The differential diagnosis for failure to wean from mechanical ventilation

Jonne Doorduin, Johannes G. van der Hoeven, and Leo M.A. Heunks

Purpose of review
In this review, we discuss the causes for a failed weaning trial and specific diagnostic tests that could be conducted to identify the cause for weaning failure. We briefly highlight treatment strategies that may enhance the chance of weaning success.

Recent findings
Impaired respiratory mechanics, respiratory muscle dysfunction, cardiac dysfunction, cognitive dysfunction, and metabolic disorders are recognized causes for weaning failure. In addition, iatrogenic factors may be at play. Most studies have focused on respiratory muscle dysfunction and cardiac dysfunction. Recent studies demonstrate that both ultrasound and electromyography are valuable tools to evaluate respiratory muscle function in ventilated patients. Sophisticated ultrasound techniques and biomarkers such as B-type natriuretic peptide, are valuable tools to identify cardiac dysfunction as a cause for weaning failure. Once a cause for weaning failure has been identified specific treatment should be instituted. Concerning treatment, both strength training and endurance training should be considered for patients with respiratory muscle weakness. Inotropes and vasodilators should be considered in case of heart failure.

Summary
Understanding the complex pathophysiology of weaning failure in combination with a systematic diagnostic approach allows identification of the primary cause of weaning failure. This will help the clinician to choose a specific treatment strategy and therefore may fasten liberation from mechanical ventilation.

Keywords
cardiac failure, diaphragm, differential diagnosis, mechanical ventilation, weaning

INTRODUCTION
Weaning from mechanical ventilation covers the entire process of liberating a patient from the ventilator and the endotracheal tube [1]. Weaning failure is usually defined as an unsuccessful spontaneous breathing trial (SBT) or need for ventilator support (including noninvasive ventilation) within 48 h after extubation [1]. In patients that require more than 7 days of weaning after a first failed SBT, mortality is significantly increased (13 vs. 7% of patients that need shorter weaning time [2]). The pathophysiology of a failed weaning trial may be complex, but it is in our opinion important to understand the reason for a failed weaning trial. Identification of the cause of weaning failure will help the clinician to choose a rationale treatment strategy that improves the chances of success for the next weaning trial. The aim of this study is to summarize the differential diagnosis of a failed weaning trial and discuss recent studies that help the clinician to identify the cause for weaning failure. Finally, we briefly discuss new treatment strategies that may fasten liberation from mechanical ventilation.

CAUSES OF WEANING FAILURE
The transition from positive inspiratory pressure during mechanical ventilation to negative airway pressure during spontaneous breathing challenges the patients’ physiological reserve. When an
imbalance develops between the patients’ ventilatory needs and capacity, weaning fails. Below we will discuss the causes of weaning failure and the techniques that are most helpful in the diagnostic work-up.

**Impaired respiratory mechanics**

The load imposed upon the respiratory muscles is determined by the resistance and compliance of the respiratory system and the presence of intrinsic positive end-expiratory pressure (PEEPi). An increase in load is accompanied by an increase in work of breathing and as such may lead to weaning failure. Indeed airway resistance is higher in patients failing a weaning trial [3,4]. In the upper airways, resistance may be increased by the artificial airway and/or tracheal injury, including stenosis, tracheomalacia, and granulation tissue. In tracheostomized patients with weaning failure referred to a dedicated weaning center, endoscopy revealed significant tracheal stenosis (>50% of tracheal lumen) in 5% (14/288) of the patients [5]. Total 10 of these 14 patients could be successfully decannulated after removal of granulation tissue.

The presence of elevated small airway resistance is obvious in patients with chronic obstructive pulmonary disease (COPD) or asthma, but in acute respiratory distress syndrome (ARDS) airway resistance may be increased as well because of edema of the bronchial wall. As a result of increased airway resistance, expiratory flow is limited and consequently PEEPi may develop. PEEPi elevates work of breathing via hyperinflation and by acting as a threshold for generation of inspiratory flow. Under dynamic conditions, PEEPi can be determined only by using an esophageal balloon. Although these balloons are widely available, positioning of the catheter and interpretation of the signal is subject to pitfalls [6].

