Managing respiratory muscle weakness during weaning from invasive ventilation

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Shareable abstract (@ERSpublications)
Weaning is a critical stage of an ICU stay where respiratory muscles play a major role. Estimation of respiratory muscle function is possible by measuring maximal inspiratory pressure and by ultrasound. Promising therapeutic developments are emerging. https://bit.ly/3g1lGwH

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Abstract

Weaning is a critical stage of an intensive care unit (ICU) stay, in which the respiratory muscles play a major role. Weakness of the respiratory muscles, which is associated with significant morbidity in the ICU, is not limited to atrophy and subsequent dysfunction of the diaphragm; the extradiaphragmatic inspiratory and expiratory muscles also play important parts. In addition to the well-established deleterious effect of mechanical ventilation on the respiratory muscles, other risk factors such as sepsis may be involved. Weakness of the respiratory muscles can be suspected visually in a patient with paradoxical movement of the abdominal compartment. Measurement of maximal inspiratory pressure is the simplest way to assess respiratory muscle function, but it does not specifically take the diaphragm into account. A cut-off value of -30 cmH_2O could identify patients at risk for prolonged ventilatory weaning; however, ultrasound may be better for assessing respiratory muscle function in the ICU. Although diaphragm dysfunction has been associated with weaning failure, this diagnosis should not discourage clinicians from performing spontaneous breathing trials and considering extubation. Recent therapeutic developments aimed at preserving or restoring respiratory muscle function are promising.

Introduction

Weaning from mechanical ventilation is a critical step for many patients in an intensive care unit (ICU). The transition from positive pressure ventilation toward spontaneous breathing is driven by the (re)contraction of the respiratory muscles, which is frequently altered by several risk factors related to the ICU stay. Among them, ventilator-induced respiratory muscle unloading is well established in animal and human studies and is defined by a loss in their capacity to generate pressure [1–5]. The result is in an imbalance between the respiratory load and reduced muscle capacity, which plays an important role in prompt and safe separation from the ventilator. The respiratory pump is indeed crucial to maintain spontaneous breathing without ventilatory assistance. For a long time, a great deal of attention has been focused on the diaphragm and the development of diaphragm dysfunction in the context of weaning failure. Nevertheless, respiratory muscle weakness is not limited to the atrophy and subsequent dysfunction of the diaphragm; extradiaphragmatic inspiratory and expiratory muscles also play an important role, as demonstrated in several physiological studies [6]. Other studies suggest that respiratory muscle weakness has distinct characteristics as compared to the ICU-acquired weakness that concerns limb muscles and affects up to 25% of patients who are under mechanical ventilation for more than 7 days [7]. There is an

overlap between the two diseases, but they have different risk factors and do not lead to the same outcomes. ICU-acquired weakness is associated with long-term mortality after the ICU, whereas respiratory muscle weakness is associated with weaning failure but not with mortality in patients who are successfully separated from the ventilator [8]. Exploring respiratory muscle function is challenging in the ICU, but detecting patients at risk of respiratory muscle weakness is important to optimise safe separation from the ventilator. Developing strategies to preserve or restore respiratory muscle function in these patients is also an important goal for which recent developments have shown promising findings. Therefore, the aims of this review are to describe the anatomy and physiology of respiratory muscle weakness during weaning failure and then to discuss the most accessible evaluation tools and therapeutic strategies to facilitate separation from the ventilator.

Anatomy and physiology of respiratory muscles

Several respiratory muscles are involved in the generation of breathing (see figure 1). The extradiaphragmatic inspiratory muscles support the diaphragm to maintain adequate ventilation, but each muscle has other specific tasks. The alae nasi and genioglossus maintain upper airway patency [9–11], the parasternal intercostal muscles stabilise the chest wall and facilitate rotation of the trunk [12], while the scalene and sternocleidomastoid muscles are involved in the rotation of the head and flexion of the neck. The external intercostals in the dorsal portion and the intercartilaginous portion of the internal intercostals (so-called parasternal intercostals), as well as the scalene muscles, induce rib cage expansion during inspiration. Expiratory muscles are also involved in breathing, notably during the expiratory phase. The abdominal muscles located in the ventrolateral wall of the abdomen include the rectus abdominis, transversus abdominis, internal oblique and external oblique muscles. They have a postural function as well as an important role in breathing and coughing. The abdominal muscles have a basic tone during quiet breathing in sitting or standing positions that enhances diaphragmatic force and optimises its length–tension relationship to generate pressure [13]. They also enhance diaphragmatic activity when ventilatory loads or minute ventilation are increased *via* phasic expiratory activity [14, 15]. The expulsive expiratory efforts developed by the contraction of the abdominal muscles generate coughing and the elimination of secretions [16]. The transversus abdominis appears to be the main contributor in generating abdominal expiratory pressure during progressive expiratory efforts whereas the external oblique is preferentially involved during trunk rotation [17].

The diaphragm, which is frequently presented as the main inspiratory muscle, is dome-shaped, composed of a thin musculotendinous membrane and serves to separate the thorax from the abdominal cavity. From a

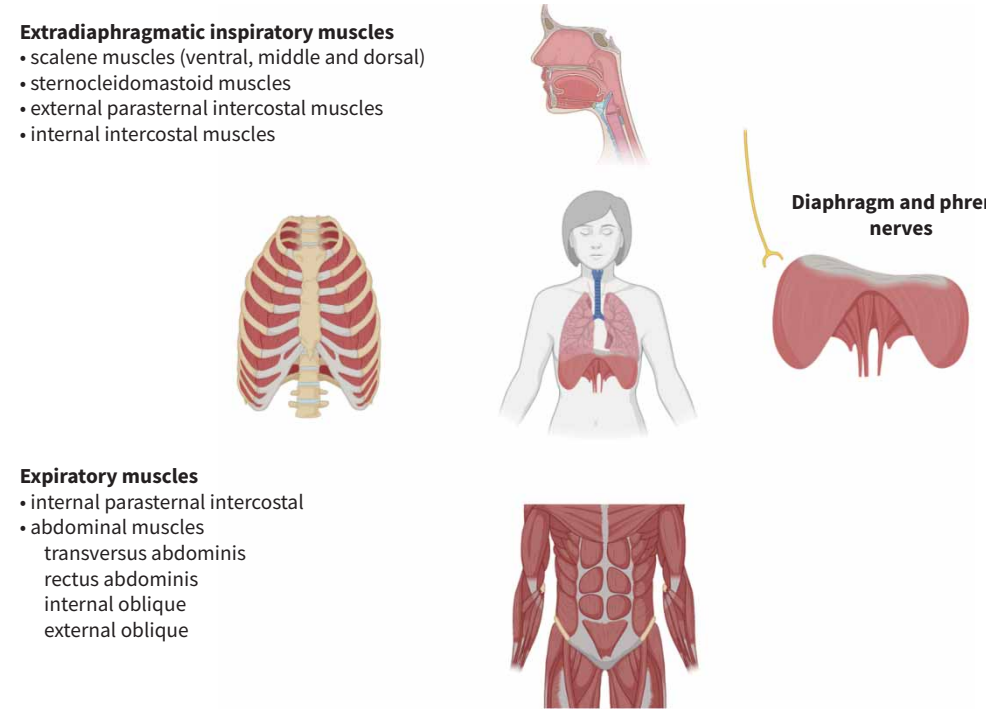

FIGURE 1 The respiratory muscles involved in the generation of respiration. Figure created using BioRender.

