



Techniques to monitor respiratory drive and inspiratory effort

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Purpose of review

There is increased awareness that derangements of respiratory drive and inspiratory effort are frequent and can result in lung and diaphragm injury together with dyspnea and sleep disturbances. This review aims to describe available techniques to monitor drive and effort.

Recent findings

Measuring drive and effort is necessary to quantify risk and implement strategies to minimize lung and the diaphragm injury by modifying sedation and ventilation. Evidence on the efficacy of such strategies is yet to be elucidated, but physiological and epidemiological data support the need to avoid injurious patterns of breathing effort.

Some techniques have been used in research for decades (e.g., esophageal pressure or airway occlusion pressure), evidence on their practical utility is growing, and technical advances have eased implementation. More novel techniques (e.g., electrical activity of the diaphragm and ultrasound) are being investigated providing new insights on their use and interpretation.

Summary

Available techniques provide reliable measures of the intensity and timing of drive and effort. Simple, noninvasive techniques might be implemented in most patients and the more invasive or time-consuming in more complex patients at higher risk. We encourage clinicians to become familiar with technical details and physiological rationale of each for optimal implementation.

Keywords

airway occlusion pressure, electrical activity of the diaphragm, esophageal pressure, respiration artificial, respiratory drive, ultrasound

INTRODUCTION

Respiratory drive is the intensity of the neural output from the respiratory centers that control the magnitude of inspiratory effort [1^{**}]. In normal conditions, the respiratory centers adapt breathing effort to the patient's needs. However, derangements of respiratory drive during critical illness are frequent [2^{*}], placing the patients at risk of lung and diaphragm injury (i.e., patient self-inflicted lung injury -P-SILI- and myotrauma, respectively). Additionally, an abnormal drive can result in dyspnea, sleep disturbances, and hinder weaning. For example, low respiratory drive because of excessive sedation and overassistance [3] results, not only in disuse atrophy, but also in frequent apneas leading to sleep fragmentation. On the other hand, high respiratory drive, as in the context of pneumonia and systemic inflammation, leads to excess loading of the diaphragm, stress and strain to the lungs, and dyspnea.

Consequently, monitoring respiratory drive and effort is necessary to quantify the risk of injury by

detecting low drive and effort in the context of over-assistance and excessive drive and effort frequent during underassistance. Techniques to monitor drive and effort have not been implemented at the bedside despite being used in research for many years. Integrating the information arising from these techniques with patient's clinical condition and ventilator settings can assist in implementing strategies aimed at

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KEY POINTS

- Monitoring respiratory drive and inspiratory effort are necessary to quantify the risk of injury and control the magnitude and timing of breathing effort.
- There are various techniques to monitor respiratory drive and effort, each of which provides unique information.
- Respiratory muscle weakness can result in measures of effort underestimating respiratory drive.
- Reference technique to monitor inspiratory effort requires the insertion of a nasogastric tube to measure esophageal pressure.
- Noninvasive techniques such as airway occlusion pressure or diaphragm ultrasound might be used in all patients to screen for potentially injurious patterns of drive and effort.

protecting the lung and the diaphragm, avoiding dyspnea, and improving sleep. The aim of this review is to describe the available techniques and help clinicians to integrate the unique information arising from each into the global clinical assessment.

DETERMINANTS OF RESPIRATORY DRIVE AND RELATIONSHIP WITH EFFORT

Understanding the determinants of respiratory drive and the relationship between drive and effort allows for the interpretation of any given physiological measurement. The chemoreflex control system (i.e., related to changes in pH and PaO₂) is the main controller of the respiratory drive in normal conditions [1[■]]. However, during critical illness other factors modify respiratory drive. These include dyspnea, anxiety or pain, sleep depth, lung injury, inflammation, drugs (e.g., sedatives and opioids), and mechanical ventilation itself [2[■]].

Respiratory drive controls the magnitude of inspiratory effort (Fig. 1). Therefore, measures of respiratory drive (e.g., airway occlusion pressure) can be used to estimate inspiratory effort and measures of effort (e.g., esophageal pressure) to estimate drive. In fact, there is no available technique to directly measure drive arising from the brainstem, so it is always inferred on the basis of its output, including muscular effort. However, altered respiratory muscle function modifies the relationship between drive and effort resulting in a dissociation between them which needs to be considered when interpreting the measurements. For example, a patient with respiratory muscle dysfunction despite having a high respiratory drive will produce a low effort. Nonetheless, muscle function is relatively

stable within a patient in a short period, allowing to use these monitoring techniques to follow changes in individual patients.

