

REVIEW

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Mechanical ventilation weaning issues can be counted on the fingers of just one hand: part 1

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Abstract

Although mechanical ventilation may be a patient's vital ally during acute illness, it can quickly transform into an enemy during chronic conditions. The weaning process is the fundamental phase that enables the resumption of physiological respiratory function; however, it is also associated with a number of life-threatening complications, and a large percentage of critically ill patients never achieve airway device removal or require the resumption of mechanical ventilation just a few days post-weaning. Indeed, the weaning process is, at present, more of an art than a science. As such, there is urgent need for novel contributions from the scientific literature to abate the growing rates of morbidity and mortality associated with weaning failure. The physician attempting to wean a patient must integrate clinical parameters and common-sense criteria. Numerous studies have striven to identify single predictive factors of weaning failure and sought to standardize the weaning process, but the results are characterized by remarkable heterogeneity. Despite the lack of benchmarks, it is clear that the analysis of respiratory function must include a detailed overview of the five situations described below rather than a single aspect. The purpose of this two-part review is to provide a comprehensive description of these situations to clarify the "arena" physicians are entering when weaning critically ill patients from mechanical ventilation.

Keywords: Weaning, Mechanical ventilation, Ultrasound, Echocardiography, Diaphragm, Diaphragm dysfunction

Introduction

Up to 25% of critically ill patients experience difficulties in weaning from invasive mechanical ventilation (IMV), burdening the intensive care unit (ICU) with long lengths-of-stay, prolonged mechanical ventilation (IMV), and increased morbidity and mortality [1]. Weaning failure is commonly described as a failed spontaneous breathing trial (SBT) or the reinstatement of mechanical ventilation within 2 to 7 days after extubation [2]. Failed

extubation complicates up to 30% of successful spontaneous breathing trials [3] and correlates with higher morbidity and mortality rates [4, 5].

Determining the optimal time to extubate a patient continues to be a challenge. Prolonged mechanical ventilation is associated with a series of adverse effects (e.g., tracheal lesions, ventilator-associated pneumonia, ventilator-induced lung injury, and ventilator-induced diaphragm injury) [6, 7], whereas premature extubation exposes the patient to cardiovascular stress due to spontaneous breathing, often requiring the reinstatement of ventilatory support [8]. Although international guidelines recommend the implementation of spontaneous breathing trials [9], used alone this practice is ineffective in predicting weaning failure and reintubation [10–13]. A number of studies have investigated and proposed

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different parameters as outcome predictors of weaning from mechanical ventilation; however, a clear understanding of the ideal time to proceed with extubation for a successful outcome continues to elude us [14, 15]. Cardiac failure, diaphragmatic dysfunction and acute respiratory illness (lung parenchyma disease, or upper or lower airway obstructions), neurological status, and intra-abdominal issues are among the known leading causes of failed weaning [3, 16].

Significant advancements have been achieved in ultrasound technology over the last 20 years, most notably in bringing these techniques to the bedside, with all the advantages that this conveys. In fact, our capacity to study the individual organs ultrasonographically has become so finely tuned and specialized that physicians risk overlooking a more integrated examination of the patient. A comprehensive approach to invasive mechanical ventilation should include an extensive ultrasonographic assessment of cardiac function, diaphragmatic activity, and lung parenchyma. In particular, much light has been shone on the use of ultrasonographic assessment of diaphragmatic dysfunction as a predictor of weaning failure. That said, it is fundamental that the diaphragm does not receive excessive attention at the expense of other predictive factors. A simultaneous and comprehensive ultrasound examination of the cardio-pulmonary-diaphragmatic district may confer valuable predictive information regarding successful weaning from mechanical ventilation, although literature in this regard is still limited [17]. It is also important to bear in mind that other factors able to negatively influence the weaning outcome exist outside the cardio-pulmonary-diaphragmatic area (i.e., the neurological status and intra-abdominal hypertension) that cannot be evaluated with ultrasound [18, 19].

Mechanical ventilation can negatively affect the actors involved in respiratory function; for example, ventilator-induced lung injury, impaired cardiac performance, and ventilator-induced diaphragmatic dysfunction are all possible consequences. Although the concept of 'lung protection' during mechanical ventilation is well established, a more precise definition of a 'protective modality' to help preserve all the elements involved in the respiratory function is also desirable.

The purpose of this two-part review is to illustrate the main causes of unsuccessful weaning and recent advancements on the application of bedside ultrasound evaluation in these topics.