tendinous centre, striated muscle fibres radiate to the anterior sternal and intercostal insertions and posterior spinal insertions. The diaphragm is innervated by left and right phrenic nerves originating mainly from the C4 cervical plexus and descending along the mediastinum dividing into muscle nerve endings. Clinically, phrenic afferents irritation translates as referred neck and shoulder pain (C3–C5 sensory territory) [18]. As a muscle, the function of the diaphragm is to shorten and to generate a force, which is evaluated *in vivo* as its capacity to generate a pressure. The diaphragm is one of the two muscles with the myocardium whose activity is not supposed to stop and even partial rest can have important consequences. The forced rest induced by mechanical ventilation induces diaphragmatic atrophy that is not observed in other muscles such as the pectoral or lateral dorsal muscles [19, 20]. The contraction of the diaphragm decreases the intra-thoracic pressure and allows inspiratory flow; concomitantly, the diaphragm lowers and compresses the abdominal content. The resultant transdiaphragmatic pressure is the sum of the absolute changes in gastric and oesophageal pressures during breathing and is a physiological indicator of the contribution of the diaphragm in the inspiratory effort [21]. Indeed, the diaphragm is the only muscle that simultaneously increases gastric pressure (reflecting the abdominal pressure) and decreases oesophageal pressure (reflecting the intra-thoracic pressure) [22]. Transdiaphragmatic pressure can be useful for monitoring patients who are difficult to wean from mechanical ventilation [23]. Transdiaphragmatic pressure can also be measured during a nonvoluntary effort and in a standardised way by using bilateral anterior magnetic phrenic nerves stimulation (BAMPS) at the cervical level [21, 24, 25]. This technique provides supramaximal phrenic stimulation, leading to the depolarisation of a maximal number of phrenic nerve fibres. In turn, it induces a contraction of the diaphragm and a generation of pressure that can be measured. While measuring the transdiaphragmatic pressure with BAMPS is certainly meaningful [21], it requires oesophageal and gastric balloons.

Pathophysiology

The pathophysiological pathway leading to respiratory muscle weakness has been largely investigated in studies focusing on the diaphragm [27]. At the muscular level, the contractile dysfunction of respiratory muscles is linked to two main mechanisms that can be associated with 1) the loss of muscle mass (atrophy), which is the result of an imbalance between protein synthesis and degradation, and 2) contractile protein dysfunction. Evidence of extradiaphragmatic muscle weakness is scarce. Most studies have investigated expiratory muscle function by measuring the maximal expiratory pressure (MEP) and found lower values of MEP in patients with weaning failure as compared to values obtained in healthy subjects [28–31]. Others used ultrasound to quantify the atrophy of abdominal muscles [17, 32]. In a study of 77 patients in whom abdominal muscles were serially studied with ultrasound, 22% of them developed atrophy whereas an increase in diaphragm thickness was found in 12%. This increase was attributed to the increased thickness of the interparietal fasciae. Changes in expiratory muscle thickness were not associated with changes in diaphragm thickness, indicating that different muscles of the respiratory pump may respond differently to mechanical ventilation and causative disease [32]. It is not clear whether expiratory muscle weakness has the same risk factors as diaphragm weakness and further studies are required in order to shed light on this matter. While not being a comprehensive list, the following sections outline some important risk factors of respiratory muscle weakness that are particularly related to mechanical ventilation.

Excessive diaphragm unloading (ventilator-induced diaphragm dysfunction)

Animal models established that controlled mechanical ventilation induces an alteration of the contractile properties of the diaphragm as a function of time [33–35], leading to the concept of ventilation-induced diaphragmatic dysfunction [36]. The term “dysfunction” is related to the presence of diaphragmatic muscle fibre atrophy as well as a decrease in the force generated by the contraction of these fibres [35] and to structural alterations at the level of the muscle fibre such as a decrease in resistance to oxidative stress, an increase in proteolysis and a decrease in protein synthesis. Confirming these findings in humans has been a challenging task as, in the ICU, several risk factors – in addition to controlled mechanical ventilation – are likely to contribute. Studies have strongly suggested that mechanical ventilation induces diaphragm dysfunction but there is no direct evidence. A first observation of diaphragm atrophy was reported in children exposed to mechanical ventilation for at least 12 days [37] and, later, a landmark study confirmed these findings in brain dead patients ventilated for between 18 h and 69 h [19]. The control population of the latter study, composed of scheduled thoracic surgery patients ventilated for less than 3 h, did not show pathological histological lesions of the muscle fibres. These lesions were also not found in pectoral muscle fibres. This same dissociation in histological damage was observed between the diaphragm and the lateral dorsal muscle [20] and contributes to the greater sensitivity of the diaphragm as compared to the other muscles to inactivity caused by mechanical ventilation. Using an ultrasound approach, it has been shown that the thickness of the diaphragm decreases progressively over time [38] and that this decline is greater as the duration of mechanical ventilation increases [39–41]. The severity of diaphragmatic atrophy seems to be modulated by the level of the inspiratory effort [39]; the lower the effort, the greater the atrophy. Such

findings encourage maintaining an "appropriate" level of diaphragmatic activity in patients under mechanical ventilation, but the quantification of inspiratory effort level is challenging without sophisticated tools [22].

Insufficient diaphragm loading

Several studies have reported that exertion can injure limb muscles [42]. It is likely that the same mechanisms occur in the diaphragm in cases of the intense inspiratory efforts which are frequently encountered in patients with *de novo* hypoxemic acute respiratory failure [43]. While this conceptual reasoning sounds reasonable, clear evidence in ICU patients is lacking. Diaphragm biopsies were obtained in patients scheduled for thoracic surgery. Signs of diaphragm injury were reported in those who were exposed to inspiratory muscle loading prior to surgery [43]. In natural conditions, diaphragmatic dysfunction has been observed in pregnant patients who, during delivery, make intense and repeated diaphragmatic contractions [44]; in extreme cases, diaphragmatic ruptures have been observed [45]. Whether intense respiratory efforts could indeed induce diaphragm injury in patients with acute respiratory failure and whether this potential muscle injury could be translated into diaphragm dysfunction is not established. Under mechanical ventilation, it has been suggested that patient–ventilator asynchronies inducing inappropriate efforts may be involved in the development or persistence of diaphragmatic dysfunction [46], even if it is possible that the asynchronies are the result of the said dysfunction [47]. Two asynchronies can lead to excessive ventilation with the risk of dynamic hyperinflation that can alter the structure of the diaphragm; these are auto-triggers and double triggers [48]. These data encourage the detection of these asynchronies, which are also associated with an increase in the duration of mechanical ventilation [49] and mortality [47]. Overall, these elements suggest that inappropriate (over)activity of the diaphragm is deleterious, although it remains challenging to tailor ventilatory support according to the patient's needs.

Sepsis

Sepsis is a well-established risk factor of diaphragm dysfunction. In animals, sepsis decreases the contractile force of the diaphragm [50] without atrophy [51]. In humans, it has been shown that sepsis is an independent factor of diaphragmatic dysfunction a few hours after initiation of mechanical ventilation [2]. Interestingly, sepsis may behave as a transient risk factor inducing a reversible diaphragm dysfunction. Indeed, a study showed that septic patients were associated with a more severe but reversible impaired diaphragm function as compared to nonseptic patients and that an increase in diaphragm function was associated with a better survival rate [52].

Diagnosis of respiratory muscle weakness

In ICU patients, respiratory muscle weakness can be the consequence of any pathological process occurring between the respiratory centres and the muscles [35, 53]. It is therefore important to pay attention to sedation, which can reduce the respiratory drive before evaluating respiratory muscle function [54]. Likewise, phrenic nerve injury can also be involved but the diagnostic is not straightforward as it relies on electromyogram [24]. A pragmatic approach to the diagnostic management of respiratory muscle weakness is presented in figure 2. Respiratory muscle weakness can be visually suspected in a patient presenting a paradoxical movement of the abdominal compartment. This sign is present in cases of severe diaphragm dysfunction and reflects a passive movement of the muscle, which is attracted by the negative intrathoracic pressure generated by the contraction of the extradiaphragmatic respiratory muscles.

