimated by the expiratory occlusion technique.

Patients with asthma and COPD should be treated optimally to reduce bronchoconstriction. The effect of bronchodilators in patients without a history of COPD has not been tested, but if airway resistance appears elevated, latent obstructive airway disease may be present. Attention should be paid to the optimal delivery of inhaled medications as this will greatly influence its effect [15]. Clinical studies have shown that, in patients with COPD, the bronchodilating effect does not further increase after four doses of 100 µg of albuterol via metered dose inhaler. The effect of 400 µg of albuterol lasted for at least 60 minutes. The frequency of administration depends on the severity of bronchoconstriction and its clinical effect. The effect of the long-acting beta-2 agonist salmeterol (four doses of 25 µg) lasts for at least 6 hours [16]. However, it should be noted that the maximal bronchodilating effect of salmeterol is achieved after more than 30 minutes and therefore is less suitable in the acute setting. As much more experience is available for albuterol in mechanically ventilated patients, it remains the beta-2 agonist of choice.

Compliance

Respiratory compliance is determined by the compliance of the chest wall and lungs (Table 1). In patients with ARDS, compliance was significantly lower at the time of weaning failure compared with weaning success [10]. The static compliance of the respiratory system can be calculated after measuring inspiratory and expiratory plateau pressure and tidal volume (Figure 2):

compliance respiratory system = $TV / (P_{plat} - PEEP_{tot})$
(normal is 60 to 100 mL/cm H₂O). Optimizing compliance by reducing edema of the lung and chest wall, resolving atelectasis and thoracocentesis, and removing ascites may facilitate weaning.

Gas exchange

Most weaning patients still have considerable disturbances in gas exchange at the time of weaning and may develop hypoxemia or hypercapnia or both during a spontaneous-breathing trial [17]. Weaning-failure patients are frequently unable to increase minute ventilation in response to high arterial partial pressure of carbon dioxide (PaCO₂) because of respiratory muscle weakness, altered respiratory mechanics, and so on. In these patients, it is important to limit instrumental dead space (for instance, resulting from heat and moisture exchangers [18]) as much as possible.

Brain dysfunction

Delirium and depression in weaning

Brain dysfunction in difficult-to-wean patients is related mostly to delirium. Only one paper specifically studied the role of delirium in weaning, and the paper showed that impaired cognitive function was associated with a more than fourfold higher risk of failed extubation [19]. Other psychological disturbances, such as anxiety and depression, may interfere with successful weaning [20]. Sleep disruption frequently occurs in intensive care unit (ICU) patients, but no data showing the effects of disturbed sleep architecture on weaning are available.

Diagnostic approach

The confusion assessment method for ICU (CAM-ICU) is a well-validated screening tool for delirium in mechanically ventilated patients [21] and is available in numerous languages, but other screening tools have been validated as well [22]. Diagnosing other cognitive disorders in the ICU is best performed by psychologists or psychiatrists. In general wards, reducing risk factors for delirium reduces the incidence of delirium [23]. Midazolam is considered a risk factor for the development of delirium [24]. A recent multicenter trial indicated that sedation with dexmedetomidine reduced the incidence of delirium and reduced the duration of mechanical ventilation compared with sedation with midazolam [25].

Therapeutic strategies

High levels of sedatives are associated with increased time spent on the ventilator. A daily wakeup call and, if appropriate, subsequent spontaneous-breathing trials are associated with reduced time spent on the ventilator [26]. The role of sedatives in failed-spontaneous breathing trials or failed extubation is less clear. Depression is associated with weaning failure in patients admitted to a long-term weaning facility [27], and preliminary data suggest that pharmacological treatment of depression favors weaning from mechanical ventilation [20]. Sleep may be improved by limiting noise and light during sleep hours and adequately treating pain/discomfort. The effect of ventilator mode on sleep quality has been a subject of discussion [28,29], and differences in outcome are probably related to the level of pressure support.

Cardiac dysfunction

The transition from mechanical ventilation to spontaneous breathing imposes an additional load on the cardiovascular system because of intrathoracic pressure changes, which affect ventricular preload and afterload and increased oxygen consumption by the respiratory muscles.