The weaning path

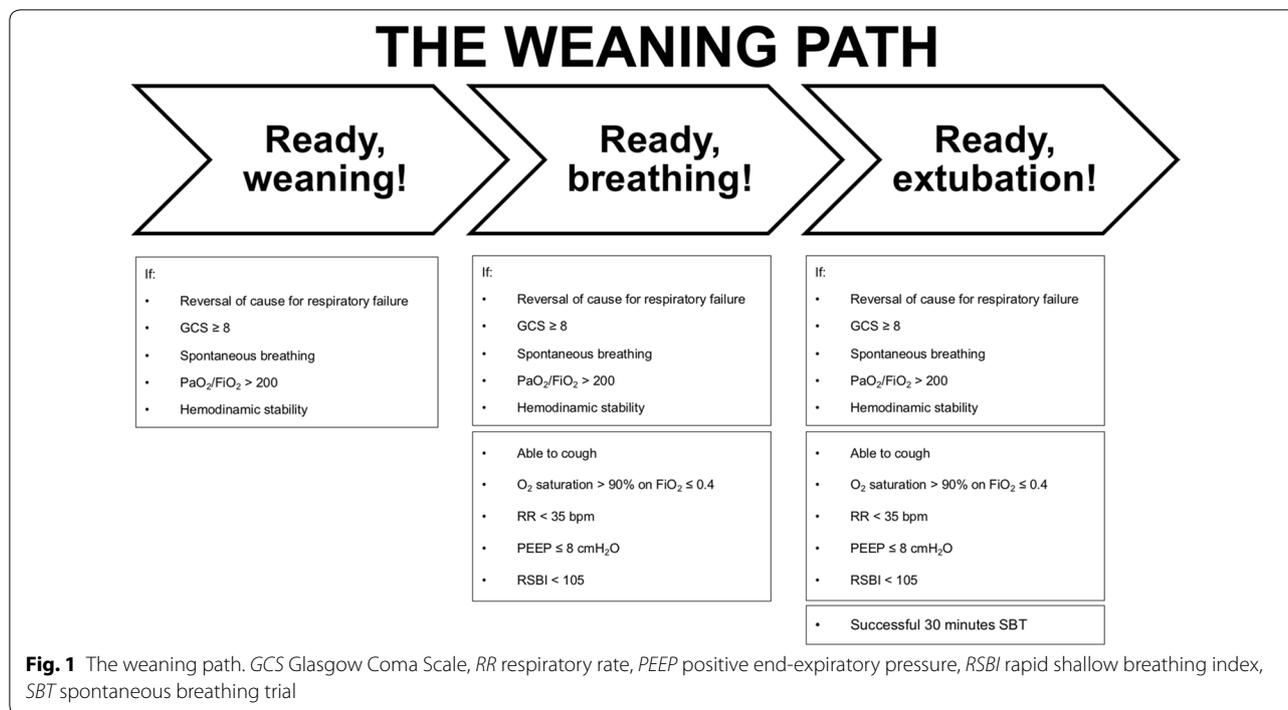
Weaning from mechanical ventilation starts with the institution of mechanical ventilation; from the outset, the physician assesses the patient on a daily basis to

determine when they might be ready to wean. Invasive mechanical ventilation is a risky journey for a critically ill patient admitted to the intensive care unit because of acute illness, IMV itself, or a failed weaning attempt. Weaning is the process in which the breathing effort is progressively returned from the machine to the patient. This process consists of 3 key steps, Fig. 1: first, when the patient's clinical conditions permit it, ventilation supports are progressively decreased (*Ready, weaning!*); second, a spontaneous breathing trial (SBT) assesses the patient's capability to breathe autonomously (*Ready, breathing!*); and third, the patient is liberated from mechanical ventilation (*Ready, extubation!*) [20, 21]. Three main SBT strategies are described in the literature: the T-piece trial; the continuous positive airway pressure (CPAP) trial—in which the CPAP applied is equal to the previously applied positive end-expiratory pressure (PEEP); and positive support ventilation, which uses a low level of pressure support (5–8 cmH₂O).

No standardized SBT method has been identified to date in terms of type or duration (30–120 min) that can ensure a higher rate of successful weaning. However, strong evidence does exist supporting the employment of a short-term (30 min) breathing trial and low-level pressure support (8 cmH₂O) [22]. If the SBT is accompanied by patient discomfort (i.e., anxiety or fatigue) and/or cardio-respiratory distress (i.e., RR \geq 35 bpm, SpO₂ < 90%, HR variability > 20%, hemodynamic instability) [23], then it is considered to have failed. In the absence of such responses, the SBT is deemed successful and the patient can be considered for airway removal (*Ready, extubing!*). Although heterogeneity exists in the definition of successful weaning, it is generally taken as the patient's capacity to maintain spontaneous breathing for at least 48 h following extubation [3]. As mentioned above, despite international guidelines recommending the implementation of spontaneous breathing trials [3, 9], used alone SBTs are ineffective in predicting weaning failure and reintubation [10–13]. One possible solution to this may be the implementation of integrated cardio-pulmonary-diaphragmatic assessments for the detection of predictive indicators of weaning failure.

