Respiratory Medicine 134 (2018) 54–61

Contents lists available at ScienceDirect

Respiratory Medicine

journal homepage: www.elsevier.com/locate/rmed

Review article

Weaning failure and respiratory muscle function: What has been done and what can be improved?

Paulo A.F. Magalhães[a,b], Carlos A. Camillo[c,d], Daniel Langer[b,d], Lívia B. Andrade[a,e], Maria do Carmo M.B. Duarte[a], Rik Gosselink[b,d,*]

[a] *Maternal and Child Health Doctoral Program, Prof. Fernando Figueira Integral Medicine Institute, Recife, Brazil*
[b] *KU Leuven, Respiratory Rehabilitation and Respiratory Division, University Hospitals, Leuven, Belgium*
[c] *State University of Londrina, Department of Physiotherapy, Londrina, Brazil*
[d] *KU Leuven, Faculty of Kinesiology and Rehabilitation Sciences, Department of Rehabilitation Sciences, Leuven, Belgium*
[e] *Federal University of Rio Grande Do Sul, Pneumology Science Postgraduate Program, Porto Alegre, Brazil*

ARTICLE INFO

Keywords:
Ventilator
Weaning failure
Respiratory muscles
Physiotherapy

ABSTRACT

Introduction: Respiratory muscle dysfunction, being a common cause of weaning failure, is strongly associated with prolonged mechanical ventilation (MV) and prolonged stay in intensive care units. Inspiratory muscle training (IMT) has been described as an important contributor to the treatment of respiratory muscle dysfunction in critically ill patients. Its effectiveness is however yet controversial.
Objective: To discuss evidence for assessment of readiness and the effectiveness of interventions for liberation from MV, with special attention to the role of IMT.
Methods: PubMed, LILACS, PEDro and Web of Science were searched for papers of assessment and treatment of patients who failed liberation from MV after at least one attempt published in English or Portuguese until June 2016.
Results: Weaning predictors are related to weaning success (86%–100% for sensitivity and 7%–69% for specificity) and work of breathing (73%–100% for sensitivity and 56%–100% for specificity). Spontaneous breathing trials (SBT), noninvasive MV and early mobilization have been reported to improve weaning outcomes. Two modalities of IMT were identified in five selected studies: 1) adjustment of ventilator trigger sensitivity 2) inspiratory threshold loading. Both IMT training modalities promoted significant increases in respiratory muscle strength. IMT with threshold loading showed positive effect on endurance compared to control.
Conclusion: Methods to indentify respiratory muscle weakness in critically ill patients are feasible and described as indexes that show good accuracy. Individualized and supervised rehabilitation programs including IMT, SBT, noninvasive MV and early mobilization should be encouraged in patients with inspiratory muscle weakness.

1. Introduction

The respiratory pump works as a result of integration between metabolic demands, the nervous system and the muscles of respiration. The latter is responsible for generating pressure gradients between the respiratory system and the atmospheric air allowing air to flow into the lungs [1]. When the workload attributed to the pump exceeds its capacity, commonly observed in diseases that increase the work of breathing or diseases affecting the strength of the respiratory muscles, the respiratory muscles start an exhaustive process evolving with muscle fatigue, alveolar hypoventilation and hypercapnia [2].

Up to two-thirds of patients admitted to intensive care units (ICU) need respiratory support [3,4]. Mechanical ventilation (MV) is a common life support strategy used in critically ill patients and has proven to decrease mortality rates [5–7]. Despite the technological advances with different ventilation modes, MV is still associated with ICU acquired complications, such as diaphragm weakness. This condition is defined as ventilator-induced diaphragm dysfunction (VIDD) [8,9], which contributes significantly to increased duration of MV [10], weaning failure [11], morbidity and hospital length of stay [12]. A key mechanism responsible for the development of VIDD lies on the mitigation of the diaphragm activity (‘silencing of the muscle’), a potent trigger of proteins breakdown and activation of the ubiquitin–proteasome pathway of proteolysis [13]. Rats anesthetized and ventilated with controlled mechanical ventilation (CMV) from one to three days showed destruction of myofibrils and reductions in diaphragm force by

* Corresponding author. Respiratory Rehabilitation and Respiratory Division, University Hospitals, 3000 Leuven, Belgium.
E-mail address: Rik.Gosselink@kuleuven.be (R. Gosselink).

https://doi.org/10.1016/j.rmed.2017.11.023
Received 1 May 2017; Received in revised form 18 September 2017; Accepted 28 November 2017
Available online 02 December 2017