Pressure-based diagnosis

The measurement of maximal inspiratory pressure (MIP) is probably the easiest way to assess respiratory muscle function. However, it is important to note that MIP assesses the global respiratory muscle function and not specifically the diaphragm. MIP is measured at the mouth (or endotracheal tube or tracheostomy) during a maximal static inspiratory effort. This manoeuvre is not easy to perform in ICU patients because it requires the full cooperation of the patient. However, in mechanically ventilated patients, it is possible to obtain equivalent information using a unidirectional valve positioned at the tip of the endotracheal tube allowing the patient to perform successively increasing inspiratory efforts to obtain an effort comparable to a maximal inspiratory effort at a lung volume close to the residual volume [26, 55]. A threshold of MIP of -30 cmH_2O seems relevant to classify patients having respiratory muscle weakness [6] and importantly this threshold is associated with outcomes [8, 56].

Ultrasonography-based diagnosis

Ultrasound is an increasingly popular and available tool for assessing respiratory muscle function, particularly the diaphragm, in the ICU [57]. When the diaphragm contracts, it lowers toward the abdominal compartment and thickens, allowing its visualisation. Thus, the immediate availability, direct visualisation

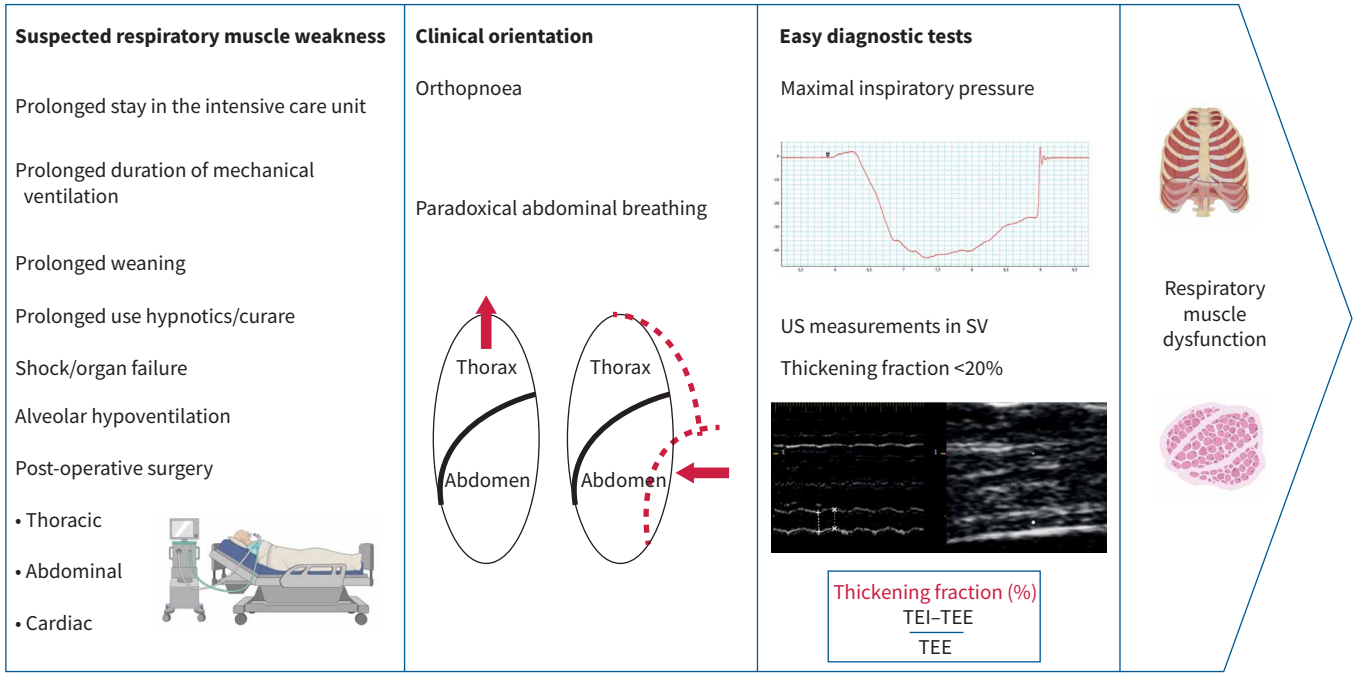

FIGURE 2 Pragmatic approach for the diagnostic management of respiratory muscle weakness. SV: spontaneous ventilation; TEE: thickness at end expiration; TEI: thickness at end inspiration; US: ultrasound. Figure created using BioRender.

and noninvasive approach of ultrasound are appreciated at the bedside. The diaphragm is located between the peritoneal and pleural layers and appears hyperechoic. The observation of an echogenic sheet floating between the peritoneal and pleural layers is possible in the majority of subjects and testifies to the good localisation of the diaphragm. Ultrasound offers two main descriptive approaches of diaphragm function [58]. The subcostal approach evaluates the motion of the diaphragmatic dome through the abdominal approach. It is necessary to use a low-frequency abdominal or cardiac probe and position it under the right costal margin, perpendicular to the midclavicular line and directed toward the liver. The diaphragm then appears as a hyperechoic line diametrically opposite the probe and surrounding the liver. The motion (also called excursion) of the dome of the diaphragm during inspiration can be quantified to assess diaphragm function, but only during nonassisted breathing; otherwise, the downward displacement of the diaphragm may reflect passive insufflation of the chest by the ventilator. Diaphragm excursion $\leqslant$1 cm during resting unsupported breathing is diagnostic for diaphragm dysfunction. To assess thickening, the diaphragm is examined on its zone of apposition to the rib cage. In this location, ultrasound can measure end-expiratory and peak-inspiratory diaphragm thickness. Diaphragm thickening fraction is computed as the fractional increase in diaphragm thickness during inspiration. Thickening fraction is moderately correlated with transdiaphragmatic pressure in some studies [57, 59, 60] and poorly if not correlated in others [61, 62]. Thickening fraction is also correlated with the twitch pressure generated by BAMPS (r=0.87), provided that patients trigger the ventilator. A thickening fraction below 20% has been proposed as a diagnostic threshold of diaphragm dysfunction but caution is needed when using ultrasound to estimate diaphragm function as the reliability of measurements varies a great deal [57]. A recent group of experts proposed a consensus statement on diaphragm ultrasound methodology and, notably, they recommended using 40 examinations as minimum training before using diaphragm ultrasonography in clinical practice [63]. Ultrasound remains dependent on the acquisition conditions and the operator despite frequent good inter-observer reproducibility [59]. The subcostal approach is the easiest to perform in practice, notably because of the centimetre scale of measurement, whereas the intercostal approach is at the millimetre scale and is rather reserved for research [64, 65]. Ultrasound measurements have also been used to assess muscle structure, activity and function of the abdominal muscles [14, 66, 67]. Ultrasound measurement of abdominal muscle thickness has been shown to be highly reproducible, with low coefficients of variation to assess changes in muscle thickness for either the lateral abdominal muscles or the rectus abdominis [17]. This is also true in critically ill patients on mechanical ventilation [32]. It is also possible to measure the stiffness of the diaphragm [68], which may be interesting in order to analyse the structure of the muscle [69]. A new ultrasound-based medical device for continuous diaphragm monitoring quantifies

diaphragm excursion in a manner similar to standard ultrasound and changes in diaphragm excursion align with simultaneously measured transdiaphragmatic pressure [70]. In addition, this device could reliably predict weaning failure [70]. A multicentre, multinational, prospective single-arm blinded study to validate this device is in progress (clinicaltrials.gov identifier: NCT04696406).