The (he)art of weaning from mechanical ventilation

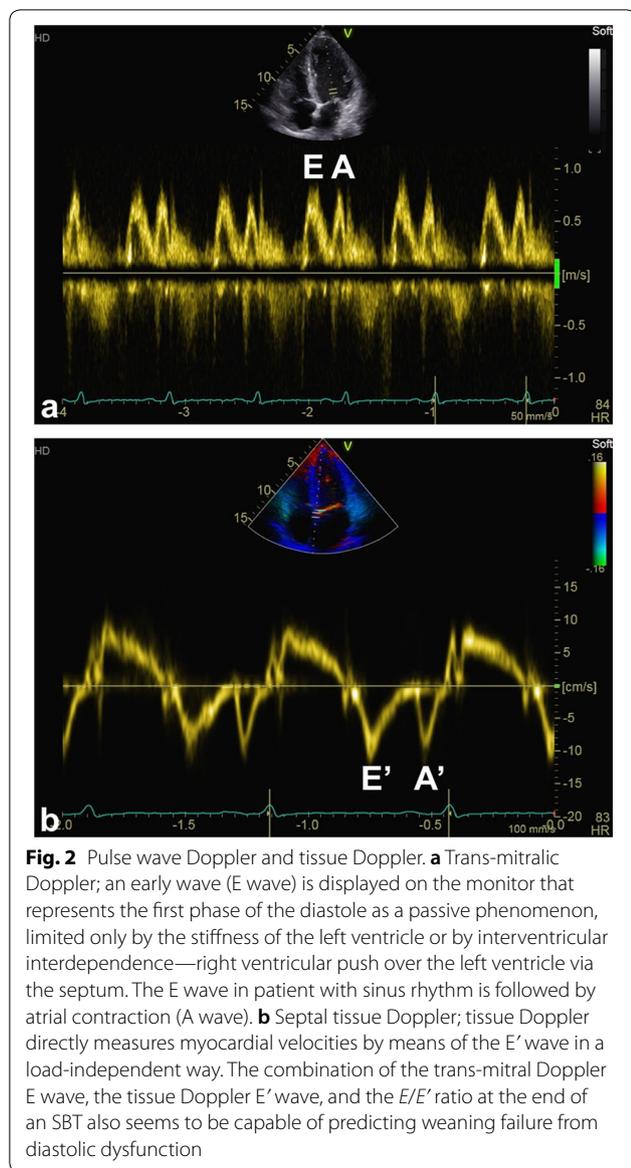
In the case of shock patients admitted to intensive care, most are resuscitated with the use of mechanical ventilation and intravenous fluid for respiratory and circulatory support. Regarding fluid management procedures in shock patients, recent literature has schematized its practice into four different phases, adopting the acronym ROSE: resuscitation (R), optimization (O), stabilization (S), and evacuation (E) [24]. Resuscitation, in some cases, could be too aggressive with the risk of fluid-overload,



whereas evacuation could be too fast with the risk of hypovolemia and low cardiac output state (see below). In the first case, previous over-hydration with a positive fluid balance has been associated with death and an increased risk of failed weaning from mechanical ventilation in surviving patients [25, 26]. This could be explained by the fact that shifting the patient from mechanical ventilation (positive airway pressure) to a T-piece trial (negative airway pressure) can increase cardiac preload and unmask an underlying cardiac problem. Lemaire and colleagues were the first to demonstrate this vicious circle [8]. Potential cardiac complications can be monitored in 3 main ways: one is direct but invasive—measurement of the cardiac filling pressure by pulmonary arterial catheter (PAC); the remaining two are indirect and un-invasive—one entails the use of heart or lung ultrasound, and the other the rapid measurement of natriuretic peptide for the diagnosis of acute heart failure [27, 28].