Cardiac function during weaning

In patients with COPD but without cardiac disease, weaning was associated with a significant reduction in left ventricle ejection fraction and this reduction was probably due to increased left ventricular afterload [30]. Several studies have specifically investigated the effects of weaning with spontaneous-breathing trials on cardiac performance. In patients with COPD (FEV₁ [forced expiratory volume in 1 second] 1.0 ± 0.2 L) but without a history of cardiac disease, weaning was associated with a reduction in left ventricle ejection fraction (54% ± 12% versus 47% ± 13% during mechanical ventilation and spontaneous breathing, respectively; *P* < 0.01) [30]. As the authors did not find evidence for myocardial ischemia when using technetium radionuclide angiography in these patients, it was proposed that increased left ventricle afterload imposed by disconnection from the ventilator caused the reduction in left ventricle ejection fraction. Moreover, in difficult-weaning patients with COPD and a history of heart disease, spontaneous-breathing trials resulted in elevated pulmonary artery occlusion pressure and left ventricular end diastolic pressure, suggesting reduced ventricular compliance [31]. Elevated left ventricular end diastolic pressure during weaning may induce pulmonary and bronchial wall edema and thus increase the work of breathing.

In a heterogeneous group of patients with a failed-weaning trial, a progressive decline in mixed venous oxygen saturation (SvO₂) was found [32]. The decrease in SvO₂ resulted from the inability to improve cardiac

output and therefore oxygen transport. Increased afterloads of both the right ventricle and left ventricle were found in these patients.

Brain natriuretic peptide (BNP) is a hormone released from the myocardium upon stretch. In patients with failed-spontaneous breathing trials and in failed-extubation patients, changes in BNP are significantly higher than in patients with successful extubation [33]. This response of BNP does support a role for cardiac failure in selected difficult-weaning patients.

Diagnostic approach

The first step to assess cardiac dysfunction as a cause for weaning failure is electrocardiography at the final stages of the weaning trial to detect ischemia. Subsequently, SvO₂ could be used as a screening tool for cardiac dysfunction in difficult weaning. It should be noted that reduction in SvO₂ is the normal response to increased loading. In healthy subjects performing moderate exercise, SvO₂ decreases below 50% [34]. Accordingly, a decrease in SvO₂ should not be regarded as a sign of cardiac failure. On the other hand, in weaning-failure patients, without a reduction in SvO₂, cardiac failure is highly unlikely but rather is the result of hypoventilation, lack of motivation, or cognitive dysfunction. Accordingly, in patients who do exhibit a decrease in SvO₂ during failed weaning, cardiac failure may play a role and measurement of pulmonary artery occlusion pressure and cardiac output by means of a Swan-Ganz catheter [35] or echocardiography [36] must be considered.

Treatment strategies

In difficult-to-wean patients with evidence of cardiac failure, afterload reduction and ultimately the use of inotropes must be considered. Notably, amelioration of pulmonary mechanics will reduce left ventricle afterload. No studies have compared the different classes of inotropes in these patients. Levosimendan is a new inotropic used in the treatment of cardiac failure [37]. One of the mechanisms of action is enhanced calcium sensitivity of the cardiac contractile proteins, resulting in elevated pressure generation. In a preliminary study [38], levosimendan was tested in 12 patients who had heart failure (left ventricular ejection fraction of 28% ± 5%) and who were difficult to wean from mechanical ventilation (ventilator dependency for more than 10 days). Within 51 hours of levosimendan treatment, 7 of the 12 patients could be weaned from the ventilator. The other 5 patients could not be weaned at all and died in the ICU. Though promising, levosimendan has not been tested in placebo-controlled trials or directly compared with the older inotropes in weaning-failure patients. Interestingly, it was recently shown that levosimendan improves contractility of human diaphragm muscle fibers as well [39].

Diaphragm/respiratory muscle function

Initiating a spontaneous-weaning trial puts an acute load on the inspiratory muscles. The elevated load is imposed on a weakened respiratory muscle pump. When considering the inspiratory muscles as a cause for weaning failure, it should be kept in mind that dysfunction of the ventilatory pump may result from a lesion anywhere between the afferent chemo-receptors of the respiratory centers and the contractile proteins.