Weaning from mechanical ventilation and respiratory muscle weakness

Weaning failure results from an imbalance between the loads that are applied against the capacity of the respiratory system. On one side, loads are typically related to cardiogenic pulmonary oedema, atelectasis, intrinsic positive end-expiratory pressure and chest wall disease. On the other side, the respiratory drive and muscles manage to overcome the respiratory loads. Diaphragm dysfunction is frequently associated with weaning failure, which is present in 63% of patients ready to undergo their first spontaneous breathing trial [71]. However, it must be stressed that weaning-induced pulmonary oedema has been shown to be as frequent as diaphragm dysfunction [72]. On the one hand, diaphragm dysfunction reduces the rise in thoraco-abdominal gradient that could potentially decrease the risk of cardiogenic pulmonary oedema [73]. On the other hand, the respiratory distress that occurs during a failed spontaneous breathing trial involves large negative swings in pleural pressure that influence cardiac performance by increasing the venous return and left ventricular afterload. A study showed that diaphragm dysfunction and cardiogenic pulmonary oedema are frequent, both individually and combined [73]. Therefore, in the case of weaning failure, it is important to first rule out cardiogenic pulmonary oedema, which is easy to diagnose and treat before exploring the respiratory muscle function. In patients equipped with oesophageal and gastric balloons undergoing a spontaneous breathing trial, diaphragm dysfunction can be documented by a negative gastric pressure associated and with a reduced transdiaphragmatic pressure [74]. Diaphragm dysfunction is confirmed by BAMPS when the endotracheal pressure generating capacity is not higher than -11 cmH_2O [71, 75, 76]. The measurement of MIP is easier to implement. An MIP value of -30 cmH_2O corresponded to the value below which patients were successfully weaned, whereas MIP values less negative than -20 cmH_2O were associated with weaning failure [77]; the cut-off value of -30 cmH_2O also differentiated patients with prolonged ventilatory weaning from others [6]. High values for MIP rule out clinically significant weakness, but low values are common and may also reflect poor technique or insufficient effort [78]. Interestingly, one study showed that diaphragm dysfunction assessed by ultrasound performed in patients who had successfully passed a spontaneous breathing trial was not associated with an increased risk of extubation failure [64]. This is an interesting finding that suggests that diaphragm function may be a determinant of the success of spontaneous breathing trial but not of extubation. Likewise, another study reported that diaphragm function is not associated with long-term survival in patients who were successfully separated from the ventilator [79]. It is also possible to use a combined approach of respiratory muscle ultrasound to predict weaning outcome. In patients who successfully passed the spontaneous breathing trial and who were extubated, ultrasound of the respiratory muscles (diaphragm and intercostal muscle) measured within 2 h of extubation predicted subsequent extubation failure [80]. A diaphragm thickening fraction value greater than 25–35% predicts successful weaning [81, 82], whereas an excursion of diaphragm measurement greater than 1 cm is associated with a successful spontaneous ventilation test [71]. While diaphragm dysfunction has been associated with weaning failure, the diagnosis of diaphragm dysfunction should not discourage clinicians from performing spontaneous breathing trials and considering extubation. Thus, some patients with respiratory muscle weakness and especially diaphragmatic dysfunction can ultimately be successfully separated from the ventilator [71, 75]. Abdominal muscles contribute to the total respiratory muscle effort in patients who have failed a weaning trial [15]. Therefore, attention to abdominal muscles during weaning may be useful. Among patients who undergo a spontaneous breathing trial, reduced abdominal muscle thickening during coughing was associated with extubation failure [83].

Treatment of respiratory muscle dysfunction

Preventive and curative interventions to manage respiratory muscle weakness in the ICU are shown in figure 3.

Preventive approach

The diagnosis of diaphragmatic dysfunction, often made at a later stage of the ICU stay, requires the implementation of preventive measures. On top of all other measures, preserving diaphragmatic activity with spontaneous breathing is certainly the easiest to implement and the most useful. However, this strategy is not straightforward. Spontaneous efforts should be encouraged as soon as possible provided that tidal volumes are not excessive to keep in line with the goals of lung-protective ventilation. To accommodate lung and diaphragm ventilation, a conceptual strategy has been developed, so-called lung- and diaphragm-protective ventilation [84, 85]. Continuous measurement of oesophageal pressure may be useful to detect excessive inspiratory efforts, but no safe ranges are currently available. A group of experts

recommended maintaining the oesophageal pressure at between 3 and 15 cmH_2O, but this must be explored in clinical studies [84]. Two recent studies report on the feasibility of clinical algorithms implemented at the bedside to tailor sedation and ventilator settings in order to allow the diaphragm to contract while lung distending pressures are limited [86, 87]. Those algorithms may require tools to monitor features such as transdiaphragmatic pressure, diaphragmatic electrical activity or diaphragm ultrasound, which are not easy to use and not widely available. Further developments are therefore needed to facilitate lung- and diaphragm-protective ventilation at the bedside. Other options may rely on "proportional" ventilation modes such as proportional assisted ventilation (PAV) and neurally adjusted ventilatory assist (NAVA) to titrate the ventilator support to the patient's demand and help to reduce patient–ventilator asynchrony [88, 89]. NAVA and PAV could be of interest in lung- and diaphragm-protective ventilation strategies [90], but clinical evidence of efficacy is lacking.

Curative approach

Training or rehabilitation of the muscles is used in athlete, healthy and clinical populations such as COPD patients [91–93]. Therefore, it was suggested that the respiratory muscles can be trained by following the same training principles as any other skeletal muscle, increasing their strength, contraction velocity and endurance. Since respiratory muscle weakness has been identified as an important risk factor for weaning failure, inspiratory muscle training (IMT) seems to be a promising treatment strategy for mechanically ventilated patients with prolonged weaning. The value of IMT in this population is still under debate, given that the few studies available describing IMT are often of low quality and questionable methodology, thereby providing limited evidence for its effectiveness [94–96]. Substantial heterogeneity is present in IMT studies, related to the employed training methods, training intensity, frequency, duration and type of load imposed on the inspiratory muscles, and the timing of initiating IMT. IMT can be implemented for different distinct purposes such as improving endurance or muscle strength, which requires different strategies *via* distinct physiological responses. It has been shown that the sensation of inspiratory effort is dependent on MIP [97]. The timing of initiating IMT varied substantially and included 24 h after initiation of mechanical ventilation, when the patient first awoke, at the transition to partially assisted ventilation, when the patient was deemed ready to be weaned and after a failed weaning attempt. The IMT protocols available in the literature describe training intensities that vary in external load between 20% and 50% of MIP with or without daily intensity progression [96, 98]. The most-used IMT device provides pressure threshold loading. This type of loading provides a constant external loading throughout the inspiration by means of a spring-loaded valve. Most commonly, patients are instructed to expire up to residual volume and subsequently perform a fast, full vital capacity inspiration against the external load of approximately 30–50% of the MIP. However, due to the pressure–volume relationship of the inspiratory muscles, the pressure-generating capacity decreases during inspiration, reaching virtually 0 cmH_2O at total lung capacity. Thereby, when IMT is performed with pressure threshold loading (*i.e.* constant loading throughout the inspiration), at a certain lung volume the patient will not be able to overcome the initial loading of 50% MIP (measured at residual volume). Subsequently, the inspiratory valve will close prematurely and limit the ability to perform full vital capacity inspirations. An alternative type of loading, tapered flow resistive loading, has gained popularity in recent years [99]. After overcoming the initial external load at residual volume, the external load gradually decreases during inspiration. This allows inspiration with nearly constant intermediate flow rates over a larger range of lung volumes compared to pressure threshold loading. Several randomised studies have investigated IMT in ICU patients [100–102]. In a first study, an inspiratory load of 30% of MIP for 5 min, twice a day, 7 days a week, resulted in a significant increase in MIP in the treatment group as opposed to the control group (standard of care), with no significant effect on weaning success [100]. Another study carried out in patients who had been ventilated for an average of 44 days investigated an IMT protocol consisting of four series of 6–10 breaths per day against a threshold load with an individualised level that could be just tolerated with 2 min of rest between each series [102]. The control group was exposed to a sham protocol to simulate training. This IMT protocol significantly improved MIP in the intervention group and had a higher proportion of successful weaning than in the control group (71% *versus* 47%) [102]. Eventually, two systematic reviews of the literature [96, 98] conclude that respiratory muscle training is feasible and well tolerated in critically ill patients and improves both inspiratory and expiratory muscle strength in patients with respiratory muscle weakness. Both systematic reviews could not demonstrate a positive effect on clinical outcomes, such as weaning success. A pilot, prospective, randomised study of tracheostomised patients requiring mechanical ventilation in one ICU describes that the electronic IMT device is safe, promotes an increase in MIP and leads to a shorter ventilator weaning time than that seen in patients treated using an intermittent nebulisation programme [103]. The IMweanT study is a double-blind, parallel-group, randomised controlled superiority trial to evaluate the effects of a novel IMT method on weaning outcomes in selected patients with weaning difficulties [104]. No standardised protocol is described at the moment and the moment of initiation of this therapy remains to be defined. A multidisciplinary practice guide for clinicians

