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# **Clinical strategies for implementing lung and diaphragm-protective ventilation: avoiding insufficient and excessive effort**

Ewan C. Goligher<sup>1,2,3</sup>, Annemijn H. Jonkman<sup>4,5</sup>, Jose Dianti<sup>1,2</sup>, Katerina Vaporidi<sup>6</sup>, Jeremy R. Beitler<sup>7</sup>, Bhakti K. Patel<sup>8</sup>, Takeshi Yoshida<sup>9</sup>, Samir Jaber<sup>10</sup>, Martin Dres<sup>11,12</sup>, Tommaso Mauri<sup>13,14</sup>, Giacomo Bellani<sup>15</sup>, Alexandre Demoule<sup>11,12</sup>, Laurent Brochard<sup>1,5</sup> and Leo Heunks<sup>4\*</sup>

1 Interdepartmental Division of Critical Care Medicine, University of Toronto, Toronto, Canada.

2 Department of Medicine, Division of Respiriology, University Health Network, Toronto, Canada.

3 Toronto General Hospital Research Institute, Toronto, Canada.

4 Department of Intensive Care, Amsterdam UMC, Location VUmc, De Boelelaan 1117, 1081 HV Amsterdam, the Netherlands.

5 Keenan Centre for Biomedical Research, Li Ka Shing Knowledge Institute, St. Michael's Hospital, Toronto, Canada.

6 Department of Intensive Care Medicine, University Hospital of Heraklion, Medical School, University of Crete, Heraklion, Greece.

7 Center for Acute Respiratory Failure, Division of Pulmonary, Allergy, and Critical Care Medicine, Columbia University College of Physicians and Surgeons, New York, NY, USA.

8 Department of Medicine, Section of Pulmonary and Critical Care, University of Chicago, Chicago, IL, USA.

9 Department of Anesthesiology and Intensive Care Medicine, Osaka University Graduate School of Medicine, Suita, Japan.

10 Critical Care and Anesthesia Department (DAR B), Hôpital Saint-Éloi, CHU de Montpellier, PhyMedExp, Université de Montpellier, Montpellier, France.

11 Sorbonne Université, INSERM, UMRS1158 Neurophysiologie Respiratoire Expérimentale et Clinique, 75005 Paris, France.

12 Service de Pneumologie, Médecine Intensive et Réanimation (Département R3S), AP-HP, Groupe Hospitalier Universitaire APHP-Sorbonne Université, Site Pitié-Salpêtrière, 75013 Paris, France.

13 Department of Anesthesiology, Intensive Care and Emergency, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy.

14 Department of Pathophysiology and Transplantation, University of Milan, Milan, Italy.

15 Department of Medicine and Surgery, University of Milan-Bicocca, Via Cadore 48, Monza, MB, Italy.

**\*Correspondence:**

[L.Heunks@Amsterdamumc.nl](mailto:L.Heunks@Amsterdamumc.nl)

4 Department of Intensive Care, Amsterdam UMC, Location VUmc, De Boelelaan 1117, 1081 HV Amsterdam, the Netherlands

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## Abstract

Mechanical ventilation may have adverse effects on both the lung and the diaphragm. Injury to the lung is mediated by excessive mechanical stress and strain, whereas the diaphragm develops atrophy as a consequence of low respiratory effort and injury in case of excessive effort. The lung and diaphragm-protective mechanical ventilation approach aims to protect both organs simultaneously whenever possible. This review summarizes practical strategies for achieving lung and diaphragm-protective targets at the bedside, focusing on inspiratory and expiratory ventilator settings, monitoring of inspiratory effort or respiratory drive, management of dyssynchrony, and sedation considerations. A number of potential future adjunctive strategies including extracorporeal CO<sub>2</sub> removal, partial neuromuscular blockade, and neuromuscular stimulation are also discussed. While clinical trials to confirm the benefit of these approaches are awaited, clinicians should become familiar with assessing and managing patients' respiratory effort, based on existing physiological principles. To protect the lung and the diaphragm, ventilation and sedation might be applied to avoid excessively weak or very strong respiratory efforts and patient-ventilator dysynchrony.