The compliance of the respiratory system is determined by the elastic properties of both the lungs and the chest wall. In a population of ARDS patients, compliance was found to be lower in the failure group compared to successful weaning [4]. Lung compliance may be reduced because of alveolar filling (edema or pus), atelectasis, interstitial lung disease, pulmonary fibrosis, and hyperinflation. Pleural effusion, edema, obesity, and elevated abdominal pressure decrease chest wall compliance. Measurement of esophageal pressure (Pes) is required to differentiate lung compliance from chest wall compliance. However, in clinical practice when total respiratory compliance is decreased clinical and/or radiological work-up will generally identify the cause of reduced compliance.

**Respiratory muscle dysfunction**

Critical illness has profound effects on respiratory muscle structure and function [7]. Rapid development of diaphragm weakness, indicated by approximately a third reduction in diaphragm force, was found in the first 5–6 days of invasive mechanical ventilation in a small group of critically ill patients [8]. Diaphragm muscle fiber cross-sectional area is decreased by more than 10% in the first week on mechanical ventilation in a small group of critically ill patients ventilated for 7 days compared with patients referred for elective surgery [9]. In addition, in-vitro force generation of these fibers was severely reduced compared to controls. Goligher and colleagues [10] found that in 44% of the ventilated ICU patients’ diaphragm thickness, as assessed by ultrasound, decreased by more than 10% in the first week on the ventilator. The reduction in diaphragm thickness was associated with weakness [10].

Clinical evaluation of respiratory muscle function in ventilated critically ill patients is a challenge. Previously, we discussed the available techniques in detail [11,12]. Here, we will briefly discuss clinically relevant and feasible techniques. Maximal inspiratory pressure and maximal expiratory pressure are tests of global respiratory muscle strength and can be measured using a hand-held device connected to the artificial airway. A maximal inspiratory pressure above 30 cmH₂O is associated with a shorter time to successful extubation [13]. Simultaneous recording of Pes and gastric pressure (Pga) using dedicated balloons allows calculation of transdiaphragmatic pressure (Pdi = Pga – Pes), a specific measure of diaphragm contractility. The latter is useful for close monitoring and evaluation of diaphragm function in difficult-to-wean patients (Table 1). However, as mentioned before, acquisition and interpretation of Pes, Pga, and their derived measures, such as work of breathing, requires expertise.

Diaphragm ultrasonography is a practical and noninvasive tool for assessment of diaphragm
thickness, thickening fraction, and displacement (Fig. 1). Using M-mode ultrasonography, diaphragmatic dysfunction (vertical excursion < 1 cm or paradoxical movements) was found in 24 of 82 patients who met criteria for an SBT [14]. These patients showed frequent early and delayed weaning failures. DiNino and colleagues [15] found in 63 mechanically ventilated patients that diaphragm thickening fraction above 30% predicts extubation success with a sensitivity and specificity of 88 and 71%, respectively. Very recently, it was proposed that thickening fraction of the diaphragm as assessed with ultrasound could be used to detect dysfunction [10]. Future fields of ultrasonography application may be detection of patient-ventilator asynchrony [16], and assessment of respiratory workload [17,18].

Diaphragm electromyography (EMG) reflects neural respiratory drive to the diaphragm. The (processed) EMG signal can be obtained continuously using commercially available multielectrode esophageal catheters required for neurally adjusted ventilatory assist ventilator mode (Maquet, Solna, Sweden). The ratio between diaphragm EMG and tidal volume is called the neuro-ventilatory efficiency (NVE). NVE has been shown to identify weaning failure in multiple studies [19–22]. Evidently, NVE is sensitive to changes in diaphragm function as well as a patient’s load of breathing. Diaphragm EMG may also be used to monitor