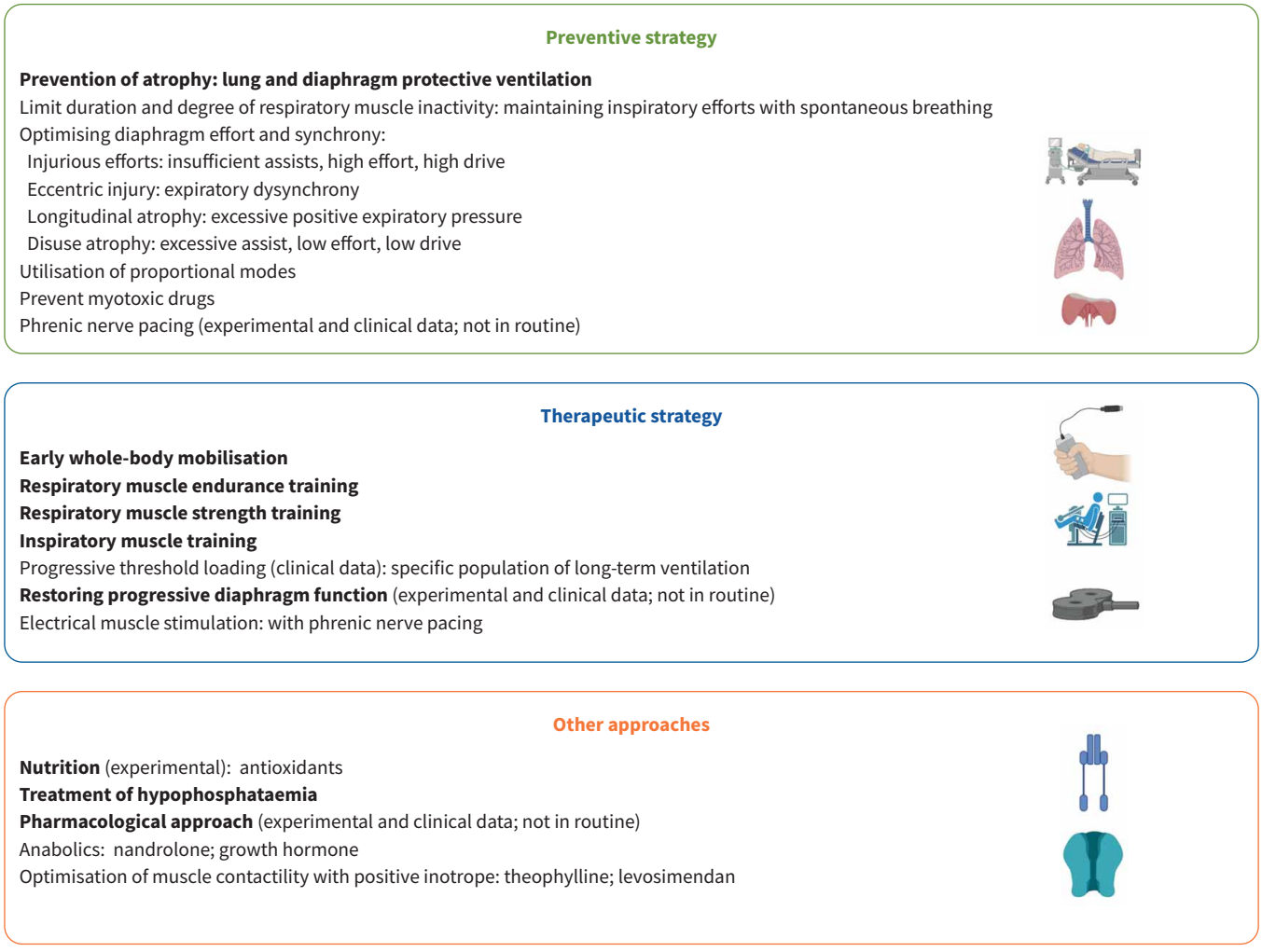

FIGURE 3 Interventions to manage respiratory muscle weakness in the intensive care unit. Figure created using BioRender.

has been published specifically on IMT for critical care patients [105]. One of the main issues with IMT is the need for patient cooperation, which may be challenging in patients with delirium. This raises the interest for automatic muscle stimulation devices. Transvenous phrenic nerve stimulation is a method that allows temporary and noninvasive stimulation of the phrenic nerves using a dedicated catheter equipped with electrodes [106]. In a multicentre, open-label, randomised, controlled study in patients on mechanical ventilation for more than 4 days and who had failed at least two weaning attempts, temporary transvenous phrenic nerve stimulation could improve the MIP, suggesting that it interfered with diaphragm function [107]. However, this increase was not associated with a higher proportion of successful weaning [107]. Phrenic nerve stimulation appeared feasible, as 75% of the patients in the treatment group could successfully receive the therapy, which was well tolerated. An ongoing larger trial is currently on its way and should clarify whether transvenous phrenic nerve stimulation can help to reduce to burden of prolonged weaning (clinicaltrials.gov identifier: NCT03783884). Another interesting approach would be to use phrenic nerve stimulation early on in order to limit diaphragm atrophy, as nicely demonstrated in a pig model [108]. Such a strategy could represent a new mode of ventilation combining positive pressure ventilation and diaphragm neuromodulation, *i.e.* diaphragm neuromodulation assisted ventilation (DiNAV). DiNAV represents a promising lung- and diaphragm-protective ventilation approach for the future and will need to be investigated further to confirm these appealing features.

Other approaches

Catabolism is a leading mechanism of respiratory muscle weakness, logically suggesting that optimising nutrition may be an interesting target. A study evaluated the effects of two nutritional strategies and found

that ICU-acquired muscle weakness (not respiratory) was significantly less frequent in the late parenteral nutrition group (34% *versus* 43%) [109], but muscle atrophy was not significantly different between the two groups. This study suggests that macronutrient deficiency during the first week of intensive care is not associated with the development of muscle atrophy and may even improve muscle contractility. Whether these findings are applicable in respiratory muscles is not yet elucidated. The presence of hypophosphataemia is associated with rapidly reversible diaphragmatic dysfunction after correction in resuscitation patients, encouraging electrolyte monitoring during weaning from mechanical ventilation [110]. Research on the use of drug therapy for diaphragmatic dysfunction is an interesting perspective. Calcium sensitisers may have beneficial effects on diaphragmatic function [111] and improve respiratory muscle contractility. In humans, treatments promoting muscle inotropism such as calcium sensitisers (levosimendan) and theophylline [112] have been evaluated. Experimental studies have shown that levosimendan improves the calcium sensitivity of diaphragm muscle fibres in COPD patients [111]. In healthy subjects, levosimendan administration improved diaphragmatic function by more than 20% [113], but this result was not confirmed in a randomised trial in patients being weaned from mechanical ventilation [114].

Conclusion

Respiratory muscle weakness is frequent in the ICU, often hindering weaning from mechanical ventilation. In addition to mechanical ventilation, other risk factors are likely to intervene and induce such a dysfunction. Weakness of the respiratory muscles can be suspected visually in a patient with paradoxical movement of the abdominal compartment. Measurement of MIP is the simplest way to assess respiratory muscle function, not specifically the diaphragm. The place of ultrasound in this indication is interesting but remains to be clarified. Recent therapeutic developments are promising but the only ones generally used remain the promotion of spontaneous inspiratory efforts within physiological limits and muscle training.