42% when compared to animals breathing spontaneously [14,15]. In humans, loss of diaphragmatic strength was identified in adults patients admitted to ICU unit after only 6 h of the initiation of MV with progressive worsening of function over a period of 6 days [8,10,16]. Prolonged MV periods are an important contributing factor to patient's overall respiratory pump decline [10,17]. Weaning is the gradual liberation from MV to spontaneous breathing allowing the patient to breathe without mechanical support [18]. According to its difficulty and duration, weaning can be classified into three groups: simple weaning (successful extubation on the first attempt), difficult weaning (failure on the first attempt and requiring up to 3 Spontaneous Breathing Trials (SBT) or as long as 7 days from the first SBT) and prolonged weaning (fail on at least 3 attempts or > 7 days from the first SBT) [18]. Weaning failure from mechanical ventilation occurs to a subset of patients (12–50%) [19]. Several ICU acquired conditions such as critical illness polyneuropathy/myopathy, sepsis, corticosteroid myopathy, and phrenic nerve injury, especially in some post-cardiac surgery patients, are likely to contribute to weaning failure. Other conditions that that interfere with muscle function include rhabdomyolysis or myositis, along with the effects of excessive sedation or analgesia and other medications [20]. The inability to breath spontaneously relates to an imbalance between *load on* the respiratory muscles and *capacity of* the respiratory muscles [2]. Respiratory muscle weakness is a factor observed in patients on mechanical ventilation that increases the risk of developing respiratory muscle fatigue during weaning [18,21–24]. Indeed increased inspiratory muscle effort (ratio of work load and muscle capacity [PI/PImax]) is noted in cases of ventilator dependency and is a predictor of weaning failure [25]. Of note, other factors may potentially decrease the capacity to restart spontaneous breathing such as patients' cognitive and psychological status [26], nutrition [27], and medication [28].

Identifying strategies to reduce the duration of MV and to restore ventilatory autonomy is an immediate priority from the moment of its commencing [29]. To date, results are still controversial and the best strategy has not yet been established, due to the multifactorial origin of liberation from mechanical ventilation [30]. Inspiratory muscle conditioning has been identified as a treatment modality to avoid the decrease of respiratory muscle function by providing muscle stimulus to improve strength and endurance to the respiratory muscles [29,31].

Respiratory muscle dysfunction is often unrecognized or underemphasized as a potential contributor to weaning failure. The aim of the present review is to summarize available methods to evaluate respiratory muscle weakness in critically ill patients and to describe the effects of different interventions to address it.

2. Review of the literature

A clinical review was performed through bibliographic search of randomized controlled trials of IMT in patients (aged 18 years or older) who failed liberation from mechanical ventilation after at least one attempt. The research was performed in the electronic data bases PubMed/Medline (National Library of Medicine), Lilacs (*Literatura Latino-Americana e do Caribe em Ciências da Saúde*), PEDro (physiotherapy evidence database) and Web of Science. Descriptors were selected based on consultations to MeSH (Medical Subject Headings) and DeCS (*Descritores em Ciências da Saúde*). The following descriptors were considered, in English and Portuguese from 2000 until 2016: 1) *respiratory muscle training; "or" 2) inspiratory muscle training; "and"* 3) *ventilator weaning; "or" 4) mechanical ventilation; "or"* 5) *artificial respiration.* The following outcomes were considered for the analysis of the influence of IMT on liberation patients from MV: inspiratory muscle strength and endurance, days on mechanical ventilation, success rate in liberation from MV, and quality of life after successful weaning.

Table 1
Measures of suitability for weaning.

Parameter	Tolerance
Oxygen fraction ($F_{I,O2}$)	≤ 40%
Positive end-expiratory pressure (PEEP)	≤ 8 cmH_2O
Arterial oxygen tension (PaO_2/FIO_2)	> 150 mmHg
Arterial oxygen saturation	≥ 90%

PaO_2: Partial oxygen pressure; FIO_2: Inspired fraction of oxygen [18].

2.1. How to assess patients' eligibility criteria for weaning from mechanical ventilation?

2.1.1. Assessment of suitability for weaning

The decision to attempt discontinuation of mechanical ventilation has largely been based on the clinician's assessment [30,32]. Commonly, factors in the decision making include the verification of patients' hemodynamic stability, mental and cognitive status, ability to cough, resolution of the primary cause, nutritional status and specific parameters of lung mechanics [18,33]. Table 1 indicates patient parameters that indicate suitability of weaning.