Monitoring for cardiac complications is necessary because the sensitivity and specificity of clinical signs of acute heart failure in intensive care patients are poor [29]. PAC is reserved for specific severe cases. It is used for the diagnosis and treatment of pulmonary arterial hypertension and to guide fluid and catecholamine management; however, its routine use has been abandoned globally due to the lack of any outcome benefits [30, 31]. Ultrasound, on the other hand, has become an invaluable tool in the ICU thanks to its widespread availability at the patient’s bedside and the absence of any known

side effects [28]. Moreover, the role of echocardiography in the detection of cardiac origins of weaning failure has grown significantly over the last 15 years. In particular, we now know that impaired systolic function (i.e., a small left ventricular ejection fraction [LVEF]) is less frequently associated with weaning failure in patients who failed the SBT (33% of cases) than left ventricular diastolic dysfunction (67% of cases) [28, 32, 33]. To investigate this latter condition, trans-mitral flow is interrogated using a pulse wave Doppler placed over the mitral valve in an apical four-chamber view. An early wave (E wave) is displayed on the monitor, Fig. 2a, that represents the first phase of the diastole as a passive phenomenon, limited only by the stiffness of the left ventricle or by interventricular interdependence—right ventricular push over the left ventricle via the septum. A stiff ventricle generates an elevated filling pressure, leading to pulmonary edema. In addition to trans-mitral Doppler, an E wave inpatient with sinus rhythm is followed by atrial contraction (A wave, Fig. 2a). The left ventricular preload is the sum of the E and A waves at a price of low or average left ventricular end-diastolic pressure (LVEDP) less than 12–14 mmHg. However, to estimate the LVEDP non-invasively, the E/A ratio has shown to be preload dependent and insufficient [34]. On the other hand, tissue Doppler directly measures myocardial velocities by means of the E’ wave in a load-independent way, Fig. 2b. The combination of the trans-mitral Doppler E wave, the tissue Doppler E’ wave, and the E/E’ ratio at the end of an SBT also seems to be



capable of predicting weaning failure from diastolic dysfunction in patients with arrhythmia, immediately after and 10 min after extubation, with an area under the curve (AUC) of 0.75 and 0.86, respectively [33]. However, two main limitations of these methods need to be recognized. First, although an E/E' value < 8 can accurately identify patients with a normal LVEDP, and an E/E' value > 15 can identify those with an elevated LVEDP, a gray zone exists between the values of 8 and 15 [33–35]; second, not all intensive care clinicians possess advanced echocardiography skills; and third, LVEDP may also be elevated in cases of increased intra-abdominal pressure (see below).

In a very recent study, lung ultrasound evaluating the delta-B-lines before and after SBT in the four anterior chest wall regions was shown to provide excellent

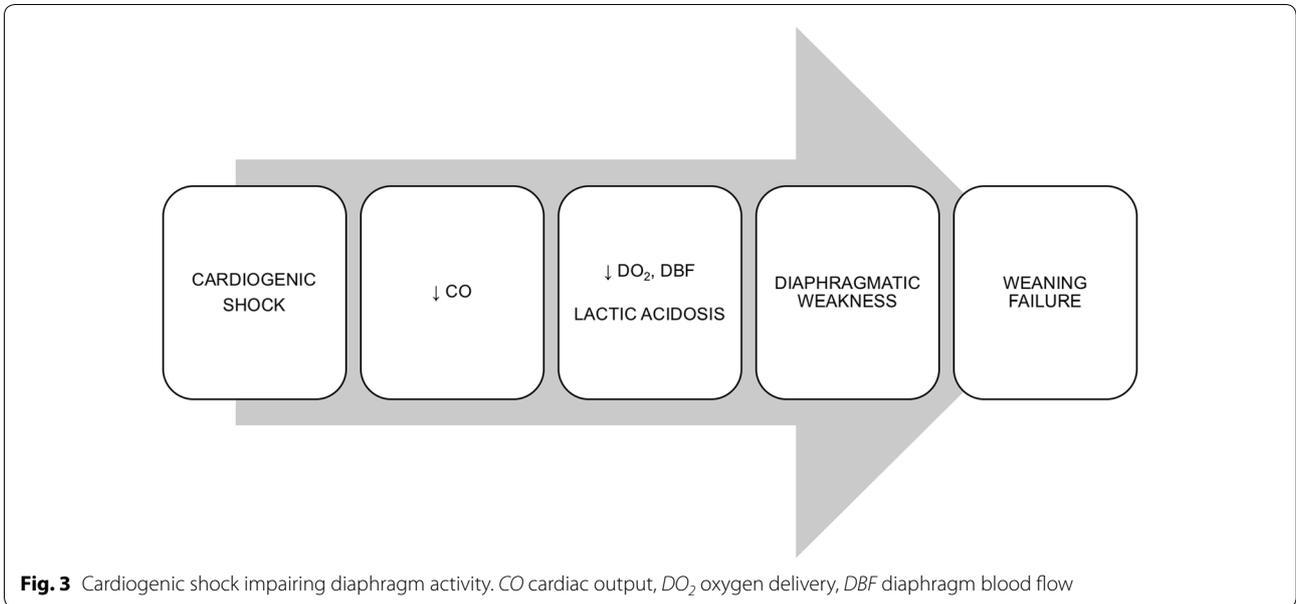
correlation with successful weaning [36]. However, the shift from mechanical to spontaneous ventilation may alone justify the appearance of such artifacts. Furthermore, distinguishing between cardiogenic and inflammatory causes of delta-B-lines may be a challenge.