INVASIVE TECHNIQUES

Esophageal and gastric pressures

The reference technique to monitor inspiratory effort requires measurement of esophageal pressure (Pes) by insertion of a nasogastric tube with an air-filled balloon close to the tip [4] in the distal third of the esophagus [5,6]. Esophageal pressure (Peso) can be displayed on the screen of several ventilators, some providing basic calculations (e.g., transpulmonary pressure). Alternatively, Peso can be transduced using dedicated respiratory monitors which usually perform more complex calculations. If none is available, regular ICU monitors can also be used. Using Peso is simple but requires some technical and physiological expertise for insertion (i.e., positioning and balloon filling) and interpretation [5,6]. Peso is a surrogate of pleural pressure [7[■]]; therefore, inspiratory effort results in a negative deflection in Peso.

Several parameters can be calculated on the basis of Peso (Fig. 1, Table 1). The simplest is the negative deflection in Peso during inspiration (Δ Peso or swing in Peso). In a recent study by Yoshida *et al.* [8[■]], a decrease in Δ Peso following an increase in positive end-expiratory pressure (PEEP) accurately reflected changes in lung stress and strain measured by electrical impedance tomography.

However, Δ Peso somewhat underestimates the muscular pressure (P_{mus}) during inspiration and does not account for the duration of the effort. Therefore, the reference parameter for measuring inspiratory effort is the pressure-time product of the esophagus (PTPes) [9]. It is the pressure developed by all respiratory muscles over the duration of inspiration and correlates with energy expenditure [10]. PTPes is calculated as the area enclosed between the chest wall elastic recoil pressure and Peso during inspiration. It requires a special software for calculation and to estimate or measure chest wall elastance. Work of breathing is calculated using the Campbell diagram [11] as the area enclosed within the Peso–volume loop and quantifies effort during volume displacement. It has been recently used to recognize expiratory muscle activity and a special patient–ventilator dyssynchrony (reverse triggering) in patients with acute respiratory distress syndrome [12[■]–14[■]].

Gastric pressure (P_{ga}) is measured using a nasogastric tube with an additional balloon in the stomach. It allows to calculate transdiaphragmatic