Several weaning predictors have been used in clinical practice trying to objectively assist the decision-making of the weaning process [34]. Importantly, a significant number of these predictors were developed considering the capacity of the respiratory muscles. A detailed overview of these predictors is provided in Table 2.

2.1.2. The rapid shallow breathing index

The rapid shallow breathing index (RSBI) is a physiological index collected during the SBT to predict success of weaning. It corresponds to the ratio of respiratory frequency to tidal volume (RR [br/min]/Vt [L]). Despite of lower specificity, a RSBI < 105 is reported to be the most accurate predictor of successful patient extubation (Table 2) [25,35–37]. The index assumes that the better the lung compliance associated with adequate gas exchange and lower respiratory rate, the greater the likelihood of sustaining spontaneous ventilation without ventilatory support [38]. While the rapid shallow breathing index (RSBI) is the cornerstone of weaning assessment, it is important to highlight that its calculation was primarily done using a T-piece. This has important implication as the threshold of normality for the RSBI may vary with the method of assessment [39]. Critically ill patients are nowadays supported with ventilators that allow easy transition from controlled to spontaneous modes and already integrate the measurement of the RSBI. In fact, a recent guideline from the American

Table 2
Summary of predictive parameters for weaning from mechanical ventilation and assessment of respiratory effort.

	Criterium	Sensitivity	Specificity	Reference
Weaning success				
RSBI	< 105	97%	64%	Yang et al. [35]
PImax	< −30cmH_2O	86%–100%	7%–69%	El-Khatib [34]
CROP	> 13 ml/cmH_2O/cpm	81%	57%	Yang [46]
DTF	> 36%	82%	88%	Ferrari et al. [47]
Respiratory effort				
P0.1	> 2.33cmH_2O	73%	56%	Souza et al. [51]
TTdi	> 0.15	100%	100%	Currie et al. [37]* Harikumar et al. [36]*

RSBI: Rapid shallow breathing Index; PImax: Maximum Inspiratory Pressure; DTF: Diaphragm thickening fraction; P0.1: The airway occlusion pressure 0.1s; TTdi:tension–time index.* Reference values only available for pediatric population.

Thoracic Society/American College of Chest Physicians on the liberation from mechanical ventilation in critically ill adults recommend that SBT be conducted with inspiratory pressure augmentation (5–8 cmH_2O) rather than without (T-piece or continuous positive airway pressure [CPAP]) [40] Importantly, most patients who are successfully weaned will have an acceptable RSBI irrespective of the method of assessment.

2.1.3. Maximal inspiratory pressure

Maximal inspiratory pressure (PImax), also known as negative inspiratory force (NIF), is the maximal negative pressure generated for at least 1 s during a maximal inspiratory effort from residual volume during a forced inspiratory maneuver against a closed airway [46,48].The PImax estimates inspiratory muscle strength and has been widely used to identify and to quantify respiratory muscle weakness [43]. The test measures the pressure generated by all the inspiratory muscles as well as the elastic recoil pressure of the lungs and chest wall [42]. It is also possible to perform the assessment without the patient's cooperation. A one-way valve that permits exhalation and occludes during inspiration is attached to the tube during occlusion periods order of 12–15 s, at most 15–25 s [41,44]. To obtain reliable results, 3 trials are necessary with the highest value considered as the PImax [42]. The assessment of PImax tests is safe and feasible in ICU patients [43]. During the procedure, oxygen saturation, electrocardiography, blood pressure, dyspnea and anxiety should be monitored [43,44]. PImax values of more than -30 cmH_2O have a high sensitivity, but low specificity in predicting a successful weaning (Table 2) [45].

This evaluation was once part of a standard set of weaning parameters which are no longer routinely obtained. Nevertheless, it may be useful in some patients to assess their respiratory muscle strength.

2.1.4. The compliance/rate/oxygenation/pressure (CROP) index

CROP is an index calculated from the dynamic compliance (Cdin), respiratory ratio (RR), alveolar-arterial oxygen ratio (PaO_2/PAO_2) and PImax. The practitioner needs to have information of the individual values above and to include them in the following equation: CROP = (Cdin x PImax x [(PaO_2/PAO_2))/RR]. Higher values indicate an adequate combination of good compliance and PImax and gas exchange for a given respiratory rate. A value greater than 13 ml × cmH_2O^{-1} *cpm^{-1} has predictive power to extubation success for adult patients, with 81% of sensitivity and 57% of specificity [46].