## Introduction

Lung and diaphragm-protective mechanical ventilation is a novel approach that aims to limit side effects of mechanical ventilation in critically ill patients. This approach integrates the principles of lung-protective ventilation with the new concept of diaphragm-protective ventilation in an effort to simultaneously protect both organs. The approach centers on optimizing patient respiratory effort to avoid lung and diaphragm injury while maintaining acceptable respiratory homeostasis. Ultimately, the goal of the approach is to reduce the duration of mechanical ventilation, enhance survival, accelerate recovery, and prevent long-term disability in patients with acute respiratory failure.

# Principles and rationale

## Principles of lung-protective ventilation

Lung-protective ventilation can best be understood in terms of limiting global and regional mechanical stress (pressure applied to the lung) and strain (deformation from resting shape) (Fig. 1). Lung injury may occur from overdistension (volutrauma/barotrauma), repetitive tidal recruitment and collapse (atelectrauma), both resulting from heterogeneous insufflation of patchy alveolar flooding or collapsed alveoli [1]. Importantly, lung injury may occur irrespective of whether the ventilator (ventilator-induced lung injury, VILI), patient breathing effort (patient self-inflicted lung injury, P-SILI), or both together are generating the forces applied to the lung [2].

Bedside measures of stress are available (changes in transpulmonary pressure, driving pressure), but not for measuring the resulting strain, making it challenging to appropriately individualize mechanical ventilation settings to maximize lung protection. Furthermore, even if global stress can be measured quite precisely using transpulmonary pressure calculated from airway and esophageal pressure, the effect of gravity on the edematous lung makes the distribution of collapse and aeration very uneven between the dependent and non-dependent lung regions; therefore, global indices do not reflect regional stress or strain. To minimize total stress and strain, dependent regions (usually prone to atelectasis) often require recruitment while non-dependent regions (usually well ventilated) require relief of overdistension.

During invasive ventilation, tidal volume (VT) is routinely scaled to predicted body weight (PBW), which correlates with lung volume in healthy subjects. This correlation is much less accurate in patients with acute respiratory distress syndrome (ARDS) because of alveolar flooding and atelectasis, resulting in a “baby lung” much smaller than the predicted lung volume [3, 4]. Using the driving pressure to scale tidal volume to respiratory system compliance ( $C_{rs}$ ,  $VT/C_{rs}$  = airway driving pressure,  $\Delta P_{aw}$ ) is particularly attractive because  $C_{rs}$  is affected by the aerated lung size and could, therefore, better reflect the global strain ( $VT/\text{baby lung}$ ). Driving pressure correlates with ARDS outcomes among patients with the same  $VT/PBW$  [5] and may be useful to guide tidal ventilation, although its role remains to be tested in a prospective trial. It should be acknowledged that static airway pressure is not a very reliable marker of lung stress (both at end-inspiration and end-expiration), because it reflects contributions from both the lung and chest wall (two pressures acting in series). Obese patients are an example where high intrathoracic pressure (and therefore higher plateau pressure) exist because of the weight imposed by the chest wall [6]. Lung stress is preferably measured as transpulmonary pressure (PL), which allows to quantify the contribution of the lung and chest wall to changes in airway pressure.

## Principles of diaphragm-protective ventilation

The respiratory muscle pump drives alveolar ventilation and is composed of a number of skeletal muscles acting in a highly organized fashion. The diaphragm is the primary muscle of inspiration and the lateral abdominal wall muscles are the most prominent expiratory muscles [7]. Mechanical ventilation is employed to unload the respiratory muscle pump and limit the consequences of high breathing effort (e.g., dyspnea sensation, respiratory failure, possible respiratory muscle injury). However, mechanical ventilation delivered as the predominant