Provenance: Commissioned article, peer reviewed.

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References

1 Jaber S, Petrof BJ, Jung B, *et al.* Rapidly progressive diaphragmatic weakness and injury during mechanical ventilation in humans. *Am J Respir Crit Care Med* 2011; 183: 364–371.
2 Demoule A, Jung B, Prodanovic H, *et al.* Diaphragm dysfunction on admission to the intensive care unit. Prevalence, risk factors, and prognostic impact–a prospective study. *Am J Respir Crit Care Med* 2013; 188: 213–219.
3 Dres M, Jung B, Molinari N, *et al.* Respective contribution of intensive care unit-acquired limb muscle and severe diaphragm weakness on weaning outcome and mortality: a *post hoc* analysis of two cohorts. *Crit Care* 2019; 23: 370.
4 Supinski GS, Callahan LA. Diaphragm weakness in mechanically ventilated critically ill patients. *Crit Care* 2013; 17: R120.
5 Hooijman PE, Beishuizen A, de Waard MC, *et al.* Diaphragm fiber strength is reduced in critically ill patients and restored by a troponin activator. *Am J Respir Crit Care Med* 2014; 189: 863–865.
6 De Jonghe B, Bastuji-Garin S, Durand MC, *et al.* Respiratory weakness is associated with limb weakness and delayed weaning in critical illness. *Crit Care Med* 2007; 35: 2007–2015.
7 Ali NA, O'Brien JM, Hoffmann SP, *et al.* Acquired weakness, handgrip strength, and mortality in critically ill patients. *Am J Respir Crit Care Med* 2008; 178: 261–268.
8 Van Aerde N, Meersseman P, Debaveye Y, *et al.* Five-year outcome of respiratory muscle weakness at intensive care unit discharge: secondary analysis of a prospective cohort study. *Thorax* 2021; 76: 561–567.
9 Oppersma E, Doorduin J, van der Heijden EH, *et al.* Noninvasive ventilation and the upper airway: should we pay more attention? *Crit Care* 2013; 17: 245.
10 Strohl KP, Hensley MJ, Hallett M, *et al.* Activation of upper airway muscles before onset of inspiration in normal humans. *J Appl Physiol Respir Environ Exerc Physiol* 1980; 49: 638–642.
11 Saboisky JP, Jordan AS, Eckert DJ, *et al.* Recruitment and rate-coding strategies of the human genioglossus muscle. *J Appl Physiol* 2010; 109: 1939–1949.
12 Hudson AL, Butler JE, Gandevia SC, *et al.* Interplay between the inspiratory and postural functions of the human parasternal intercostal muscles. *J Neurophysiol* 2010; 103: 1622–1629.
13 De Troyer A, Boriek AM. Mechanics of the respiratory muscles. *Compr Physiol* 2011; 1: 1273–1300.

14 Shi ZH, Jonkman A, de Vries H, *et al.* Expiratory muscle dysfunction in critically ill patients: towards improved understanding. *Intensive Care Med* 2019; 45: 1061–1071.
15 Laghi F, Shaikh HS, Morales D, *et al.* Diaphragmatic neuromechanical coupling and mechanisms of hypercapnia during inspiratory loading. *Respir Physiol Neurobiol* 2014; 198: 32–41.
16 Ishida H, Kobara K, Osaka H, *et al.* Correlation between peak expiratory flow and abdominal muscle thickness. *J Phys Ther Sci* 2014; 26: 1791–1793.
17 Misuri G, Colagrande S, Gorini M, *et al. In vivo* ultrasound assessment of respiratory function of abdominal muscles in normal subjects. *Eur Respir J* 1997; 10: 2861–2867.
18 Orr TG. Importance of phrenic shoulder pain in disease involving the diaphragm. *JAMA* 1923; 80: 1434–1436.
19 Levine S, Nguyen T, Taylor N, *et al.* Rapid disuse atrophy of diaphragm fibers in mechanically ventilated humans. *N Engl J Med* 2008; 358: 1327–1335.
20 Welvaart WN, Paul MA, Stienen GJ, *et al.* Selective diaphragm muscle weakness after contractile inactivity during thoracic surgery. *Ann Surg* 2011; 254: 1044–1049.
21 Laveneziana P, Albuquerque A, Aliverti A, *et al.* ERS statement on respiratory muscle testing at rest and during exercise. *Eur Respir J* 2019; 53: 1801214.
22 Akoumianaki E, Maggiore SM, Valenza F, *et al.* The application of esophageal pressure measurement in patients with respiratory failure. *Am J Respir Crit Care Med* 2014; 189: 520–531.
23 Heunks LM, van der Hoeven JG. Clinical review: the ABC of weaning failure–a structured approach. *Crit Care* 2010; 14: 245.
24 Demoule A, Morelot-Panzini C, Prodanovic H, *et al.* Identification of prolonged phrenic nerve conduction time in the ICU: magnetic versus electrical stimulation. *Intensive Care Med* 2011; 37: 1962–1968.
25 Similowski T, Fleury B, Launois S, *et al.* Cervical magnetic stimulation: a new painless method for bilateral phrenic nerve stimulation in conscious humans. *J Appl Physiol* 1989; 67: 1311–1318.
26 Watson AC, Hughes PD, Louise Harris M, *et al.* Measurement of twitch transdiaphragmatic, esophageal, and endotracheal tube pressure with bilateral anterolateral magnetic phrenic nerve stimulation in patients in the intensive care unit. *Crit Care Med* 2001; 29: 1325–1331.
27 Friedrich O, Reid MB, Van den Berghe G, *et al.* The sick and the weak: neuropathies/myopathies in the critically ill. *Physiol Rev* 2015; 95: 1025–1109.
28 American Thoracic Society/European Respiratory Society. ATS/ERS statement on respiratory muscle testing. *Am J Respir Crit Care Med* 2002; 166: 518–624.
29 Savi A, Teixeira C, Silva JM, *et al.* Weaning predictors do not predict extubation failure in simple-to-wean patients. *J Crit Care* 2012; 27: 221.e1–221.e8.
30 Chao CM, Lai CC, Cheng AC, *et al.* Establishing failure predictors for the planned extubation of overweight and obese patients. *PLoS One* 2017; 12: e0183360.
31 Su WL, Chen YH, Chen CW, *et al.* Involuntary cough strength and extubation outcomes for patients in an ICU. *Chest* 2010; 137: 777–782.
32 Shi ZH, de Vries H, de Grooth HJ, *et al.* Changes in respiratory muscle thickness during mechanical ventilation: focus on expiratory muscles. *Anesthesiology* 2021; 134: 748–759.
33 Le Bourdelles G, Viires N, Boczkowski J, *et al.* Effects of mechanical ventilation on diaphragmatic contractile properties in rats. *Am J Respir Crit Care Med* 1994; 149: 1539–1544.
34 Sassoon CS, Caiozzo VJ, Manka A, *et al.* Altered diaphragm contractile properties with controlled mechanical ventilation. *J Appl Physiol (1985)* 2002; 92: 2585–2595.
35 Jaber S, Jung B, Matecki S, *et al.* Clinical review: ventilator-induced diaphragmatic dysfunction–human studies confirm animal model findings!. *Crit Care* 2011; 15: 206.
36 Vassilakopoulos T, Petrof BJ. Ventilator-induced diaphragmatic dysfunction. *Am J Respir Crit Care Med* 2004; 169: 336–341.
37 Knisely AS, Leal SM, Singer DB. Abnormalities of diaphragmatic muscle in neonates with ventilated lungs. *J Pediatr* 1988; 113: 1074–1077.
38 Grosu HB, Lee YI, Lee J, *et al.* Diaphragm muscle thinning in patients who are mechanically ventilated. *Chest* 2012; 142: 1455–1460.
39 Goligher EC, Fan E, Herridge MS, *et al.* Evolution of diaphragm thickness during mechanical ventilation. Impact of inspiratory effort. *Am J Respir Crit Care Med* 2015; 192: 1080–1088.
40 Schepens T, Verbrugghe W, Dams K, *et al.* The course of diaphragm atrophy in ventilated patients assessed with ultrasound: a longitudinal cohort study. *Crit Care* 2015; 19: 422.
41 Zambon M, Greco M, Bocchino S, *et al.* Assessment of diaphragmatic dysfunction in the critically ill patient with ultrasound: a systematic review. *Intensive Care Med* 2017; 43: 29–38.
42 Fridén J, Seger J, Sjöström M, *et al.* Adaptive response in human skeletal muscle subjected to prolonged eccentric training. *Int J Sports Med* 1983; 4: 177–183.
43 Orozco-Levi M, Lloreta J, Minguella J, *et al.* Injury of the human diaphragm associated with exertion and chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2001; 164: 1734–1739.