2.1.5. Measurement of diaphragm function

A decrease in diaphragm thickness is common during mechanical ventilation and is associated with diaphragmatic weakness [17]. The measurement of the diaphragm thickening fraction (*DTF: thickness at end-inspiration minus thickness at end-expiration divided by the thickness at end-expiration*) with ultrasonography has been presented as a potentially new weaning index [47]. The DTF is considered an indicator of respiratory effort in critically ill patients undergoing assisted mechanical ventilation [48]. Visualization of the diaphragm is achieved by placing the transducer perpendicularly to the chest wall (at the 8th/9th intercostal space, between the anterior and mid axillary lines) to observe the zone of apposition of the muscle 0.5–2 cm below the cost phrenic sinus [47]. Unlike traditional tools that require invasive methods to evaluate diaphragm dysfunction (e.g. transdiaphragmatic pressure (Pdi) measurement and fluoroscopy) [49], ultrasonography allows to investigate noninvasively the diaphragm excursion, the DTF and the speed of contraction during MV [7]. In a prospective study in 46 adult tracheostomized patients with pressure support ventilation, the assessment of DTF (> 36%) by diaphragm ultrasound was associated with a successful weaning (sensitivity of 82%; specificity of 88%; positive and negative predictive values 92% and 72% respectively) (Table 2) [47].

The first step in proceeding with this assessment is an increased index of suspicion for diaphragmatic dysfunction which may be evident on physical examination or plain film imaging. Diaphragmatic EMG and transdiaphragmatic pressures are other methods of assessing diaphragmatic function and have a longer track record of experience than diaphragmatic ultrasound. It should be noted that maximal pressures have to be obtained and this requires patient cooperation. If this is not possible, the phrenic nerve can be stimulated to provide a maximal pressure and this is an aspect of measurement that may not be familiar to most clinicians. Diaphragmatic ultrasound may also provide a bedside assessment of diaphragm function separate from measures of diaphragmatic thickness. This would be separate from the measure described in the assessment of weaning, but just a measure of current and potential diaphragm function.

2.1.6. The airway occlusion pressure

The airway pressure generated in the first 0.1 s (P0.1) during an inspiratory effort against an occluded airway is directly related to neural stimulation and evaluates the activity of the central respiratory drive [50]. A cut-off value estimated from ROC curve analysis suggest that P0.1 values higher than 2.33 cmH_2O are associated with weaning failure (sensitivity 73%; specificity 56%) [51]. (Table 2) Conversely, values below 0.5 cmH_2O are also associated with weaning failure due to a *reduced* central stimulus resulting in insufficient breathing to maintain adequate alveolar ventilation [52–55]. Airway occlusion is not a routine measure, given the technical expertise required for this. The technique requires an esophageal balloon to measure esophageal pressure or a mechanical ventilator with a setup permitting determination of the P0.1 [56]. To obtain reliable results, the P0.1 must be calculated as an average of 4 maneuvers [57]. It is important to identify the group of patients for whom this would be useful. These were likely those in the latter weaning groups and those with some injury or impairment of their central drive to breath.

2.1.7. Tension–time index of the diaphragm

The tension–time index (TTI, di) assesses the load relative to the capacity of the diaphragm and is considered to be the major determinant of weaning failure or weaning success [25]. TTI, di is derived by multiplying the mean transdiaphragmatic pressure per breath to the maximal inspiratory trans-diaphragmatic pressure (Pdimax) and the inspiratory time (Ti) to the total respiratory cycle time (Ttot) [25,36]. It indicates the measure of respiratory load and helps to determine if the patient breathing represents a sustainable pattern. TTdi in excess of 0.15 is indicative of respiratory fatigue (Table 2). Measurement of the TTdi, however, is invasive, requiring the use of 2 balloon catheters in the esophagus and stomach. A noninvasive TTI measurement (TTmus), based on airway pressure has been validated and reflects the contribution of all the inspiratory muscles, rather than being specific to the diaphragm [25,36,37].

The tension time index is only a measure of diaphragm function and is not really used as a weaning assessment, but more as a measure of respiratory muscle load and function to determine if patient breathing represents a sustainable pattern. While it can identify a patient's potential ability to maintain unsupported breathing, it's actual role in weaning remains undefined. In the intensive care use, measures that may be influenced by respiratory muscle weakness include vital capacity, arterial blood gases and respiratory mouth pressures. These may not be very sensitive indicators as other factors are also involved, but the most important measurement would be of diaphragmatic strength. This is typically assessed by measurement of the transdiaphragmatic pressure or mouth pressures. They do require some technical expertise and may not be easy to obtain in the ICU from patients receiving mechanical ventilation. Ancillary tests include nerve conduction studies, electromyograms (EMG), and phrenic nerve stimulation studies. The above issues serve to provide a background for the evaluation of respiratory muscle function and some framework as to how respiratory muscle dysfunction contributes to weaning failure.