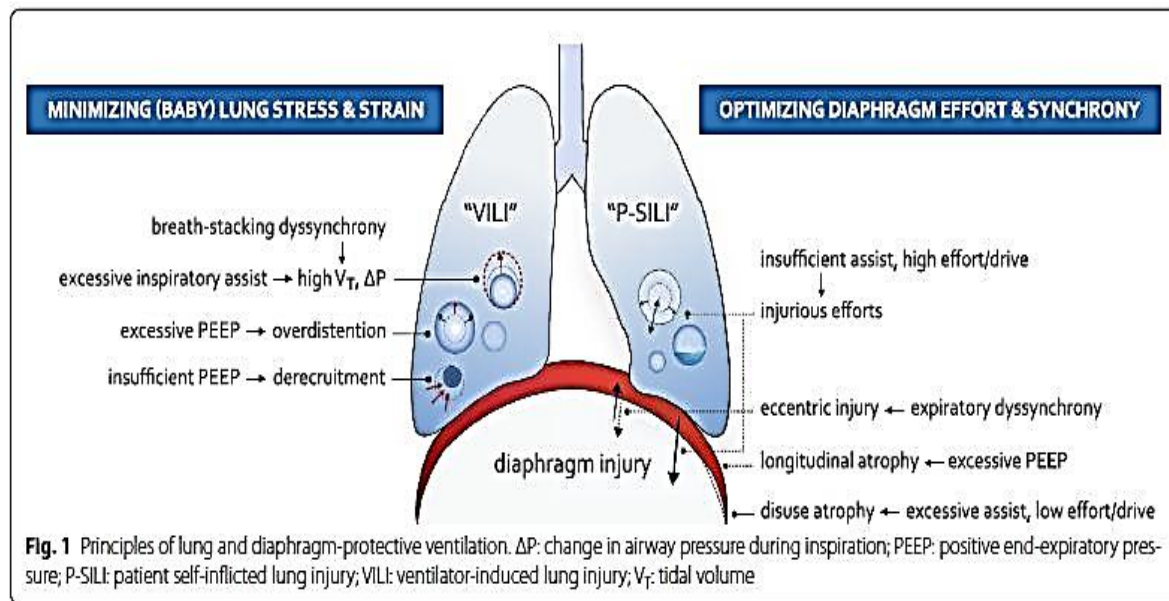
breathing source can also lead to diaphragm atrophy and injury with a substantial deleterious impact on patient outcome [8]. Clinical studies demonstrate that after 24 h of mechanical ventilation, 64% of patients exhibit diaphragm weakness [9] and at the time of weaning, diaphragm weakness is present in up to 80% of patients with weaning difficulties [10]. While many factors contribute to diaphragm weakness in the critically ill [11], both excessive and insufficient respiratory muscle unloading rapidly result in deleterious changes in diaphragm structure and function [11]. Low respiratory muscle effort, due to ventilator over-assist or sedation, may result in muscle atrophy, while high effort has been associated with load-induced injury (Fig. 1). In a landmark study, Levine et al. demonstrated the development of diaphragm disuse atrophy in brain dead patients on controlled mechanical ventilation [12] and subsequent studies confirmed the presence of time-dependent fiber atrophy in the diaphragm of ventilated patients [13, 14]. In line with these findings, ultrasound studies demonstrated that low diaphragm effort during mechanical ventilation is associated with time-dependent development of atrophy [15] and that atrophy is associated with poor outcomes [8]. It may be hypothesized that patients are at risk of developing load-induced diaphragm injury, as suggested by the presence of fiber injury, sarcomeric disruption, inflammation and contractile dysfunction in biopsies [13] and acute increases in diaphragm thickness on ultrasound [15]—this hypothesis requires further confirmation.

Taken together, these considerations suggest that the diaphragm might be protected by titrating ventilation and sedation to restore early diaphragm activity while avoiding excess respiratory effort. The various lines of physiological and clinical evidence suggesting that a respiratory effort level similar to that of resting quiet breathing is probably optimal for both lung and diaphragm protection were recently summarized elsewhere [16].

## Monitoring strategies

To implement lung and diaphragm-protective mechanical ventilation, the variables that mediate injury, principally lung stress and respiratory effort, should be monitored. The available monitoring techniques, their advantages and disadvantages, and proposed specific targets are summarized in Table 1.