Drive, weakness, and fatigue

Impaired respiratory drive is an uncommon cause of weaning failure. In fact, in most weaning-failure patients, respiratory drive is increased [17]. Occasionally, clinically relevant diaphragm dysfunction results from damage to the phrenic nerve(s). The most frequent disorder affecting the phrenic nerves is critical illness polyneuropathy. As biopsy studies have shown that critical illness polyneuropathy and critical illness myopathy often coexist [40], the term 'ICU-acquired weakness' has gained popularity. There is convincing evidence that contractility of the respiratory muscles is impaired in mechanically ventilated patients. Laghi and colleagues [41] found that, in a heterogeneous group of mechanically ventilated patients (± 29 days), transdiaphragmatic pressure obtained after magnetic stimulation of the phrenic nerves was only approximately 35% compared with healthy subjects [42]. Levine and colleagues [43] found profound muscle fiber atrophy accompanied by activation of the proteolytic ubiquitin-proteasome pathway in the diaphragm of patients mechanically ventilated for 18 to 96 hours. Thus, there is little discussion of whether respiratory muscles are weak in ICU patients, but the development of muscle fatigue after a failed-weaning trial is the subject of debate. Laghi and colleagues [41] assessed diaphragm force before and 30 minutes after a failed-weaning trial. Surprisingly, these patients did not develop inspiratory muscle fatigue. Possible explanations for these unexpected findings include early reconnection of the patient to the ventilator, recruitment of other inspiratory muscles, or muscle recovery from fatigue within 30 minutes after the weaning trial. Although ICU-acquired weakness is the most frequent neurological disorder in the ICU, other neurological disorders may be associated with difficult weaning (reviewed in [44]).

Diagnostic approach

The diagnostic approach of diaphragm dysfunction is sophisticated, and an in-depth neurological examination should be performed by a neurologist. The most frequently used test to evaluate respiratory drive in mechanically ventilated or spontaneously breathing patients is the airway occlusion pressure at 100 ms (P_{0.1}). To this end, the inspiratory limb of the ventilator is occluded and

the drop in airway pressure is continuously monitored. In normal subjects, $P_{0.1}$ is about 0.5 to 1.5 cm H₂O. It should be noted that $P_{0.1}$ depends not only on respiratory drive but also on inspiratory muscle capacity. Accordingly, a reduced $P_{0.1}$ is not a very specific sign of impaired drive, but in patients with normal/high $P_{0.1}$, impaired drive is highly unlikely.

Generalized skeletal muscle weakness will guide the clinician to respiratory muscle weakness but does not prove inspiratory muscle weakness, and vice versa. A global assessment of inspiratory muscle function can be obtained by measuring maximal inspiratory pressure. Lower limits for maximal inspiratory pressure in healthy subjects younger than 65 years old are -75 cm H₂O in men and -50 cm H₂O in women [45]. Values that are more negative virtually exclude significant inspiratory muscle weakness (good negative predictive value). Values that are less negative do not prove muscle weakness (poor positive predictive value), as this method depends on cooperation and lung volume. Accordingly, maximal inspiratory pressure may be useful in evaluating the differential diagnosis of difficult weaning. As this test does not evaluate the endurance of the inspiratory muscles, the value of maximal inspiratory pressure as a weaning predictor is much more controversial [46].

The definite diagnosis of respiratory muscle fatigue after a trial of spontaneous breathing is not feasible in routine clinical care. The development of hypercapnia during a weaning trial is not a very specific finding, as hypercapnia may result from causes other than muscle fatigue, such as central hypoventilation and rapid shallow breathing. The absence of hypercapnia in a weaning-failure patient virtually excludes inspiratory muscle fatigue.

Treatment strategies

I. Mechanical ventilation is a double-edged sword for the respiratory muscles

Unloading prevents the development of fatigue, but inactivity is associated with the development of weakness. Very few studies have assessed the effect of inspiratory muscle training on muscle strength and in particular on clinical outcome such as duration of ventilatory assist. In an observational study, 10 difficult-to-wean patients (mechanical ventilation for 34 ± 31 days before the start of the study) were subjected to inspiratory muscle training with a pressure threshold training device [47]. Training bouts consisted of three to five sets of six inhalation maneuvers through the device, 5 to 7 times a week. In 44 ± 43 days, inspiratory pressure could be increased from 7 ± 3 cm H₂O at inclusion up to 18 ± 7 cm H₂O at the time of successful weaning. It should be noted that this is a small uncontrolled study and the training intensity was set at rather subjective criteria. However,

from a physiological point of view, it seems reasonable to train the inspiratory muscles, as part of a generalized training program [48], in patients with inspiratory muscle weakness and prolonged weaning from mechanical ventilation. When considering a training schedule, clinicians should keep in mind that the diaphragm operates mostly at its submaximal force level. Therefore, when the clinician decides that inspiratory muscle training may facilitate weaning from mechanical ventilation, from a physiological point of view, an endurance training strategy is most appropriate.