Patients' clinical condition is the foremost criterium to consider weaning from MV. Although not every weaning failure is due to

respiratory muscle dysfunction, it is necessary that preserved respiratory drive and a minimum respiratory muscle force and endurance is present to avoid failure in the process. In addition, assessment of the workload imposed to the ventilatory system is necessary to guarantee continuity of spontaneous breathing. Despite the predictive values of the described indexes in Table 2 not showing the desired accuracy, they can be useful tools to assist in the clinical decision making.

2.2. Interventions for weaning from mechanical ventilation

Previous studies suggest that a weaning protocol should be implemented in order to provide daily assessments of patients who may be ready for weaning from mechanical ventilation [39]. The most conventional interventions used for this purpose related are [1]: Spontaneous breathing trials (SBT) [39,2] early mobilization [58,3] noninvasive ventilation [59]; and [4] inspiratory muscle training [29]. Of note, while all the interventions described are instrumental in weaning patients form the ventilator, none of these can be used in isolation and must be part of an overall protocol or approach to the mechanically ventilated patient.

2.2.1. Early mobilization

Early mobilization (EM) is provided by the practice of exercises (passive, assisted, active and/or resistive exercises, body positioning, transfer to the chair, and standing) [58]. There is a large body of evidence reporting EM to positively affect critically ill patients requiring prolonged MV. Benefits of EM, however, vary in different studies. Morris et al. showed that a large cohort of patients with acute respiratory failure benefitted from EM mostly only after discharge [60], whereas others report EM to accelerate the process of recovery, decrease the duration of MV, length of stay in the ICU and hospital and better functional outcomes [61–65]. The implementation of EM in clinical practice also needs to be enhanced as it remains underutilized in most of intensive care units. For example, a multi-center study from the TEAM group conducted in 12 ICUs reported that EM was applied by the professionals (as physical therapists, respiratory therapists and nurses who are all part of the early mobilization team) in only 35% of patients under MV [66].

2.2.2. The spontaneous breathing trial

The SBT can be used as weaning strategy either using a T-tube (T-piece) for longer periods or by gradual reduction of the applied airway pressure to provide low levels of pressure support ventilation (PSV) (5–10 cm H_2O). A systematic review compared the effect of both strategies on weaning outcomes. No significant differences were observed between PSV and T-tube regarding to successful weaning, reintubation, ICU mortality, pneumonia and RBSI. Pressure support values of 5–10 cm H_2O for 2 h allowed 79.5% of patients in the simple weaning category to be extubated compared with 73.5% with the T-tube group (NNT = 14; $p < 0,01$) [39]. More recently, a clinical practice guideline from the American College of Chest Physicians/American Thoracic Society recommended that once patients meet several readiness criteria, a preferred approach is to conduct a SBT involving little or no ventilator support. Moreover, the authors suggest the initial SBT to be conducted with inspiratory pressure augmentation (5–8 cm H_2O) rather than without (T-piece or CPAP) for acutely hospitalized patients ventilated more than 24 h [40].

2.2.3. Noninvasive ventilation

In patients at risk for failing the weaning process, *unloading* of the respiratory muscles with non-invasive ventilation (NIV) reduces the duration of intubation and improved patient prognosis [59]. NIV allows larger tidal volumes, improves gas exchange and, reduces respiratory effort, psychological stress and the need for sedation [67]. A meta-analysis on the effects of NIV in patients with chronic respiratory failure (16 trials, 994 participants, adults) reported that NIV significantly reduced the rates of death and pneumonia without increasing the risk of weaning failure or reintubation [59]. Further effects were observed on reduction of tracheostomy need (RR 0.19, 95% CI 0.08 to 0.47) and reintubation (RR 0.65, 95% CI 0.44 to 0.97). However, NIV in this meta-analysis did not reduce time on MV [59].

2.2.4. Inspiratory muscle training

The clinical impact of IMT as an adjunct therapy to wean chronically ill patients from MV is still under debate [29,31,68]. The effectiveness of inspiratory training in weaning failure patients, as well as the most effective type of training for this particular population have been investigated. The studies performed so far on IMT in mechanically ventilated patients were however heterogeneous with regard to specific inclusion criteria, training modalities and outcomes evaluated. Not all studies specifically focused on patients with known weaning difficulties and not all studies evaluated weaning related outcomes. Timing of inclusion of patients was also not consistent between studies.