Lastly, natriuretic peptides, and in particular brain natriuretic peptide (BNP), have been studied for their potential to predict weaning failure. In their study, Mekontso-Dessap et al. reported the outcome of two weaning strategies, one of which was driven by BNP level, whereas the other followed no explicit protocol [37]. They found that the BNP-guided fluid strategy was associated with increased use of diuretics, more negative fluid balance leading to a shorter mechanical ventilation time, and more ventilator-free days, but no change in ICU length-of-stay, morbidity, or mortality. The authors suggest that the changes in BNP that occur in the ICU are relatively slow and may be influenced by renal insufficiency or by the use of extracorporeal renal replacement therapy.

As previously mentioned, one-third of weaning failures with a cardiac origin depend on systolic dysfunction. In the case of cardiogenic shock, the diaphragmatic blood flow decreases and diaphragm muscular function can become compromised. In normal conditions, the diaphragmatic blood flow significantly increases with a high level of muscle contraction [38]. Indeed, the diaphragmatic blood flow is strictly dependent on cardiac output in both individuals at rest and with increased muscular activity [39]. Thus, since the diaphragm requires a high blood flow—in fact it is the skeletal muscle receiving the largest volume of blood per gram of tissue—diaphragm function may be impaired by a reduction in blood flow [40].

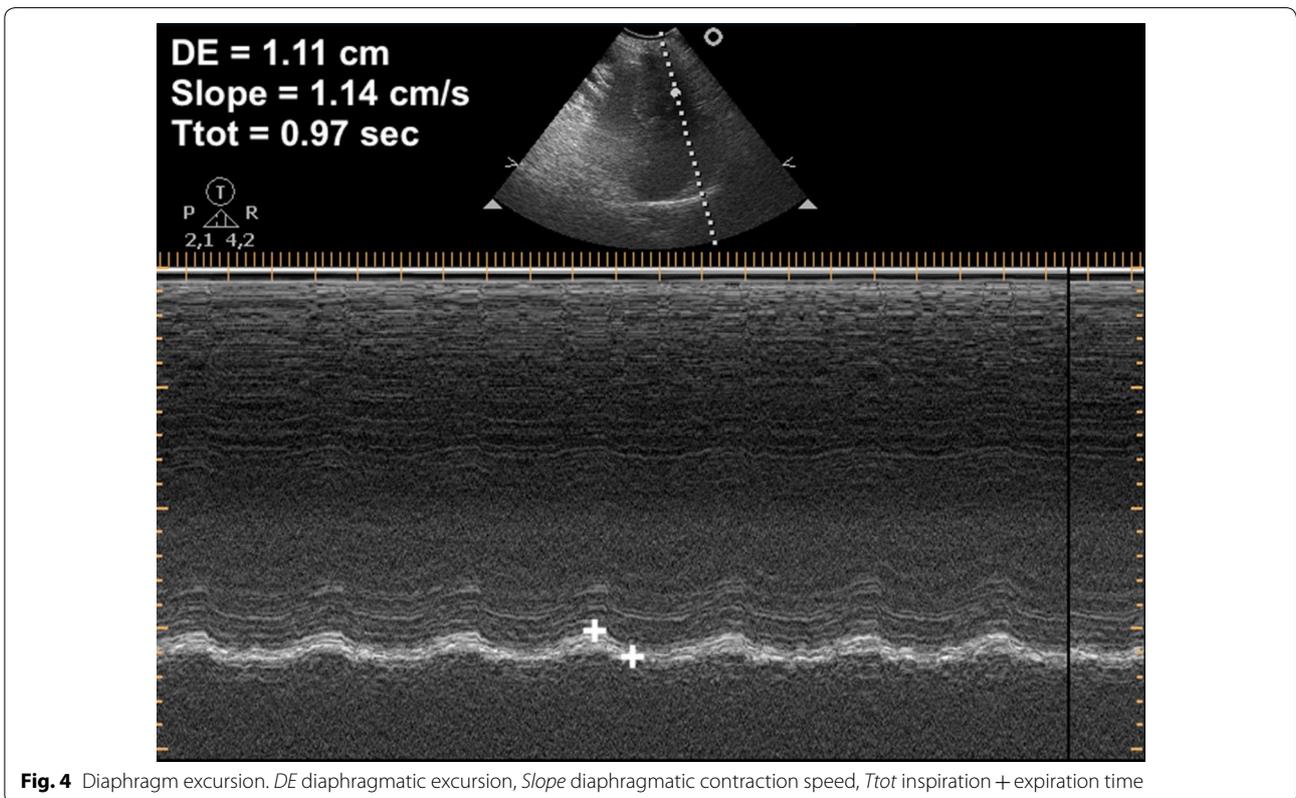
In patients with cardiogenic shock, respiratory muscles, which are the only muscles working during low cardiac output, shift to anaerobic metabolism resulting in lactate production even though they may be receiving a large fraction of the cardiac output [41]. As a consequence, skeletal muscles and vital organs receive less blood flow, contributing to an increased production and impaired removal of lactate [41]. The onset of acidemia and hypoxemia then leads to an increase in the work of breathing due to induced compensatory hyperventilation. Of note, whenever the muscle oxygen and nutrient demands exceed the supply, the diaphragm's ability to generate and sustain force decreases and muscle failure ensues [42]. During cardiogenic shock, the imbalance between demand and supply is facilitated by the reduced cardiac output and diaphragmatic blood flow (see Fig. 3).