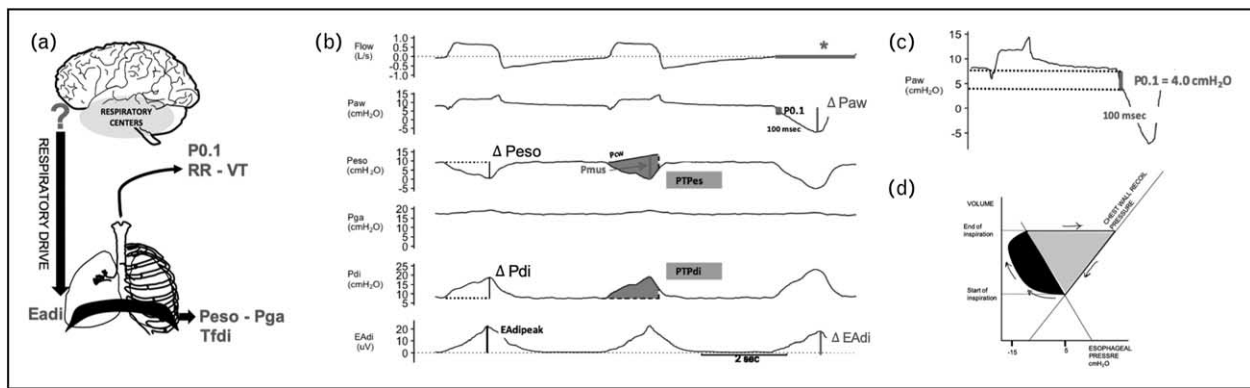


FIGURE 1. Parameters used to monitor respiratory drive and inspiratory effort. Panel (a) Anatomical distribution of the parameters used to measure respiratory drive and effort. Activation of respiratory centers results in depolarization of the diaphragm (Eadi) and other respiratory muscles (not shown), muscle contraction occurs (muscular pressure measured with Tfdi and parameters derived from Peso and Pga,) and breathing pattern (Vt – RR) resulting from the interaction between inspiratory effort, respiratory mechanics and ventilatory support. (b) Tracings of respiratory signals over time showing the most relevant parameters. (c) Detailed representation of the measurement of P0.1. (d) Campbell diagram represented as the area enclosed in the esophageal pressure-volume loop relative to the chest wall recoil pressure. Black area represents resistive work and grey, elastic work. $\Delta EAdi$, change in EAdi during occluded breath; ΔPaw , change in Paw during occluded breath; ΔPdi : change in Pdi during tidal breathing; $\Delta Peso$, change in Peso during tidal breathing; Eadi, electrical activity of the diaphragm; $EAdi_{peak}$, maximal electrical activity of the diaphragm during tidal breathing; P0.1, airway occlusion pressure; Paw, airway pressure; Pcw, chest-wall recoil pressure; Pdi, transdiaphragmatic pressure; Peso, esophageal pressure; Pga, gastric pressure; Pmus: muscular pressure; PTPdi, pressure-time product of the diaphragm; PTPes, pressure-time product of the esophagus; RR, respiratory rate; Tfdi, thickening of the diaphragm measured with ultrasound; VT, tidal volume.

pressure (Pdi, i.e., pressure developed by the diaphragm calculated as the difference between Pga and Peso). Pga is also useful to quantify the contribution of expiratory muscles to inspiration [15[□]]. Expiratory muscles are activated in the context of high respiratory drive and decreased inspiratory muscle function such as during weaning failure (Fig. 2). In that context, relaxation of expiratory muscles (abdominal and intercostal) can assist inspiration [16[□]].

Electrical activity of the diaphragm

Electrical activity of the diaphragm (Eadi) (Fig. 1) is obtained continuously by a nasogastric catheter with a multiple-array of electrodes positioned in the lower esophagus behind the diaphragm connected to a special type of ventilator (Servo, Getinge, Solna, Sweden) [17]. The electromyogram signal is processed [18] and Eadi is continuously displayed on the ventilator screen representing the electrical activation of the crural diaphragm, which is proportional to the stimulus by the phrenic nerve [19]. Eadi is, anatomically, the closest signal to the respiratory center's output, however, to be a good surrogate of respiratory drive various assumptions need to be valid: First, phrenic nerve and neuromuscular junction should be intact; second, the patient should use

the diaphragm as the main inspiratory muscle (rather than accessory muscles); and third, activity of the crural diaphragm should be representative of the total diaphragm.

Additionally, maximum Eadi during tidal breathing ($EAdi_{peak}$) can be used to quantify inspiratory effort given that is strongly correlated with Pdi and Peso [20]. However, prevalence of diaphragm weakness in the ICU is high [21]. Therefore, in many patients, $EAdi_{peak}$ may underestimate inspiratory effort [1[□]]. The range of $EAdi_{peak}$ varies considerably between patients [22[□]], but might still serve as a reliable parameter to follow changes in individual patients.

Muscular pressure during tidal breathing can be estimated from Eadi by multiplying $EAdi_{peak}$ by a coefficient that represents the neuromechanical efficiency of the diaphragm (NME_{occ}). NME_{occ} is the ratio of the change in airway pressure over the change in Eadi during an end-expiratory occlusion ($\Delta Paw/\Delta EAdi$) [20]. A recent study showed that an average of at least three values of NME_{occ} should be measured [23[□]]. Pressure-time product of the diaphragm (PTPdi) can also be calculated on the basis of Eadi using NME_{occ} . It was recently shown that over-assistance during pressure support is frequent because of excessive unloading of the diaphragm measured with PTPdi estimated from Eadi [24].