Airway driving pressure,  $\Delta P_{aw}$  (i.e., plateau pressure— $PEEP_{tot}$ ), is a measure that aims to estimate global tidal lung stress [5].  $\Delta P_{aw}$  can be measured either during controlled or assisted ventilation by manual or automated short end-inspiratory and end-expiratory occlusions [17–19]. Importantly,  $\Delta P_{aw}$  is determined by transpulmonary driving pressure ( $\Delta PL$ ) and driving pressure across the chest wall ( $\Delta P_{cw}$ ); thus changes in chest wall elastance affect  $\Delta P_{aw}$ , without affecting lung stress [20]. Because pendelluft and regional variations in lung stress are “dynamic” phenomena that cannot be detected under static conditions, the risk of excess regional lung stress during assisted breathing may be more accurately estimated by dynamic  $\Delta PL$  ( $\Delta PL_{dyn}$ , peak PL—end-expiratory PL) rather than by static measures like  $\Delta P_{aw}$  [21, 22]. Esophageal pressure ( $P_{es}$ ) monitoring, as an estimate of pleural pressure, can provide information about both the predisposition to end-expiratory collapse and atelectasis (end-expiratory PL) and alveolar overdistension within the baby lung (elastance-derived plateau PL) [23].



Monitoring and controlling respiratory muscle effort are major challenges in implementing lung and diaphragm-protective mechanical ventilation. The gold standard to quantify global respiratory muscle effort is the esophageal pressure–time product (PTP), while the PTP of the transdiaphragmatic pressure ( $P_{di}$ , i.e., difference between gastric pressure ( $P_{ga}$ ) and  $P_{es}$ ) during inspiration provides a measure of diaphragmatic effort [24]. The amplitude of  $P_{es}$  or  $P_{di}$  during tidal breathing provides a simple estimate of the pressure generated by all respiratory muscles ( $P_{es}$ ), or the diaphragm ( $P_{di}$ ), whereas the expiratory increase in  $P_{ga}$  reflects expiratory muscle activity. The diaphragm electrical activity (EAdi) is the most precise surrogate of respiratory drive and correlates with indices of effort [25] but with considerable variability between patients. Also, values for peak EAdi in young healthy subjects during tidal breathing may vary between 4 and 29  $\mu V$  [26]. Nevertheless, changes in EAdi are useful to monitor changes in patient's respiratory drive and effort, especially to identify patients at risk for ventilator over-assistance. Finally,  $P_{es}$  or EAdi can complement ventilator waveform analysis to facilitate the identification of patient-ventilator dyssynchronies.

Other less invasive techniques are available to monitor patient breathing efforts during mechanical ventilation at the bedside. Airway occlusion pressure ( $P_{0.1}$ ), the deflection in  $P_{aw}$  during the first 0.1 s of an inspiratory effort against an occluded airway, is an estimate of the respiratory drive and can be used to detect both very low and high effort [27]. The maximum deflection of  $P_{aw}$  during a whole breath occlusion ( $\Delta P_{occ}$ ) has been recently shown to accurately detect excessive respiratory muscle pressure ( $P_{mus}$ ) or  $\Delta P_{L,dyn}$ ; this maneuver can also be used to assess different forms of patient-ventilator dyssynchrony [28, 29]. Ultrasound can be used to visualize and quantify the thickening of the diaphragm during inspiration in the zone of apposition (thickening fraction, TFdi) [30]. TFdi provides an index of diaphragmatic contractility and correlates reasonably well with inspiratory effort ( $\Delta P_{es}$ ) and EAdi [31].