Two modalities of IMT with different ways to perform (i.e. number of repetitions, intensity, time to rest) were identified in the included studies [1]: Adjustment of ventilator trigger sensitivity (AVTS) to 20–40% of PImax [69,70] and [2] Inspiratory pressure threshold loading ranged from 20 to 50% of PImax (Table 2) [71–74]. According to literature and clinical experience, the most popular device to train the inspiratory muscles is threshold loading [29]. IMT sessions were in general well tolerated regardless of the training modality. However, only a single study (69) reported that 14% of IMT sessions with AVTS were interrupted due to adverse effects (e.g. oxygen desaturation, tachypnea). Otherwise no deleterious effects were reported in these trials (Table 3).

The lowest values of improvement on strength were identified with the threshold device set at 20% of PImax (4 cmH_2O) [75] and the highest one (≥ 10 cmH_2O) using the threshold device set at ≥ 30% of PImax [71,73,74].

Considering the effects of IMT on respiratory muscle endurance, Pascotini [72] observed, in addition to decrease in the PImax, a significant increase of RR between the first and seventh day of weaning process in the control group ($p = 0.02$). Elbouhy et al. showed that the mean respiratory rate through the respiratory muscle training sessions decreased in the IMT group from 26.3 ± 1.9 to 18.6 ± 4.0 br/min ($p = 0.000$) while the non-training group had no changes (26.1 ± 10.2; 26.7 ± 10.7, $p = 0.9$). Cader et al. [71] found increases of RSBI in both groups (control and intervention) over the weaning period, but comparing groups, the patients who performed IMT attenuated the RSBI significantly compared to the control group (between groups mean difference of 8.3 br/min/L, 95%CI 2.9–13.7).

Regardless the training method employed, 3 RCT's showed significant increases in the success weaning rates in participants who performed IMT. Martin et al. showed that 71% (95%CI 55%–84%) of subjects following IMT weaned compared to 47% (95%CI 31%–63%) with SHAM. Elbouhy et al. described successful weaning in 90% of subjects with COPD (n = 18) when IMT was offered compared to 55% (n = 11) with no training. Despite the limited sample size, Pascotini et al. observed a weaning success rate of 100% in the IMT group against 57% in the patients without training ($p < 0,05$). Only one study demonstrated a reduction in the mean duration of MV in IMT group before successful weaning (11.67 days ± 1.95 while in cases with no training 14.12 days ± 1.73, $p < 0.05$). Quality of life was not analyzed in any study to date.

In these 5 studies investigating IMT in patients with weaning failure, improvements were observed in respiratory muscle strength and endurance, enhanced successful weaning rates, but no effects on days of mechanical ventilation. The effects on respiratory muscle endurance were less pronounced compared to respiratory muscle strength. This might be justified by the fact that most IMT protocols emphasize strength gain, and less focus on endurance. Respiratory muscle endurance, which reflects the ability of respiratory pump to remain

Table 3
Randomized controlled trials investigating respiratory muscle training in subjects under mechanical ventilation.