In 1982, Aubier and colleagues investigated the influence of respiratory muscle activity on lactic acidosis and survival time in a cardiogenic shock canine model [41].



As opposed to mechanically ventilated dogs, the spontaneously breathing ones showed higher lactate levels and lower glycogen concentration due to the increased minute ventilation and respiratory workload occurring in the first hour after the onset of cardiogenic shock; afterward, minute ventilation rapidly decreased, due to

diaphragmatic fatigue, till the death of the animal [41]. Furthermore, the use of neuromuscular blocking agents in mechanically ventilated dogs may have reduced lactate production due to the absence of diaphragmatic activity [41]. Impairment of the diaphragmatic contraction process during cardiogenic shock may be the



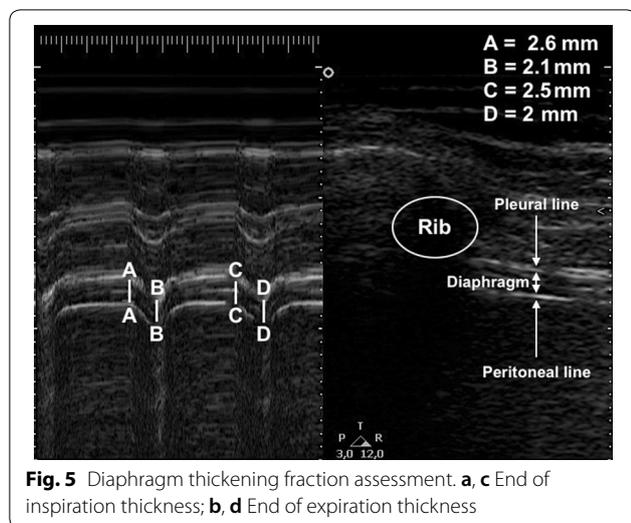


Fig. 5 Diaphragm thickening fraction assessment. **a, c** End of inspiration thickness; **b, d** End of expiration thickness

underlying mechanism responsible for ventilatory failure (see below) [43]. No studies have so far evaluated the ultrasonographic modifications of the diaphragm during the course of or after cardiogenic shock, or their impact on short- and long-term outcomes.

Diaphragm ultrasound (DUS)

The diaphragm, being the primary respiratory muscle, performs the majority of the work entailed in breathing. Diaphragm dysfunction, defined as the inability of the diaphragm to generate reasonable levels of maximal force, is an under-recognized pathological condition in critically ill patients and can render weaning from mechanical ventilation extremely difficult, resulting in protracted mechanical ventilation and prolonged intensive care unit length-of-stay [44]. The prevalence of diaphragm dysfunction in critically ill patients admitted to the intensive care unit and requiring IMV is over 60%, reaching 80% in patients requiring prolonged IMV and experiencing difficult weaning [45].

Considerable research attention has been focused on diagnosing diaphragm dysfunction over recent years, and there is strong evidence to sustain an association/correlation between diaphragm dysfunction and weaning failure [45–47]. The gold standard for evaluating diaphragm force is the measurement of trans-diaphragmatic pressure (Pdi) [48]. This test entails the insertion of a dedicated catheter with two balloons that measure the esophageal and gastric pressures, respectively. Diaphragm dysfunction occurs when Pdi < 11 cmH₂O [48].