**Table 1 Monitoring strategies and targets for lung and diaphragm-protective ventilation**

Parameter	Use	Advantages	Disadvantages	Suggested targets for lung and diaphragm-protective ventilation
Tidal volume ( $V_T$ )	Indirect surrogate marker of risk of ventilator-induced lung injury. Exhaled tidal volume may be used to detect volumes delivered above set volume in volume-controlled mode	Readily available	Strain is quantified by $V_E/EELV$ (end-expiratory lung volume), thus $V_T$ alone is not a precise measure of lung strain. Does not reflect lung stress and does not correct for "baby lung" size	$V_T$ 4–8 ml/PBW
Airway driving pressure ( $\Delta P_{AW}$ )	Monitor lung stress and strain resulting from inflation with tidal volume	Readily available	Does not reflect regional lung stress when respiratory effort is high. Overestimates the transpulmonary pressure ( $P_L$ ) if chest wall elastance is increased and in the presence of expiratory muscle activity	$\Delta P_{AW} < 15$ cmH <sub>2</sub> O
Paw and flow waveforms	Detect patient-ventilator dyssynchronies	Readily available. Readily detects flow starvation, breath stacking, and premature cycling dyssynchronies	Some dyssynchronies may not be immediately evident without close inspection and additional monitoring of effort	Maintain patient-ventilator synchrony
Airway occlusion pressure ( $P_{0.1}$ )	Monitor respiratory drive and detect presence of low or high respiratory effort	Non-invasive. Automated measurement available on most ventilators	Elevated respiratory drive does not always result in elevated respiratory effort (i.e., in the presence of respiratory muscle weakness or short inspiratory time)	$P_{0.1}$ 1–4 cmH <sub>2</sub> O
Airway pressure swing during a whole breath occlusion ( $\Delta P_{occl}$ )	Assess for excessive respiratory effort and tidal lung stress	Non-invasive. Easily measured at the bedside. Can predict respiratory muscle effort ( $P_{mus}$ ) and transpulmonary pressure swing ( $\Delta P_{L, dyn}$ ). Detect apnea, auto-triggering. Differentiate different forms of dyssynchrony	Though sensitive and specific for high respiratory effort and dynamic lung stress, the technique is not sufficiently accurate to replace direct measurement	Predicted $P_{mus}$ 5–10 cmH <sub>2</sub> O ( $\Delta P_{occl}$ 8–20 cmH <sub>2</sub> O). Predicted $\Delta P_{L, dyn} < 15$ –20 cmH <sub>2</sub> O
Esophageal pressure ( $P_{es}$ ) and transpulmonary pressure ( $P_L$ )	Directly measure and monitor respiratory effort and tidal lung stress	Minimally invasive. Provides gold standard information about lung stress ( $\Delta P_L$ ) and respiratory effort ( $\Delta P_{es}$ , $PTP_{es}$ )	Requires equipment and training. Balloon must be calibrated before each measurement. Absolute values of $P_{es}$ of unclear utility	$\Delta P_{es}$ 3–15 cmH <sub>2</sub> O (diaphragm protective). $\Delta P_{L, dyn} < 15$ –20 cmH <sub>2</sub> O (lung protective)
Transdiaphragmatic pressure swing ( $\Delta P_{di}$ ) and gastric pressure swing ( $\Delta P_{ga}$ )	Directly measure and monitor diaphragmatic effort and expiratory effort	Minimally invasive. Provides direct measurement of diaphragmatic effort. Provides information about expiratory muscle activity	Requires equipment and training. Balloon must be calibrated before each measurement. No calibration for $P_{ga}$ . Difficult to assess post-inspiratory effort (eccentric loading)	$\Delta P_{di}$ 15 cmH <sub>2</sub> O

**Table 1 (continued)**

Parameter	Use	Advantages	Disadvantages	Suggested targets for lung and diaphragm-protective ventilation
Diaphragm inspiratory thickening fraction on ultrasound (TFd)	Non-invasive assessment of diaphragmatic contractility	Provides an index of diaphragmatic effort during mechanical ventilation (tidal TFd). Provides an index of diaphragmatic function (maximal TFd)	Requires equipment and training. Continuous monitoring is not feasible	TFd 15–30%
Diaphragm electrical activity (EAdi)	Monitor electrical activity of the diaphragm	Minimally invasive. Continuous information with automated output. Ventilation in ENIV correlates with variation in respiratory effort	Requires equipment and training. No reference values	Normalize target EAdi based on $P_{0.1}$ , $\Delta P_{di}$ , or $\Delta P_{es}$

Abbreviations: EAdi, diaphragm electrical activity; EELV, end-expiratory lung volume; P<sub>0.1</sub>, airway occlusion pressure during 0.1 s; Paw, airway pressure; A/E, airway pressure/flow; P<sub>L</sub>, transpulmonary pressure; P<sub>0.1</sub>, change in transpulmonary pressure during tidal inflation; P<sub>mus</sub>, respiratory muscle pressure; P<sub>occl</sub>, whole breath airway occlusion pressure; PTP, pressure-time product; TFd, diaphragm thickening fraction; V<sub>T</sub>, tidal volume

In conclusion, although estimation of pleural pressure using an esophageal balloon appears to be the preferred technique to quantify lung stress and respiratory effort, the technique is currently not widely implemented; moreover, the potential impact on patient outcome remains to be determined in clinical studies. We suggest routine monitoring of tidal volume, inspiratory plateau pressures and airway driving pressure to limit lung injury, and P0.1 to monitor respiratory drive and prevent inadequate effort (Table 1).