Table 1. Parameters used to monitor respiratory drive and inspiratory effort

Parameter	Clinical meaning	Caveats as measure of respiratory drive	Caveats as measure of inspiratory effort	Reference values
Require activation of the muscle		Not useful during paralysis	Respiratory muscle weakness: overestimation of inspiratory effort	
Eadi _{peak} (μV)	Maximal electrical activation of the diaphragm during tidal breathing	Only if diaphragm is the main inspiratory muscle Variable between patients	Eadi _{peak} × NME _{occ} to estimate P _{mus}	HS 17 [13–22]
Require muscle contraction		Muscle weakness: underestimation of respiratory drive (except P0.1) Not useful during paralysis		
ΔPes _o (cmH ₂ O)	Negative deflection in pleural pressure during inspiration		Some underestimation of effort	Intermediate in ICU ~ 5–10
P _{mus} –PTP _{es} (cmH ₂ O–cmH ₂ O s/min)	Pressure generated by all inspiratory muscles		Require calculations and E _{cw}	HS 86 ± 21 High in ICU > 200 Low in ICU < 50
P _{di} –PTP _{di} (cmH ₂ O–cmH ₂ O s/min)	Pressure generated by the diaphragm		Requires calculation	
WOB (J/l)	Patient's work during inspiration		Require calculations and E _{cw} . Work only during volume displacement	HS 0.2–0.9
T _f di (%)	Reflects diaphragmatic contraction. Association with clinical outcomes		Diaphragmatic contribution to inspiration. Not continuous	HS 20 ± 15
EX _{di} (cm)	Vertical displacement the diaphragm		Idem + valid during unassisted breathing	<1 weakness
P0.1 (cmH ₂ O)	Drop in P _{aw} during first 100 ms of occluded breath. Available in most ventilators	Not influenced by mechanics and muscle dysfunction; however, some muscle contraction required (i.e., absence of paralysis)	Muscle weakness: overestimation of inspiratory effort. Still useful for low and high effort	HS 0.5–1.5 High in ICU > 3.5 Low in ICU < 1.3
RR, VT	Interaction: inspiratory effort, ventilator and mechanics	RR: not variable PaCO ₂ 23–45 mmHg, decreases with opioids and insufflation. VT: Influenced by settings and mechanics.	Dependent on settings and mechanics.	RR < 17 low drive-effort in ICU
Paw and flow waveform	Patient–ventilator interaction results in unique waveform patterns	Informative on the status of drive		

ΔPes_o, negative deflection in esophageal pressure during tidal breathing; Eadi_{peak}, maximal electrical activity of the diaphragm during tidal breathing; E_{cw}, chest wall elastance; EX_{di}, diaphragmatic excursion measured with ultrasound; HS, healthy subjects; NME_{occ}, index of neuromechanical efficiency of the diaphragm (ΔPaw/ΔEadi during end-expiratory occlusion); P0.1, airway occlusion pressure; Paw, airway pressure; P_{di}, transdiaphragmatic pressure; P_{mus}, muscular pressure; PTP_{di}, transdiaphragmatic pressure–time product; PTP_{es}, pressure–time product of the diaphragm; RR, respiratory rate; T_fdi, thickening fraction of the diaphragm measured by ultrasound; VT, tidal volume; WOB, work of breathing.

Additional use of esophageal pressure and electrical activity of the diaphragm

Peso can also be used to quantify driving pressure, transpulmonary pressures and auto-PEEP. Additionally, both Eadi and Peso are useful to confirm lack of muscle activation if complete

passive mechanical ventilation is desired. Eadi and Peso are also a valuable tool to diagnose dyssynchronies [25]. Finally, if already in place at time of extubation they can be used to quantify inspiratory effort after extubation [26] and potentially guide prophylactic noninvasive