Table 1. Respiratory effects of a spontaneous breathing trial

<table>
<thead>
<tr>
<th>Resp rate (per min)</th>
<th>Vt (ml)</th>
<th>Edi (µV)</th>
<th>ΔPes (cm H2O)</th>
<th>ΔPga (cm H2O)</th>
<th>ΔPdi (cm H2O)</th>
<th>PEEPi (cm H2O)</th>
<th>WOB (J/l)</th>
<th>PaO2 (mmHg)</th>
<th>PaCO2 (mmHg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PS*</td>
<td>34</td>
<td>211</td>
<td>20</td>
<td>12</td>
<td>1</td>
<td>13</td>
<td>5</td>
<td>1.0</td>
<td>75</td>
</tr>
<tr>
<td>5 min</td>
<td>36</td>
<td>246</td>
<td>48</td>
<td>25</td>
<td>1</td>
<td>26</td>
<td>10</td>
<td>2.1</td>
<td>61</td>
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<tr>
<td>10 min</td>
<td>37</td>
<td>260</td>
<td>43</td>
<td>24</td>
<td>2</td>
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<td>9</td>
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<tr>
<td>60 min</td>
<td>23</td>
<td>352</td>
<td>52</td>
<td>30</td>
<td>2</td>
<td>32</td>
<td>10</td>
<td>2.6</td>
<td>70</td>
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</tbody>
</table>

Successfull spontaneous breathing trial in a COPD patient despite an increase in PEEPi and WOB. COPD, chronic obstructive pulmonary disease; Edi, electrical activity of the diaphragm; PaCO2, arterial carbon dioxide pressure; PaO2, arterial oxygen partial pressure; Pdi, transdiaphragmatic pressure; PEEPi, intrinsic positive end-expiratory pressure; Pes, esophageal pressure; Pga, gastric pressure; Resp rate, respiratory rate; Vt, tidal volume; WOB, work of breathing.

*PS = 3 cm H2O, PEEP = 10 cm H2O.

FIGURE 1. Normal diaphragm ultrasonography. From left-to-right, top-to-bottom: B-mode diaphragm thickness during expiration, B-mode diaphragm thickness during inspiration, M-mode diaphragm displacement during normal inspiration, measurements obtained from images. Dia, diaphragm; exp, expiration; ICS, intercostals muscles; insp, inspiration; SC, subcutis.
respiratory muscle unloading [23], patient-ventilator interaction [24], and the effect of residual sedation on respiratory drive [25]. In a preliminary observation, it was reported that diaphragm EMG can be used to detect development of fatigue after extubation [26].

**Cardiac dysfunction**

The lungs and heart are functionally and anatomically coupled and therefore transition of assisted breathing to unassisted breathing has profound cardiovascular effects that may induce weaning failure. First, during positive pressure ventilation the intra-thoracic pressure (ITP) increases during inspiration, whereas during unassisted breathing ITP decreases during inspiration as a result of activation of the inspiratory muscles. The decrease in ITP during a weaning trial will enhance venous return by reducing right atrial pressure, end diastolic right ventricular (RV) volume and as such in patients with normal cardiac function increase RV and left ventricular (LV) output, but may result in heart failure in patients with compromised cardiac function. Second, increased sympathic tone (emotional stress, hypercapnia, and hypoxemia) may further increase LV afterload. Finally, the transition to unassisted breathing puts an elevated load on the respiratory muscles, which increases oxygen consumption and as such is a stress to the heart. The final effects of unassisted breathing on the cardiovascular system are much more complex. We refer to recent studies for review [27,28]. Table 2 shows the cardiovascular effects of a successful prolonged spontaneous breathing trial in a typical ICU patient.

As an alternative to the pulmonary artery catheter, less invasive techniques are currently used to identify cardiac failure during a weaning trial. Transthoracic echocardiography during an SBT can identify both systolic and diastolic dysfunction [29]. With tissue Doppler imaging, myocardial relaxation can be quantified by measuring the early diastolic mitral annulus velocity (Ea). In combination with transmitral early diastolic filling velocity (E), measured by conventional pulsed wave Doppler, the resulting E/Ea ratio closely correlates with left ventricular filling pressure [30]. Moschietto and colleagues [29] found in a nonselected population of 68 patients, performing an SBT, that the E/Ea ratio before and during the SBT was higher in the failure group than in the successful group. In this study, an E/Ea ratio during the SBT of 14.5 predicted weaning failure with a sensitivity of 75% and a specificity of 95.8%. It should be recognized that performing ultrasound at the time of weaning failure might be quite a challenge.