## Clinical strategies to facilitate lung and diaphragm-protective ventilation

Several strategies can be used to facilitate lung and diaphragm protective ventilation, including modulation of ventilator inspiratory and expiratory assist, drugs that modify respiratory drive and/or effort, extracorporeal CO<sub>2</sub> removal (ECCO<sub>2</sub>R) and electrical stimulation of the respiratory muscles, as shown in Fig. 2. Here, we will briefly discuss these different strategies.

### Inspiratory ventilator settings

A lung and diaphragm-protective ventilation approach aims to minimize lung stress and strain while limiting diaphragm atrophy and injury. To achieve these goals, inspiratory ventilator

settings can be adjusted to (1) modulate the patient's inspiratory effort, (2) minimize the dynamic lung stress, and (3) prevent or correct patient-ventilator dyssynchrony or any form of mismatch between needs and support.

Titration of the inspiratory ventilator settings to optimize respiratory effort requires a thorough understanding of the control of breathing under mechanical ventilation [32, 33], acknowledging that the control of breathing system responds to changes in ventilatory demands by modifying inspiratory effort (and thus tidal volume) to a greater extent than respiratory rate [34]. Therefore, the inspiratory ventilator settings will affect the inspiratory effort by modifying the delivered tidal volume, and thus, in spontaneously breathing patients, increasing pressure or volume assist will increase the delivered tidal volume and reduce the inspiratory effort (as respiratory drive depends mainly on the chemoreflex control of arterial pH). Excessive assist, resulting in a tidal volume that is higher than the patient's demands, may almost abolish the patient's inspiratory effort, and as such promote diaphragmatic atrophy. However, increasing inspiratory support may not attenuate inspiratory effort in the presence of high respiratory drive due to stimuli other than arterial pH/PaCO<sub>2</sub>, such as pain, anxiety, or stimulation of peripheral lung receptors by lung edema or inflammation [32]. In such case, transpulmonary pressure (and hence dynamic lung stress) may progressively increase with increasing inspiratory support. Increasing FiO<sub>2</sub> to increase PaO<sub>2</sub> and reduce the hypoxic stimulus to breathe may alleviate increased respiratory drive in some patients (hyperoxemia is not required to achieve this effect) [35].

In a volume-targeted mode, the patient's effort will be modified mainly by the set tidal volume and the flow delivery profile (flow pattern and peak flow). In pressure targeted modes, the delivered tidal volume, and thus the patient's inspiratory effort, is influenced by the set inspiratory pressure, rise time and cycling-off criterion, and of course the mechanical properties of the respiratory system [36]. Irrespective of the mode of assist, the delivered tidal volume and respiratory effort will together determine global and regional lung stress, depending on the mechanical properties of the respiratory system [37].

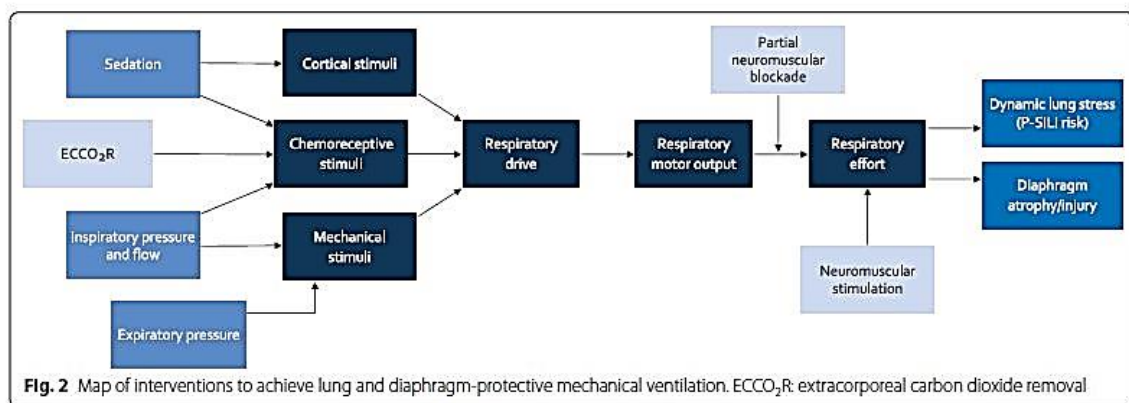
Neurally adjusted ventilatory assist (NAVA) delivers inspiratory assist proportional to the electrical activity of the diaphragm [38]. Increasing inspiratory assist will reduce diaphragm electrical activity (and vice versa) over a wide range of respiratory demand, and consequently tidal volume remains relatively stable over a wide range of assist [39]. In theory, pulmonary reflex mechanisms prevent patients from spontaneously inspiring large tidal volumes and NAVA may therefore facilitate lung-protective ventilation. Also, diaphragm inactivity due to over-assistance is unlikely in NAVA, as low diaphragm activity will immediately reduce inspiratory assist. Future studies should confirm the role of NAVA in lung and diaphragm protective ventilation, but recent randomized trials suggest clinical benefit of NAVA (reduced time on the ventilator) compared to pressure support mode [40, 41].