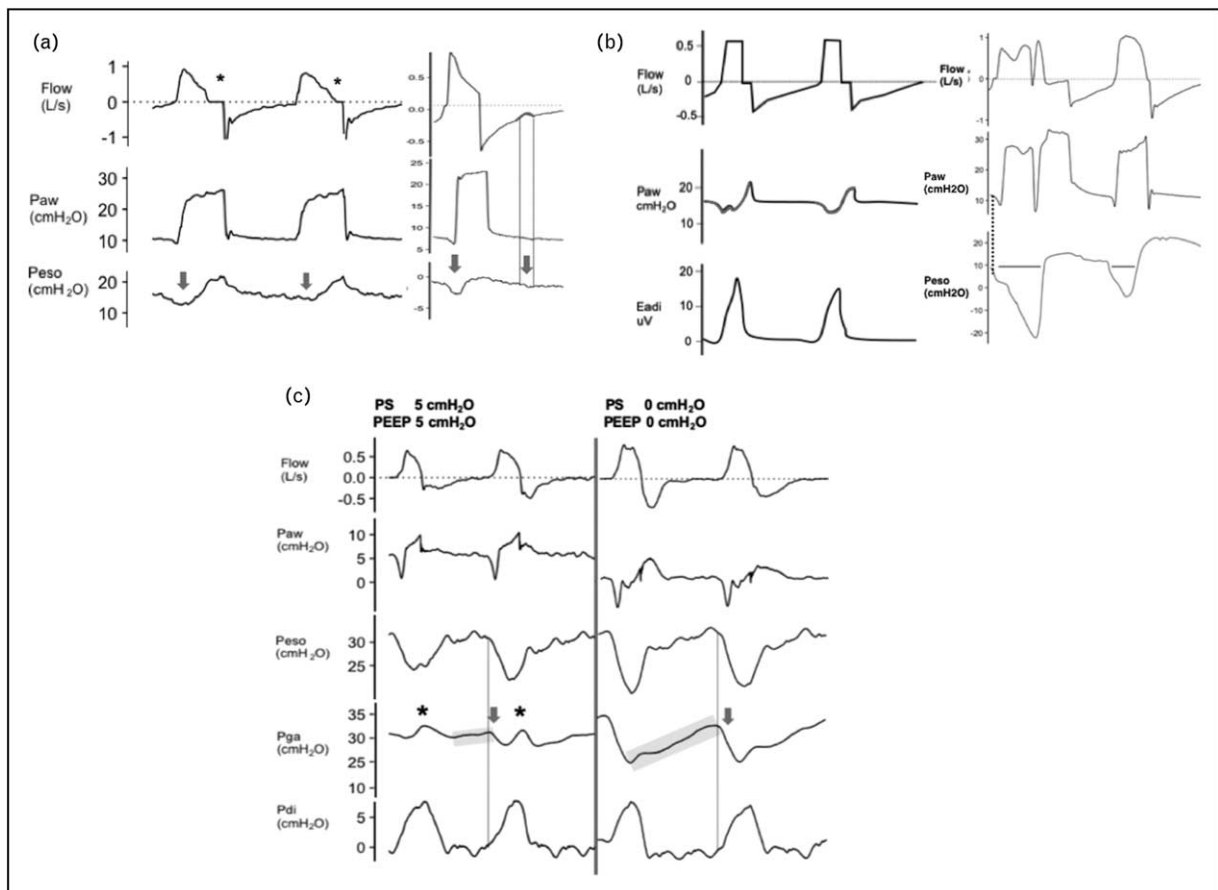


FIGURE 2. Respiratory waveforms to detect overassistance (low respiratory drive), underassistance (high respiratory drive) and expiratory muscle activity. Respiratory tracings are represented over time. Panel (a) Overassistance in pressure regulated modes. On the left, the patient performs small breathing efforts (negative deflections in Peso) that trigger the ventilator (arrow), followed by relaxation of the respiratory muscles (positive deflection in Peso). In the flow tracing, the flat line suggests that breathing effort ceased resulting in passive insufflation (asterisk). On the right, ineffective effort occurs as a result of overassistance resulting in deformation of the expiratory flow curve. In panel (b) Underassistance. On the left, flow starvation on volume-controlled ventilation with square waveform resulting in scooping of the Paw curve proportional to breathing effort. On the right, breathing effort is long and strong enough to trigger a second insufflation delivered by the ventilator resulting in double triggering with breath-stacking. In panel (c) Tracings from a patient with diaphragm dysfunction after cardiac surgery are seen with an increase in the use of expiratory muscles to assist inspiration when ventilatory support is decreased (from left to right panel). The asterisks show the positive deflection in gastric pressure due to a caudal movement of the diaphragm (asterisk) when expiratory muscles are relaxed. Progressive increase in gastric pressure during expiration indicates activation of expiratory muscles (grey bar). Sudden relaxation of expiratory muscles (arrow) contributes to inspiration. Eadi, electrical activity of the diaphragm; Paw, airway pressure; Pdi, transdiaphragmatic pressure; PEEP, positive end-expiratory pressure; Peso, esophageal pressure; Pga, gastric pressure; PS, pressure support.

ventilatory support in patients at higher risk for reintubation.