Another adjunctive test to assess diaphragm activity is the electrical activity of the diaphragm (EAdi) test. EAdi is performed using a dedicated esophageal

Table 1 Most common bias to consider before an ultrasound assessment of diaphragmatic function

	Affected parameters	
	DE	DTF
Poor echographic transthoracic window		
Obesity	∅	∅
Splenectomy (left hemidiaphragm)	∅	∅
Altered starting position of hemidiaphragm		
Downward: COPD, asthma, PLEFF	∅	
Upward: abdominal hypertension, ascites, supine position	∅	
Iatrogenic impaired function		
Drugs (sedative, myorelaxants, etc.)	∅	∅
Mechanical ventilation		
Inspiratory positive pressure	∅	
PEEP	∅	
Operator-dependent factors		
<i>a</i> angle other than 90°	∅	
ZOA identification ^a		∅

DE diaphragmatic excursion, DTF diaphragm thickening fraction, COPD chronic obstructive pulmonary disease, PLEFF pleural effusion, PEEP positive end-expiratory pressure, *a* angle angle between M-Mode and hemidiaphragm examined, ZOA zone of apposition

^a The further away from the ribs, the smaller the DTF will be

catheter that has four couples of electrodes at its distal end. Besides monitoring the diaphragm, EAdi is also used to drive the ventilator with a proportional mode of ventilation, the so-called neutrally adjusted ventilator assist (NAVA). Thus, EAdi can be used to monitor the diaphragm at the bedside, whereas NAVA can exert a rehabilitative role in the case of diaphragm dysfunction.

Bedside ultrasound assessment of the diaphragm in critically ill patients can also be used to detect diaphragm dysfunction (diaphragm activity is classified as: usual, reduced, or loss of function) [49]. Although it may help the clinician make therapeutic decisions, a possible role in ventilation and weaning from mechanical ventilation has yet to be fully determined [49–52].

Two diaphragm sonographic predictors of successful weaning have been proposed [45, 49–56]:

- Diaphragmatic excursion (DE, cm)—defined as the maximum displacement of the hemidiaphragm during breathing (Fig. 4);
- Diaphragmatic thickening fraction (DTF, %)—defined as the difference between the end-inspiration thickness (Te-Insp) and end-expiration thickness (Te-exp) divided by the end-expiration thickness (Fig. 5).

Table 2 Recent literature on predictive value of DUS

Variables	Study	Major findings
Diaphragm excursion (DE)	Jiang et al. [61]	Mean values of liver and spleen displacement during SBTs were higher in the successfully weaned group. Sensitivity and specificity for predicting successful extubation were 84.4% and 82.6%, respectively
	Spadaro et al. [62]	By replacing tidal volume (VTe) with DE in the formula for the Rapid Shallow Breathing Index (RSBI = RR/VTe), the authors created a new index called the diaphragmatic-RSBI (D-RSBI) The use of diaphragmatic excursion makes this index more accurate than the traditional rapid shallow breathing index in predicting outcome from weaning
	Kim et al. [43]	The authors describe an association between diaphragmatic dysfunction (DE < 10 mm obtained by M-Mode ultrasonography), a prolonged weaning period, and early or delayed weaning failures
	Luo et al. [63]	The authors find that a DE cut-off value < 12.6 mm was the most reliable predictor of reintubation within 1 week (sensitivity 80%, negative specificity 68.4%)
	Garrido-Aguirre et al. [64]	The authors propose a new weaning index (ULDIMex) that takes into consideration inspiration time (a), expiration time (b), and DE (c). With the conceived formula $(a + b)c/2$, the authors identified a cut-off slope value of 4.06 cm/s for ULDIMex in successfully weaned patients, with a negative predictive value of 96.5%
	Palkar et al. [65]	Greater diaphragm excursion, a longer inspiratory time, and a smaller decrease in the diaphragmatic excursion-time (E-T) index during SBT may help to predict successful extubation
	Carrie et al. [66]	According to the authors, DE was unable by itself to predict weaning failure with low sensitivity and specificity 59% and 71%, respectively
	Diaphragm thickening fraction (DTF)	Jung et al. [67]
Samanta et al. [68]		DTF assessment of the right diaphragm during pressure support ventilation (PSV) may be employed to predict successful weaning prior to a T-piece SBT
Blumhof et al. [69]		A DTF > 20% is a robust predictor of extubation success during pressure support ventilation tests with 5/5 and 10/5 cmH ₂ O with sensitivity and specificity values of 84.6% and 79.0%, 88.9% and 75.0%, respectively
DiNino et al. [70]		The authors find that a DTF threshold $\geq 30\%$ at end inspiration has a positive predictive value of 91% and a negative predictive value of 63% for extubation success (sensitivity 88% and specificity 91%, respectively), with similar results during both SBT and pressure support tests
Diaphragm excursion (DE) and diaphragm thickening fraction (DTF)	Farghaly et al. [71]	The authors found that cut-off values of DE ≥ 10.5 mm, Te-insp ≥ 21 mm, and DTF > 34.2% during SBT with pressure support were associated with successful weaning; combining a DE ≥ 10.5 mm with a Te-insp ≥ 21 mm decreased the sensitivity to 64.9%, but increased specificity up to 100% for successful weaning
	Zambon et al. [72]	The authors describe both DE and DTF to be useful weaning predictors, but only DTF is shown to be an accurate index of diaphragmatic contractility workload
	Llamas-Alvarez et al. [73]	This systematic review and meta-analysis concludes that diaphragm ultrasound measures (DTF > DE) can help predict weaning outcome. It also suggests that the accuracy of DTF and DE may be overestimated in the current literature depending on the patient subpopulation studied
	Vivier et al. [53]	The authors conducted a multicenter prospective study involving 191 patients where DTF and DE data were collected during T-piece SBTs. They found that diaphragmatic dysfunction as assessed by ultrasound (described as DE < 10 mm and DTF < 30%) was not associated with extubation failure