44 Nava S, Zanotti E, Ambrosino N, *et al.* Evidence of acute diaphragmatic fatigue in a 'natural' condition. The diaphragm during labor. *Am Rev Respir Dis* 1992; 146: 1226–1230.
45 Hamoudi D, Bouderka MA, Benissa N, *et al.* Diaphragmatic rupture during labor. *Int J Obstet Anesth* 2004; 13: 284–286.
46 Damiani LF, Engelberts D, Bastia L, *et al.* Impact of reverse triggering dyssynchrony during lung-protective ventilation on diaphragm function: an experimental model. *Am J Respir Crit Care Med* 2022; 205: 663–673.
47 Blanch L, Villagra A, Sales B, *et al.* Asynchronies during mechanical ventilation are associated with mortality. *Intensive Care Med* 2015;41:633–641.
48 Dres M, Rittayamai N, Brochard L. Monitoring patient–ventilator asynchrony. *Curr Opin Crit Care* 2016; 22: 246–253.
49 Thille AW, Rodriguez P, Cabello B, *et al.* Patient–ventilator asynchrony during assisted mechanical ventilation. *Intensive Care Med* 2006; 32: 1515–1522.
50 Hussain SN, Simkus G, Roussos C. Respiratory muscle fatigue: a cause of ventilatory failure in septic shock. *J Appl Physiol* 1985; 58: 2033–2040.
51 Boczkowski J, Dureuil B, Branger C, *et al.* Effects of sepsis on diaphragmatic function in rats. *Am Rev Respir Dis* 1988; 138: 260–265.
52 Lecronier M, Jung B, Molinari N, *et al.* Severe but reversible impaired diaphragm function in septic mechanically ventilated patients. *Ann Intensive Care* 2022; 12: 34.
53 Petrof BJ, Jaber S, Matecki S. Ventilator-induced diaphragmatic dysfunction. *Curr Opin Crit Care* 2010; 16: 19–25.
54 Jubran A, Tobin MJ. Pathophysiologic basis of acute respiratory distress in patients who fail a trial of weaning from mechanical ventilation. *Am J Respir Crit Care Med* 1997; 155: 906–915.
55 Caruso P, Friedrich C, Denari SD, *et al.* The unidirectional valve is the best method to determine maximal inspiratory pressure during weaning. *Chest* 1999; 115: 1096–1101.
56 Medrinal C, Prieur G, Frenoy É, *et al.* Respiratory weakness after mechanical ventilation is associated with one-year mortality – a prospective study. *Crit Care* 2016; 20: 231.
57 Goligher EC, Laghi F, Detsky ME, *et al.* Measuring diaphragm thickness with ultrasound in mechanically ventilated patients: feasibility, reproducibility and validity. *Intensive Care Med* 2015; 41: 734.
58 Matamis D, Soilemezi E, Tsagourias M, *et al.* Sonographic evaluation of the diaphragm in critically ill patients. Technique and clinical applications. *Intensive Care Med* 2013; 39: 801–810.
59 Vivier E, Mekontso Dessap A, Dimassi S, *et al.* Diaphragm ultrasonography to estimate the work of breathing during non-invasive ventilation. *Intensive Care Med* 2012; 38: 796–803.
60 Umbrello M, Formenti P, Lusardi AC, *et al.* Oesophageal pressure and respiratory muscle ultrasonographic measurements indicate inspiratory effort during pressure support ventilation. *Br J Anaesth* 2020; 125: e148–e157.
61 Poulard T, Bachasson D, Fossé Q, *et al.* Poor correlation between diaphragm thickening fraction and transdiaphragmatic pressure in mechanically ventilated patients and healthy subjects. *Anesthesiology* 2022; 136: 162–175.
62 Oppersma E, Hatam N, Doorduin J, *et al.* Functional assessment of the diaphragm by speckle tracking ultrasound during inspiratory loading. *J Appl Physiol* 2017; 123: 1063–1070.
63 Haaksma ME, Smit JM, Boussuges A, *et al.* EXpert consensus on diaphragm UltraSonography in the critically ill (EXODUS): a Delphi consensus statement on the measurement of diaphragm ultrasound-derived parameters in a critical care setting. *Crit Care* 2022; 26: 99.
64 Vivier E, Muller M, Putegnat JB, *et al.* Inability of diaphragm ultrasound to predict extubation failure: a multicenter study. *Chest* 2019; 155: 1131–1139.
65 Dubé BP, Dres M, Mayaux J, *et al.* Ultrasound evaluation of diaphragm function in mechanically ventilated patients: comparison to phrenic stimulation and prognostic implications. *Thorax* 2017; 72: 811–818.
66 Tuinman PR, Jonkman AH, Dres M, *et al.* Respiratory muscle ultrasonography: methodology, basic and advanced principles and clinical applications in ICU and ED patients-a narrative review. *Intensive Care Med* 2020; 46: 594–605.
67 Rankin G, Stokes M, Newham DJ. Abdominal muscle size and symmetry in normal subjects. *Muscle Nerve* 2006; 34: 320–326.
68 Fossé Q, Poulard T, Niérat MC, *et al.* Ultrasound shear wave elastography for assessing diaphragm function in mechanically ventilated patients: a breath-by-breath analysis. *Crit Care* 2020; 24: 669.
69 Aarab Y, Flatres A, Garnier F, *et al.* Shear wave elastography, a new tool for diaphragmatic qualitative assessment: a translational study. *Am J Respir Crit Care Med* 2021; 204: 797–806.
70 Demoule A, Virolle S, Mercat A, *et al.* Prediction of successful weaning from mechanical ventilation by continuous ultrasound monitoring of diaphragm excursion. *Eur Respir J* 2021; 58: Suppl. 65, PA3312.
71 Dres M, Dubé BP, Mayaux J, *et al.* Coexistence and impact of limb muscle and diaphragm weakness at time of liberation from mechanical ventilation in medical intensive care unit patients. *Am J Respir Crit Care Med* 2017; 195: 57–66.

72 Bedet A, Tomberli F, Prat G, *et al.* Myocardial ischemia during ventilator weaning: a prospective multicenter cohort study. *Crit Care* 2019; 23: 321.

73 Dres M, Rozenberg E, Morawiec E, *et al.* Diaphragm dysfunction, lung aeration loss and weaning-induced pulmonary oedema in difficult-to-wean patients. *Ann Intensive Care* 2021; 11: 99.

74 Pourriat JL, Lamberto C, Hoang PH, *et al.* Diaphragmatic fatigue and breathing pattern during weaning from mechanical ventilation in COPD patients. *Chest* 1986; 90: 703–707.

75 Jung B, Moury PH, Mahul M, *et al.* Diaphragmatic dysfunction in patients with ICU-acquired weakness and its impact on extubation failure. *Intensive Care Med* 2016; 42: 853–861.

76 Laghi F, Segal J, Choe WK, *et al.* Effect of imposed inflation time on respiratory frequency and hyperinflation in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2001; 163: 1365–1370.