NONINVASIVE TECHNIQUES

Breathing pattern

Despite the widespread use for making clinically relevant decisions, respiratory rate and tidal volume are poor estimates of drive and effort and might lead

to the lack of recognition of over and underassistance. They are influenced by abnormal respiratory mechanics, muscle dysfunction and ventilator settings (e.g., weak efforts can result in low-minute ventilation despite a high drive). Resting respiratory rate during critical illness is high, does not follow respiratory drive within a wide range (PaCO₂ from 23–45 mmHg) [27], and is decreased by opioids [28] and long insufflation times [29] independently of the drive. Nonetheless, a respiratory rate lower than

17 has a good sensitivity and specificity (90 and 81%) to diagnose low drive and effort [3]. Additionally, increase in tidal volume in pressure regulated modes reflects an increase in drive and effort. However, a decrease in effort is not followed by a decrease in tidal volume below a certain threshold in the same context (i.e., minimum tidal volume) [30^{ss}] leading to overassistance even in spontaneous modes (e.g., pressure support).

Ventilator waveforms and dyssynchronies

Information on the drive, strength, and timing of breathing effort can be obtained from bedside analysis of airway pressure (Paw) and flow waveforms. There are different dyssynchronies represented by specific waveform patterns (Fig. 2), each with unique physiological mechanisms and potential consequences [31].

Flow starvation, short cycling, and double triggering often appear with high respiratory drive and effort. Flow starvation is characterized by an indentation in the Paw curve, proportional to patient's effort [32]. During short cycling inspiratory effort is prolonged during exhalation resulting in a deformation of the expiratory flow and, if strong enough, results in double-triggering [33]. Delayed cycling and ineffective efforts are frequent with overassistance and low drive and effort. Ineffective efforts are recognized by a decrease in Paw with a simultaneous deceleration of expiratory flow during late expiration.

Reverse triggering only appears during controlled mechanical ventilation [34] consisting of inspiratory efforts occurring immediately after passive insufflation. It is probably related to low respiratory drive in the context of sedation [35^{as}]. However, determinants of the magnitude of breathing effort in this circumstance are not known.

Waveform interpretation requires training and clinicians do not routinely detect dyssynchronies at the bedside [25]. However, it is likely a worthwhile effort, as ventilator waveforms are almost universally available, provide useful information on the patient's drive and effort, and automated systems to detect dyssynchronies are not widely available.

P0.1

Airway occlusion pressure (P0.1) is the drop in Paw during the first 100 ms of a breath against the occluded airway [36^s] (Fig. 2). Modern ventilators display P0.1, some estimate P0.1 based on the drop in Paw during the trigger phase and others perform a short-end-expiratory occlusion manoeuvre to measure P0.1.

P0.1 is an excellent measure of respiratory drive, it increases proportionally to PaCO₂ even during assisted ventilation [37] and it is still valid despite respiratory muscle weakness [38] or altered mechanics. Intrinsic PEEP can result in a small bias in P0.1 for estimation of drive in COPD patients but is still useful for titrating ventilation in these patients [39]. Breath to breath variability of P0.1 is significant; therefore, an average of three values should be considered.

P0.1 correlates with inspiratory effort, can be used to titrate support in an individual patient by following changes in P0.1 and can also be used to detect excessive and low inspiratory effort. A P0.1 higher than 3.5 cmH₂O showed a sensitivity of 92% and a specificity of 89% [40] to detect excessive inspiratory effort.

Ultrasound

The diaphragm can be visualized using ultrasound in the zone of apposition. As the diaphragm contracts, it thickens; therefore, measurement of diaphragm thickening fraction (TFdi) is a good estimate of inspiratory effort [41,42] that correlates with Eadi and PTPes [43] (Fig. 3). M-mode is used to measure diaphragm thickness at end-inspiration (Tei), end-expiration (Tee), and calculation of TFdi (TFdi = $\frac{1}{4}(\text{Tei} - \text{Tee})/\text{Tee}$) [41,42]. Additionally, TFdi during a maximal effort can be used to assess diaphragm function [44].

Limitations of ultrasound include the need for equipment, some training for acquisition and the fact that is neither continuous nor synchronized with the ventilator waveforms. However, it is simple and inspiratory effort measured by TFdi was recently correlated with clinically relevant outcomes [45^{ss}]. A decrease in diaphragmatic thickness is common during mechanical ventilation, consistent with the high prevalence of overassistance myotrauma [46], it is associated with impaired diaphragm function and worse clinical outcomes during mechanical ventilation [45^{ss}]. Excessive inspiratory effort measured with ultrasound was also associated with worse clinical outcomes and an intermediate TFdi similar to that of healthy patients at rest (15–30%) was associated with shorter duration of mechanical ventilation, lower risk of reintubation and tracheostomy [45^{ss}].