B-type natriuretic peptide (BNP) and N-terminal (NT)-proBNP are cardiac biomarkers secreted by ventricular cardiomyocytes in response to increased ventricular wall stress. Increases in BNP and NT-proBNP levels during the SBT are consistent with weaning failure of cardiac origin, in which BNP performs better than NT-proBNP [31,32]. An increase in BNP levels by more than 12% allowed diagnosing weaning failure from cardiac origin with a sensitivity of 76% and a specificity of 78%, with the pulmonary artery catheter as a reference method [32]. Mekontso Dessap and colleagues [33] showed that a BNP-guided fluid management strategy was associated with a shorter duration of mechanical ventilation, especially in patients with left ventricular systolic dysfunction. In conclusion, changes in BNP levels are a reliable and feasible alternative to the pulmonary artery catheter for diagnosing weaning-induced pulmonary edema. A passive leg raising before the SBT has also been suggested to identify weaning failure patients related to cardiac dysfunction [34]. Recently, Dres and colleagues [27] developed an algorithm for management of weaning failure from cardiac origin.

**Cognitive dysfunction**

A serious and frequent psycho-organic disorder in critically ill patients is delirium. Critically ill patients with a delirium have a seven times higher

<table>
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<th>Table 2. Cardiovascular effects of a spontaneous breathing trial</th>
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<tr>
<td>PS^a</td>
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<td>5 min</td>
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^aPS = 5 cm H2O, PEEP = 10 cm H2O.

The differential diagnosis for failure to wean Doorduin et al.
The role of endocrine dysfunction in weaning failure has never been systematically evaluated, but is most likely of limited importance. Hypothyroidism and adrenal insufficiency should be excluded in case of clinical suspicion, as treatment options are available. Malnutrition frequently occurs in critically ill patients and is associated with higher mortality [40], but also with reduced muscle mass and as such contributes to difficult weaning, as discussed above.

**Endocrine and metabolic disorders**

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**Iatrogenic factors**

The role of the clinician in weaning is crucial, in particular the assessment whether the patient still requires ventilator support. In patients with unplanned extubation, only 44% required reintubation [41]. When unplanned extubation occurred during the weaning phase, only 30% required reintubation. Patients with successful unplanned extubation during weaning phase spent less time on weaning the ventilator [41]. In a large clinical trial comparing weaning methods performed in a long-term weaning facility [42], 32% of the patients passed the initial screening weaning trial. This indicates that these patients were already weaned upon arrival in this weaning facility, although this was unrecognized by the referring ICU team. These studies stress the importance to screen patients for readiness for weaning and extubation. Appropriate tests for weaning readiness have recently been reviewed elsewhere [43]. Under certain conditions there may be a role for automated weaning [44].

Asynchrony between the patient and ventilator is associated with increased duration of weaning [45] and even mortality [46]. Although it is reasonable to aim for optimal patient-ventilator interaction, no studies have been performed to study the effect on weaning outcome.

**THERAPEUTIC CONSEQUENCES**

Once a specific reason for weaning failure has been identified, the clinician should develop a strategy that increases the chances of successful weaning.

**Respiratory mechanics**

In patients with elevated airway resistance bronchodilators should be administered. Under certain conditions (malpositioning, granulation tissue) the tracheostomy can enhance airway resistance [47]. Specifically adapted tubes may be required. In patients with impaired respiratory compliance it is often obvious how mechanics can be improved, such as evacuation of pleural fluid or ascites, diuretics to achieve negative fluid balance in case of chest-wall or pulmonary edema [48].

**Respiratory muscle dysfunction**

Disuse is a prominent risk factor for the development of respiratory muscle weakness as pointed out above. Therefore, it is reasonable to limit the duration of respiratory muscle inactivity, by using assisted modes for ventilation. Future studies should determine the optimum time point for initiation of assisted ventilation and the level of unloading of the inspiratory muscles.

Respiratory muscle strength training seems to be a reasonable intervention in weak patients. Most experience for respiratory muscle training has been obtained in patients with COPD. For instance in a randomized controlled trial (N=33; not on the ventilator) inspiratory muscle strength training improved respiratory muscle strength, 6-min walking distance and reduces dyspnea sensation, compared with sham training [49]. Very few studies have been performed in ventilated patients. The best evidence up to now comes from Martin and colleagues [50], demonstrating that inspiratory muscle training in long-term ventilated patients improves muscle strength and the chances of successful weaning. Although many questions remain concerning optimal timing and protocol [51], initiation of inspiratory muscle strength training appears reasonable in weak ventilated ICU patients difficult-to-wean from the ventilator.