77 Sahn SA, Lakshminarayan S. Bedside criteria for discontinuation of mechanical ventilation. *Chest* 1973; 63: 1002–1005.

78 Polkey MI, Green M, Moxham J. Measurement of respiratory muscle strength. *Thorax* 1995; 50: 1131–1135.

79 Saccheri C, Morawiec E, Delemazure J, *et al.* ICU-acquired weakness, diaphragm dysfunction and long-term outcomes of critically ill patients. *Ann Intensive Care* 2020; 10: 1.

80 Dres M, Similowski T, Goligher EC, *et al.* Dyspnoea and respiratory muscle ultrasound to predict extubation failure. *Eur Respir J* 2021; 58: 2100002.

81 Dres M, Goligher EC, Dubé BP, *et al.* Diaphragm function and weaning from mechanical ventilation: an ultrasound and phrenic nerve stimulation clinical study. *Ann Intensive Care* 2018; 8: 53.

82 Dres M, Demoule A. Diaphragm dysfunction during weaning from mechanical ventilation: an underestimated phenomenon with clinical implications. *Crit Care* 2018; 22: 73.

83 Schreiber AF, Bertoni M, Coiffard B, *et al.* Abdominal muscle use during spontaneous breathing and cough in patients who are mechanically ventilated: a bi-center ultrasound study. *Chest* 2021; 160: 1316–1325.

84 Goligher EC, Jonkman AH, Dianti J, *et al.* Clinical strategies for implementing lung and diaphragm-protective ventilation: avoiding insufficient and excessive effort. *Intensive Care Med* 2020; 46: 2314–2326.

85 Goligher EC, Dres M, Patel BK, *et al.* Lung- and diaphragm-protective ventilation. *Am J Respir Crit Care Med* 2020; 202: 950–961.

86 Dianti J, Fard S, Wong J, *et al.* Strategies for lung- and diaphragm-protective ventilation in acute hypoxemic respiratory failure: a physiological trial. *Crit Care* 2022; 26: 259.

87 de Vries HJ, Jonkman AH, de Grooth HJ, *et al.* Lung- and diaphragm-protective ventilation by titrating inspiratory support to diaphragm effort: a randomized clinical trial. *Crit Care Med* 2022; 50: 192–203.

88 Rolland-Debord C, Bureau C, Poitou T, *et al.* Prevalence and prognosis impact of patient–ventilator asynchrony in early phase of weaning according to two detection methods. *Anesthesiology* 2017; 127: 989–997.

89 Bureau C, Decavèle M, Campion S, *et al.* Proportional assist ventilation relieves clinically significant dyspnea in critically ill ventilated patients. *Ann Intensive Care* 2021; 11: 177.

90 Schmidt M, Dres M, Raux M, *et al.* Neurally adjusted ventilatory assist improves patient–ventilator interaction during postextubation prophylactic noninvasive ventilation. *Crit Care Med* 2012; 40: 1738–1744.

91 Illi SK, Held U, Frank I, *et al.* Effect of respiratory muscle training on exercise performance in healthy individuals: a systematic review and meta-analysis. *Sports Med* 2012; 42: 707–724.

92 Beaumont M, Forget P, Couturaud F, *et al.* Effects of inspiratory muscle training in COPD patients: a systematic review and meta-analysis. *Clin Respir J* 2018; 12: 2178–2188.

93 HajGhanbari B, Yamabayashi C, Buna TR, *et al.* Effects of respiratory muscle training on performance in athletes: a systematic review with meta-analyses. *J Strength Cond Res* 2013; 27: 1643–1663.

94 Smuder AJ, Min K, Hudson MB, *et al.* Endurance exercise attenuates ventilator-induced diaphragm dysfunction. *J Appl Physiol* 2012; 112: 501–510.

95 Worraphan S, Thammata A, Chittawatanarat K, *et al.* Effects of inspiratory muscle training and early mobilization on weaning of mechanical ventilation: a systematic review and network meta-analysis. *Arch Phys Med Rehabil* 2020; 101: 2002–2014.

96 Vorona S, Sabatini U, Al-Maqbali S, *et al.* Inspiratory muscle rehabilitation in critically ill adults. a systematic review and meta-analysis. *Ann Am Thorac Soc* 2018; 15: 735–744.

97 Campbell EJ, Gandevia SC, Killian KJ, *et al.* Changes in the perception of inspiratory resistive loads during partial curarization. *J Physiol* 1980; 309: 93–100.

98 Elkins M, Dentice R. Inspiratory muscle training facilitates weaning from mechanical ventilation among patients in the intensive care unit: a systematic review. *J Physiother* 2015; 61: 125–134.

99 Van Hollebeke M, Gosselink R, Langer D. Training specificity of inspiratory muscle training methods: a randomized trial. *Front Physiol* 2020; 11: 576595.

100 Cader SA, Vale RG, Castro JC, *et al.* Inspiratory muscle training improves maximal inspiratory pressure and may assist weaning in older intubated patients: a randomised trial. *J Physiother* 2010; 56: 171–177.

101 Condessa RL, Brauner JS, Saul AL, *et al.* Inspiratory muscle training did not accelerate weaning from mechanical ventilation but did improve tidal volume and maximal respiratory pressures: a randomised trial. *J Physiother* 2013; 59: 101–107.

102 Martin AD, Smith BK, Davenport PD, *et al.* Inspiratory muscle strength training improves weaning outcome in failure to wean patients: a randomized trial. *Crit Care* 2011; 15: R84.

103 Tonella RM, Ratti LDSR, Delazari LEB, *et al.* Inspiratory muscle training in the intensive care unit: a new perspective. *J Clin Med Res* 2017; 9: 929–934.

104 Hoffman M, Van Hollebeke M, Clerckx B, *et al.* Can inspiratory muscle training improve weaning outcomes in difficult to wean patients? A protocol for a randomised controlled trial (IMweanT study). *BMJ Open* 2018; 8: e021091.

105 Bissett B, Leditschke IA, Green M, *et al.* Inspiratory muscle training for intensive care patients: a multidisciplinary practical guide for clinicians. *Aust Crit Care* 2019; 32: 249–255.

106 Evans D, Shure D, Clark L, *et al.* Temporary transvenous diaphragm pacing *vs*. standard of care for weaning from mechanical ventilation: study protocol for a randomized trial. *Trials* 2019; 20: 60.

107 Dres M, de Abreu MG, Merdji H, *et al.* Randomized clinical study of temporary transvenous phrenic nerve stimulation in difficult-to-wean patients. *Am J Respir Crit Care Med* 2022; 205: 1169–1178.

108 Reynolds SC, Meyyappan R, Thakkar V, *et al.* Mitigation of ventilator-induced diaphragm atrophy by transvenous phrenic nerve stimulation. *Am J Respir Crit Care Med* 2017; 195: 339–348.

109 Hermans G, Casaer MP, Clerckx B, *et al.* Effect of tolerating macronutrient deficit on the development of intensive-care unit acquired weakness: a subanalysis of the EPaNIC trial. *Lancet Respir Med* 2013; 1: 621–629.

110 Aubier M, Murciano D, Lecocguic Y, *et al.* Effect of hypophosphatemia on diaphragmatic contractility in patients with acute respiratory failure. *N Engl J Med* 1985; 313: 420–424.

111 van Hees HW, Dekhuijzen PN, Heunks LM. Levosimendan enhances force generation of diaphragm muscle from patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2009; 179: 41–47.

112 Aubier M, Roussos C. Effect of theophylline on respiratory muscle function. *Chest* 1985; 88: Suppl. 2, 91S–97S.

113 Doorduin J, Sinderby CA, Beck J, *et al.* The calcium sensitizer levosimendan improves human diaphragm function. *Am J Respir Crit Care Med* 2012; 185: 90–95.

114 Roesthuis L, van der Hoeven H, Sinderby C, *et al.* Effects of levosimendan on respiratory muscle function in patients weaning from mechanical ventilation. *Intensive Care Med* 2019; 45: 1372–1381.