DUS diaphragm ultrasound, DE diaphragm excursion, DTF diaphragm thickening fraction, SBT spontaneous breathing trial, Te-insp. end-inspiratory thickness

Some studies have hypothesized that diaphragmatic excursion or liver/spleen movements could predict extubation failure. DE reflects the sum of the patient's inspiratory activity and mechanical ventilatory support, so it only has real value when assessed during a spontaneous breathing trial. Diaphragm displacement is associated with lung volume during the inspiratory phase [57], but it does not correlate with and does not quantify the

patient's inspiratory effort [58]; furthermore, its assessment is influenced by numerous factors (see Table 1) [45]. It should also be noted that diaphragmatic excursion can be influenced by PEEP and levels of ventilator support during mechanical ventilation [55]: by increasing lung expiratory volumes, higher levels of PEEP lower the diaphragmatic domes, resulting in a decreased diaphragmatic excursion; during assisted ventilation,

diaphragmatic excursion results from ventilator support plus the patient's inspiratory efforts [56]. Therefore, only diaphragm thickening can provide a reliable indicator of diaphragm function during assisted mechanical ventilation [57].

DTE, also known as the "ejection fraction" of the diaphragm, reflects active diaphragm contraction and inspiratory effort [59, 60]. It is associated with ICU length-of-stay, the duration of mechanical ventilation, and mortality [59, 60]. Whereas diaphragmatic excursion is not able to evaluate the degree of contractile activity of the diaphragm, DTE, on the other hand, has this capacity and can be used both in IMV (assisted or supported) and during an SBT [45].

A number of studies have investigated these two parameters, either individually or in combination, with the aim of identifying cut-off values as predictors of successful weaning (see Table 2) [43, 53, 61–73]. However, the results have been heterogeneous in terms of outcome results and cut-off values due to differences in study protocol design and outcome designation.

Although bilateral anterior magnetic stimulation of the phrenic nerves is considered the gold standard for the assessment of diaphragm function [48], it requires high expertise and expensive machines. By contrast, ultrasonography is a widely available non-invasive tool that provides both structural and functional information about the muscle. Regarding diaphragm evaluation by ultrasonography and the therapeutic and prognostic implications of this measure, more studies are needed to evaluate the accuracy of ultrasound measures of the diaphragm and their therapeutic and prognostic implications and applicability in mechanical ventilation (i.e., diaphragm-protective ventilation and weaning from IMV). Further research is also required to standardize the measurement techniques and teaching programs [74].

Conclusions

In the first section of this review, two of the five factors involved in successful weaning from mechanical ventilation were addressed. The remaining components will be discussed in the second section of this review entitled: "Mechanical ventilation weaning issues can be counted on the fingers of just one hand: part 2".

Abbreviations

IMV: Invasive mechanical ventilation; ICU: Intensive care unit; SBT: Spontaneous breathing trial; PEEP: Positive end-expiratory pressure; GCS: Glasgow Coma Scale; RSBI: Rapid shallow breathing index; PAC: Pulmonary artery catheter; LVEF: Left ventricular ejection fraction; LVEDP: Left ventricular end-diastolic pressure; BNP: Brain natriuretic peptide; DUS: Diaphragm ultrasound; Pdi: Trans-diaphragmatic pressure; DE: Diaphragmatic excursion; DTF: Diaphragm thickening fraction; Te-insp: End-inspiration thickness; Te-exp: End expiration thickness; EAdi: Electrical activity of the diaphragm; NAVA: Neurally adjusted ventilator assist.

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Ethics approval and consent to participate

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Consent for publication

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Competing interests

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