In contrast to cardiac muscle dysfunction, no drug is approved to optimize respiratory muscle function. However, some small pilot studies demonstrate that respiratory muscle contractility can be enhanced pharmacologically [52]. Levosimendan is a relatively novel cardiac inotrope that improves calcium sensitivity of the contractile proteins. In healthy study participants levosimendan improves contractile efficiency of the respiratory muscles [53].
A clinical trial in difficult-to-wean patients is currently conducted (NCT01721434). Anabolic hormones that directly enhance contractile protein synthesis are another potentially interesting strategy to enhance respiratory muscle function. In a randomized controlled trial, Schols et al. [54] demonstrated that nandrolone together with high-caloric feeding enhances respiratory muscle strength in patients with COPD participating in a rehabilitation program. The effect of anabolic steroids on peripheral or respiratory muscle strength in difficult-to-wean ICU patients has not been investigated and the routine use is not recommended today.

Cardiac dysfunction

Routsi et al. [55] evaluated the effects of nitroglycerin infusion on hemodynamics and weaning outcome in difficult-to-wean patients with COPD and arterial hypertension. In these patients, nitroglycerin had beneficial hemodynamic effects during a SBT, including reduction in pulmonary capillary wedge pressure, right ventricular stroke work index, and improved venous oxygen saturation. Moreover, whereas all patients [12] failed a weaning trial under control conditions, 92% successfully completed the SBT under nitroglycerin infusion. In patients with overt heart failure inotropes could be considered, despite the absence of strong evidence. Levosimendan has been shown to improve cardiac output and reduce pulmonary capillary wedge pressure and clinical outcome in patients with acute heart failure [56,57]. The effects of levosimendan on weaning outcome was evaluated in a small pilot study, including 12 patients with systolic heart failure (left ventricular ejection fraction $28 \pm 5\%$) [58]. After levosimendan infusion seven of the 12 patients were weaned from mechanical ventilation within 51 h of treatment. Although there is a strong rationale for inotropes in patients with heart failure that are difficult-to-wean from the ventilator, clinical studies should confirm the favorable effect on outcome.

Cognitive dysfunction

Reducing the level of sedation has been shown to reduce duration of mechanical ventilation [59]. More recently, in a propensity score analysis Lonardo [60] demonstrated that the use of propofol instead of benzodiazepines reduced duration of mechanical ventilation and mortality in a heterogeneous group of patients. Among other factors, it should be recognized that benzodiazepines are associated with the development of delirium [61]. In addition, benzodiazepines adversely affect sleep architecture as assessed by polysomnography in weaning patients [62]. In patients with confirmed depressive disorder that affect weaning, treatment with psychostimulants may be considered [63].

Endocrine and metabolic disorders

The role of thyroid hormone replacement therapy in difficult-to-wean patients has not been systemically evaluated. However, suppletion of thyroid hormone in patients with proven hypothyroidism is reasonable [64]. Huang and Lin [65] have demonstrated that in patients with confirmed adrenal insufficiency treatment with hydrocortisone fastens weaning from the ventilator. No specific nutritional therapy has been shown to improve weaning outcome.

CONCLUSION

The pathophysiology of weaning failure is complex and requires a systematic differential diagnostic approach to identify the primary cause for weaning failure. Several tools and techniques are available to discriminate between these causes. Identification of the cause of weaning failure allows specific treatment and thereby may fasten liberation from mechanical ventilation.

Acknowledgements

None.

Financial support and sponsorship

None.

Conflicts of interest

L.H. has received travel grants and speakers fee from Orion Pharma, Maquet Critical Care and Biomarin. L.H. has received an ongoing research grant from Orion Pharma.

REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:

* of special interest

** of outstanding interest

64. Datta D, Scalise P. Hypothyroidism and failure to wean in patients receiving prolonged mechanical ventilation at a regional weaning center. Chest 2004; 126:1307–1312.