II. Antioxidants modulate respiratory muscle function in healthy subjects

In a large, randomized, non-blinded trial, surgical ICU patients received the antioxidants alpha-tocopherol and ascorbic acid or only standard care from ICU admission until discharge [49]. Antioxidant supplementation was associated with a reduction in ventilator-dependent days from 4.6 to 3.7 ($P < 0.05$). Further trials are needed before antioxidant treatment can be recommended.

III. Effects of tight glycemic control on clinically relevant outcome parameters

The effects of tight glycemic control on clinically relevant outcome parameters (mortality and days of mechanical ventilation) in critically ill patients are complex and well beyond the scope of this review. Notably, in a recent large prospective multicenter study [50], intensive glycemic control did not affect the duration of mechanical ventilation. Although that study did not investigate the prevalence of neuropathy and myopathy, the clinical relevance of such findings would be controversial as tight glycemic control did not favor weaning and reduced survival in this trial.

IV. Effect of growth hormone treatment

The effect of growth hormone treatment (0.07 to 0.13 mg/kg of body weight per day) has been reported in two parallel studies published in 1999 [51]. Growth hormone treatment is associated with increased mortality (39% versus 20% in the Finnish study and 44% versus 18% in the European study). In addition, growth hormone increased time spent on the ventilator. However, the successful use of growth hormone supplementation in ICU patients who are more chronic has been described [52]. Future studies are needed to address this issue, but today the safety of growth hormone supplementation in weaning patients is unknown.

Endocrine and metabolic dysfunction

The role of endocrine disorders in difficult weaning has gained little interest in the literature. Huang and Lin [53] found that, in 93 selected difficult-to-wean patients, 70

fulfilled criteria for adrenal insufficiency. Cortisol supplementation in these patients reduced duration of weaning compared with placebo (3.4 ± 2.3 days versus 6.5 ± 4.7 days, respectively; $P < 0.05$). The pathophysiological mechanisms for improved clinical outcome in these cortisol-supplemented patients are, however, unknown.

For a variety of reasons, including decreased central drive [54] and respiratory muscle weakness [55], hypothyroidism may delay weaning from mechanical ventilation. In a retrospective study [56], 3% of patients (4/140) admitted to a long-term weaning facility were diagnosed with new-onset hypothyroidism. After thyroid hormone supplementation, three patients could be weaned from mechanical ventilation. Although the effect of thyroid hormone supplementation in difficult-weaning patients is anecdotal, it is reasonable in weaning-failure patients with a laboratory diagnosis of hypothyroidism.

Malnutrition frequently occurs in mechanically ventilated patients and is associated with poor prognosis [57] but also with reduced muscle mass and as such contributes to difficult weaning. Nutritional status should be evaluated by determining body mass index, plasma albumin concentration, and nitrogen balance [58]. Ideally, energetic needs should be determined by indirect calorimetry to prevent under- and overfeeding.

Electrolyte abnormalities, including very low plasma levels of phosphate and magnesium, have been shown to affect skeletal muscle function. Although these should be corrected in difficult-weaning patients, no studies have investigated the role electrolyte abnormalities in weaning failure. Other metabolic disturbances that increase the work of breathing and that therefore may be associated with difficult weaning include metabolic acidosis and fever.

Conclusions

As outlined, the reasons for failing a weaning trial are diverse. When a patient does not pass a weaning trial, structural evaluation could help to identify factors that played a role in that specific patient. Our opinion-based 'ABC' algorithm could be helpful. It should be noted that the algorithm has several loose ends as our understanding of weaning failure is far from complete.

Abbreviations

ARDS, acute respiratory distress syndrome; BNP, brain natriuretic peptide; COPD, chronic obstructive pulmonary disease; ICU, intensive care unit; $P_{0.1}$, airway occlusion pressure at 100 ms; PEEPi, intrinsic positive end-expiratory pressure; SvO_2 , mixed venous oxygen saturation.

Competing interests

The authors declare that they have no competing interests.

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