Author and year of the study	Baseline characteristics of participants	Methods of IMT	Variables				
			Weaning period (days)	PImax initial (cmH2O)	PImax final (cmH2O)	Weaning Success	Endurance
Caruso et al., 2005	- Age 67 ± 17y; - MV ≥ 3 days; - n = 25 (I = 12; C = 13); - COPD; Acute respiratory failure;	Intervention: - Load: AVTS of ≥20% of PImax ↑10–40%; - Duration: 5–30min; - 2x daily for 7 days/week until weaned; Control: No training.	I: 8.6 ± 3.5 C: 9.7 ± 8.04 (*p* = *NS)*	I: −51 ± 15 C: 48 ± 29 (*p* = *NS)*	I: ↑ −56 ± 15 C:↑-55 ± 15 (*p* = *NS)*	I: 9 (75%) C: 8 (62%) (*p* = *NS)*	Not reported
Cader et al., 2010	- Age 83 ± 7y - MV = 6 ± 2 days - n = 41(I = 21; C = 20) - Sepsis; Pneumonia; Aspiration; Trauma; Postoperative	Intervention - Threshold® IMT device; - Load: 30% of PImax; ↑ 10% daily; - Duration: 5min until weaned; - 2x daily for 7 days/week; Control: No training.	I: 3.6 ± 1.5 C: 5.3 ± 1.9 (*p* = *NS)*	I: 15.1 ± 2.6 C: −15.3 ± 2.2 (*p*=*NS)*	I: ↑-25 ± 3.9 C: ↑ −17.6 ± 1.9 (*p* = S)	Not reported	RSBI ↑ (worsened) in both groups over the weaning period, but the increase was attenuated significantly by IMT (*p* = S)
Martin et al., 2011	- Age 66 ± 12 y - MV ≥ 14 days - n = 69 (I = 35; C = 34) - Heart diseases; Adult respiratory syndrome; Interstitial disease; Pneumothorax; Pulmonary vasculitis; Acute intracranial hemorrhage; Pancreatitis; Sepsis with shock; Postoperative	Intervention: - Threshold device; - Load: ≥50% of PImax; - Duration: 4 sets of 6–10 breaths with 2min rest between sets; - 1x daily for 5 days/week until weaned; Control: Sham.	I: 14.4 ± 8.1 C: 18.0 ± 8.8 (*p* = *NS)*	I: −44.4 ± 18.4 C: 43.5 ± 17.8 (*p*=*NS)*	I: ↑-54.1 ± 17.8 C: ↑45.1 ± 19.5 (*p* = S)	I: 25 (71%) C: 16 (47%) (*p* = S)	Not reported
Elbouhy et al., 2014*	- Age 62.5 ± 12 y - MV ≥ 9 days - n = 40 (I = 20; C = 20) - Acute exacerbation of COPD with acute respiratory failure (ARF)- Exacerbation of COPD	Intervention: - AVTS to ≥20% of PImax; - Duration: 5–30min; - 2x daily for 5 days/week until weaned; Control: No training.	I: 11.67 ± 1.9 C: 14.12 ± 1.7 (*p* = S)	I: −15.2 ± 2.41 C: −14.6 ± 5.8 (*p* = *NS)*	I: ↑-24.4 ± 3.9 C:↓-13.9 ± 5.6 (*p* = S)	I: 18 (90%) C:11 (55%) (*p* = S)	Mean respiratory rate after weaning was higher in control group comparing to IMT. (*p* = S)
Pascotini et al., 2014	- Age 72,40 ± 13.9y - MV ≥ 10 days - n = 14 (I = 7; C = 7) - Traumatic brain injury; Stroke	Intervention: - Threshold device; - Load: 20% of PImax; - Duration: 3 sets of 10 breaths with 2min rest between sets; - 1x daily for 7days; Control: No training.	Not reported	I: ≈-18 C: ≈-21 (*p* = *NS)*	I:≈↑ −24 C:≈↓-18 (*p* = NS)	I: 7 (100%) C: 4 (57%) (*p* = S)	There was an increase in respiratory ratio in control group. (*p* = S)

y: year; I: intervention group; C: control group; COPD: chronic obstructive pulmonary disease; PImax: maximum inspiratory pressure; IMT: inspiratory muscle training; AVTS: adjustment of ventilator sensitivity; RSBI: rapid shallow breathing índex.
*: IMT performed using FiO_2 of 0.4. NS: not significant.

functioning during spontaneous breathing properly, is still poorly explored.

In a randomized controlled trial adverse events were similar in both intervention and control groups [70]. Clinical signs as well cardiopulmonary parameters that would mandate the cessation of a training session need to be assessed daily. These conditions may not only affect the quality of the training performance, but also avoid possible complications. The specific respiratory training, even as any training consists of adequate periods of work and rest, requiring to balance intensity, duration and recovery time [76]. However, excessive duration and intensity of the training can lead to fatigue, beside increase susceptibility to muscular injury [77]. Indeed, in some animal studies, diaphragm muscle injury was observed in rabbits training with continuous inspiratory resistive loading for 1–2 h [78]. In addition, hypoxemia and acidosis were reported during *continuous* loaded breathing with trachea banding for 6 days in hamsters [79]. Obviously, one cannot expect such an inadequate *continuous* load to provide an adequate stimulus, and therefore observe adequate training responses.

Specifically looking at quality of life measures a recent RCT involving 70 patients (mechanically ventilated ≥7 days) following 48 h of successful weaning, showed that the improvement in quality of life was greater in the IMT training group (14% vs 2%, mean difference 12%, $p = 0.03$). The IMT was performed once daily 5 days/week for 2 weeks in addition to usual care [74].

2.3. Future perspectives

This review shows that further research should be encouraged to investigate new therapeutics and tools for the assessment of respiratory muscle function. The current rehabilitation strategies to prevent or treat respiratory muscle dysfunction are still scarce and mostly targeting higher respiratory muscle strength. Moreover, spontaneous breathing trials as a surrogate marker of endurance training have not been investigated in recent years. In this context, the use of individualized protocols combining different assessment and therapeutic modalities may be promising to be successfully applied to ameliorate muscle weakness and functional status.