Diaphragmatic excursion is another measure of diaphragm activity (Fig. 3) [42] obtained using a different technique and only valid during unassisted breathing. It can be used to identify patients with diaphragm dysfunction during a weaning trial (defined as a diaphragmatic excursion < 10 mm or negative). Based on a recent study by Spadaro et al.

FIGURE 3. Ultrasonographic evaluation of the diaphragm. (a) Ultrasound evaluation of the right hemidiaphragm obtained in the zone of apposition. The diaphragm can be identified as a three-layered structure, consisting of the muscle itself (hypoechoogenic) delimited by pleural and peritoneal membranes (hyperechoogenic). This figure shows the difference between thickening fraction (TFdi) during normal breathing ((a) and (b) in the figure) and maximal inspiratory efforts ((c) and (d) in the figure) in a healthy volunteer. TFdi is calculated using the M-mode as $[\text{thickness at peak inspiration (Tep)} - \text{thickness at end expiration (Tee)}] / \text{thickness at end expiration (Tee)}$. In this case, the TFdi raised from 25 to over 200%, showing a great inspiratory reserve. (B) Ultrasonographic M-mode images from the right hemidiaphragm of a healthy volunteer. The figure shows a normal diaphragm motion. The diaphragmatic displacement is 2.8 cm during tidal breathing (from (a) to (b)) (normal range > 1.2 cm) and higher during maximal inspiratory effort (7.5 cm).

[47], this measure combined with the rapid shallow breathing index during a trial of T-piece can accurately predict weaning failure.

A recent study showed that assessment of diaphragm function in isolation using ultrasound (combining TFdi and excursion) during unassisted breathing on T-piece is not a good predictor of reintubation within one week in higher risk patients that successfully passed a trial of spontaneous breathing (SBT) [48⁸]. An adequate respiratory muscle function, including that of the diaphragm and accessory muscles, is required to maintain spontaneous breathing after extubation, predicted by a successful SBT. However, despite sufficient inspiratory muscle function, extubation failure can still occur because of decreased level of consciousness and difficulty in managing secretions. This might explain the poor diagnostic performance of diaphragm ultrasound in isolation to predict extubation failure.

There is growing interest in the role of accessory muscles in critical illness, being particularly relevant during weaning. Accessory muscles assist the diaphragm during inspiration and are key in the development of an effective cough. Ultrasound might be of great value in assessing structure and activity of accessory muscles (intercostal and abdominal)

[15⁸⁸]. Additionally, diaphragmatic ultrasound has shown striking concordance with Peso [49] and might assist in diagnosing patient-ventilator dyssynchronies in the future if technical advances in synchronization with ventilator waveforms are made.

CLINICAL APPLICATIONS, CONCLUSION, AND FUTURE DIRECTIONS

Physiological and epidemiological data suggest that avoiding injurious breathing effort (i.e., excessive or minimal efforts) is preferable. Patients at higher risk are those with more severe lung injury, systemic inflammation, baseline respiratory muscle dysfunction, or hemodynamic compromise. There are various techniques to monitor respiratory drive and effort that range from very simple (e.g., P0.1) to more complex and time-consuming (e.g., Peso). Simple techniques should be used in most patients and more precise measures such as Peso might be warranted in those at higher risk and more difficult to manage throughout the course of mechanical ventilation (from intubation to the weaning phase). Clinical research focused on what should be the target range of inspiratory effort and strategies to control respiratory drive is ongoing. Additionally,

technical advances in the monitoring techniques are also expected. For example, automated algorithms to detect injurious patterns of breathing effort are being developed. In the meantime, we encourage clinicians to combine specific information arising from different monitoring techniques to tailor mechanical ventilation to patient's individual physiological characteristics.

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Conflicts of interest

I.T. received teaching honoraria from Covidien, Argentina and consulting fees from MbMED SA, Argentina, outside the submitted work; Savino Spadaro received funding for travel/accommodation/congress registration from Getinge.

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