Differences between the IMT protocols might directly affect the quality of training and therefore the weaning. Training Protocols need to consider the initial condition of respiratory muscles by a thoroughly assessment of muscle strength. This will help the practitioner to correctly determine training parameters (intensity, power, number of contractions and time of rest). Furthermore, the practitioner can make use of the FITT training principles (Frequency, Intensity, Time and Type) to offer adequate muscle overload, and exercise progression and specificity [80]. Frequency can be of once a day and include 3 sets of 7–10 repetitions according to the patient tolerance. Initial training intensity can be set as 30% of PImax in the first session as the aim of training is to increase training resistance up to 50% of PImax. Time of each session will vary as it needs to account the time to complete all sets and the required resting time of patients between each set of repetition. Progression of training can take place at every other session or whenever the patient completes the session without symptoms of fatigue. Although IMT will require patient to breath against a given resistance, the type of resistance delivered can vary between devices. Recently, tapered flow resistive loading (TFRL) was introduced for patients with obstructive respiratory diseases [81]. This new modality of inspiratory muscle loading differs from the conventional threshold loading since during TFRL the absolute load gradually reduces during inspiration. It accommodates the relationship between volume and pressure, and thus keeps the relative intensity of the load during inspiration constant [82]. Furthermore, TFRL provides data of external work of breathing (WOB), mean pressure, power, peak flow and number of breaths during the training sessions allowing adequate feedback and adjustment of settings when necessary (Fig. 2) [81]. TFRL provides visual feedback (pressure and volume) on the performance during the session [81]. This encourages the patient to improve the quality of the training session and thus the training effects. The physical therapist is provided with, in addition to vital signs (HR, BP, ECG, SaO_2), information on the training variables such as the inspiratory pressure, tidal volume, power and energy of the breath [83]. Recently, we started to investigate the feasibility and initial effectiveness of IMT with TFRL on weaning failure patients (POWERbreathe KH2, POWERbreathe International Ltd, Southam, Warwickshire, United Kingdom) [82]. The training is performed once a day, 5 days per week set at the highest pressure tolerated, progressed daily.

Based on the previously mentioned considerations we give the following recommendations to improve the quality of the collected data in these trials. Firstly, we believe that studies should specifically focus on patients with known weaning difficulties since these are the patients that are likely to benefit the most from an IMT intervention during mechanical ventilation. It should further be aimed to initiate the training as soon as weaning difficulties have been recognized. The classification of weaning difficulties should be performed in accordance with the most recent clinical guidelines (WIND trial reference). Furthermore studies should focus on weaning success and other weaning related parameters such as weaning duration as main outcomes. Finally, an alternative, potentially more optimal way of loading the respiratory muscles during the IMT sessions should be considered in comparison to the previously used threshold loading.

Furthermore, IMT following successful extubation might also be warranted [84]. Bissett et al. [74] addressed this question in a randomized trial with 70 participants following 48 h of successful weaning to receive IMT in addition to usual care. As expected, PImax improved significantly in the intervention group (17% predicted vs 6%pred in the control group). Additionally, improvement in quality of life was greater in the training group (14% vs 2%, mean difference 12%, $p = 0.03$). Gosselink and Langer [84] highlighted some reasons that could have been involved in the lack of transfer effects to exercise performance and dyspnoea: 1) Duration of training program, 2 weeks of training may be too short to improve exercise performance and dyspnoea; 2) To obtain these effects, a rehabilitation programme combining limb muscle training and respiratory muscle training is probably warranted; 3) the progress of training intensity during the 2 weeks may not adjusted properly.

3. Conclusion

The decision to discontinue MV remains mostly based on clinician's assessment and predictors of weaning success. Strategies to improve weaning outcomes (i.e. Spontaneous breathing trials, noninvasive MV and early mobilization) successfully helped patients to interrupt MV. The addition of IMT to a general weaning protocol leads to clinically relevant improvements in chronic ill patients with difficult and prolonged weaning. The effectiveness of the training depends on [1]: the way that IMT is applied [2] the quality of assessment [3]; the correct patient selection [4]; the use of adequate levels of resistive load; and [5] adequate duration of a session. Finally, an individualized protocol with the tapered flow resistive loading might be promising for these patients. Its effectiveness, however, deserves further investigation.

4. Conflicts of interest and source of funding

The authors declare that they have no competing interests.

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