## **Expiratory ventilator settings**

The expiratory ventilator setting (i.e., positive end-expiratory pressure, PEEP) has been traditionally adjusted to optimize oxygenation and/or lung mechanics [42, 43]. A higher PEEP ventilation strategy (of which there are several, generally resulting in  $15 \pm 4$  cmH<sub>2</sub>O) is currently recommended over lower PEEP (approximately  $9 \pm 3$  cm H<sub>2</sub>O) in moderate and severe ARDS [44]. In the presence of spontaneous breathing during mechanical ventilation, a higher PEEP strategy offers several additional potential advantages to facilitate lung and diaphragm-protective ventilation (Fig. 1). First, in patients with significant lung recruitability,



PEEP reduces the amount of atelectasis ‘solid-like’ lung and, therefore, can achieve a more homogeneous distribution of the tidal pleural pressure swing ( $\Delta P_{pl}$ ) over the whole lung surface following a diaphragmatic contraction. The even distribution of inspiratory dynamic stress can diminish injurious asymmetric inflation associated with spontaneous effort (i.e., pendelluft), reducing regional lung stress in dependent lung regions [45]. Second, by increasing end expiratory lung volume, forcing the diaphragm to operate at a shorter length and thereby impairing diaphragm neuromuscular coupling [46, 47], increased PEEP can attenuate the force generated by diaphragmatic contraction [48]. Indeed, several clinical studies provide indirect evidence to suggest that higher PEEP may render spontaneous effort less injurious in patients with acute respiratory failure before intubation [49], in patients with ARDS [45, 50], and in pediatric patients with lung injury [51].



On the other hand, preliminary experimental evidence suggests that if the diaphragm is maintained at a shorter length during acute mechanical ventilation, the diaphragm muscle fibers could adapt to the reduced length by absorbing sarcomeres in series (i.e., longitudinal atrophy) [52]. This may result in fibers overstretching with the release of PEEP during a T-tube weaning trial or after extubation. The possibility of diaphragm weakness resulting from excess PEEP should therefore be borne in mind.

## Resolving dyssynchrony

Patient-ventilator dyssynchronies may cause lung and/or diaphragm injury by increasing dynamic lung stress and/ or injurious diaphragmatic contractions, respectively. Dyssynchronies may occur during inspiration (flow starvation, short cycles, prolonged insufflation and reverse triggering), during expiration (auto-triggering, ineffective effort) or both during inspiration and expiration (reverse triggering and double triggering). We will briefly discuss dyssynchronies most relevant for lung and diaphragmprotective ventilation; for more extensive discussion of dyssynchronies we refer to other reviews [53]. *Reverse triggering*, a diaphragmatic contraction triggered by mechanical inflation, is common in fully sedated patients (in whom drive is abolished) [54]. Reverse triggering can induce breath stacking resulting in excessive tidal volumes and high dynamic lung stress [55], and it may create eccentric diaphragm loading conditions with resultant muscle injury [56]. When necessary to avoid breath stacking, reverse triggering can be abolished by neuromuscular blocking agents. Alternatively, the development of reverse triggering may indicate that sedation should be stopped to allow the patient to take control of ventilation.

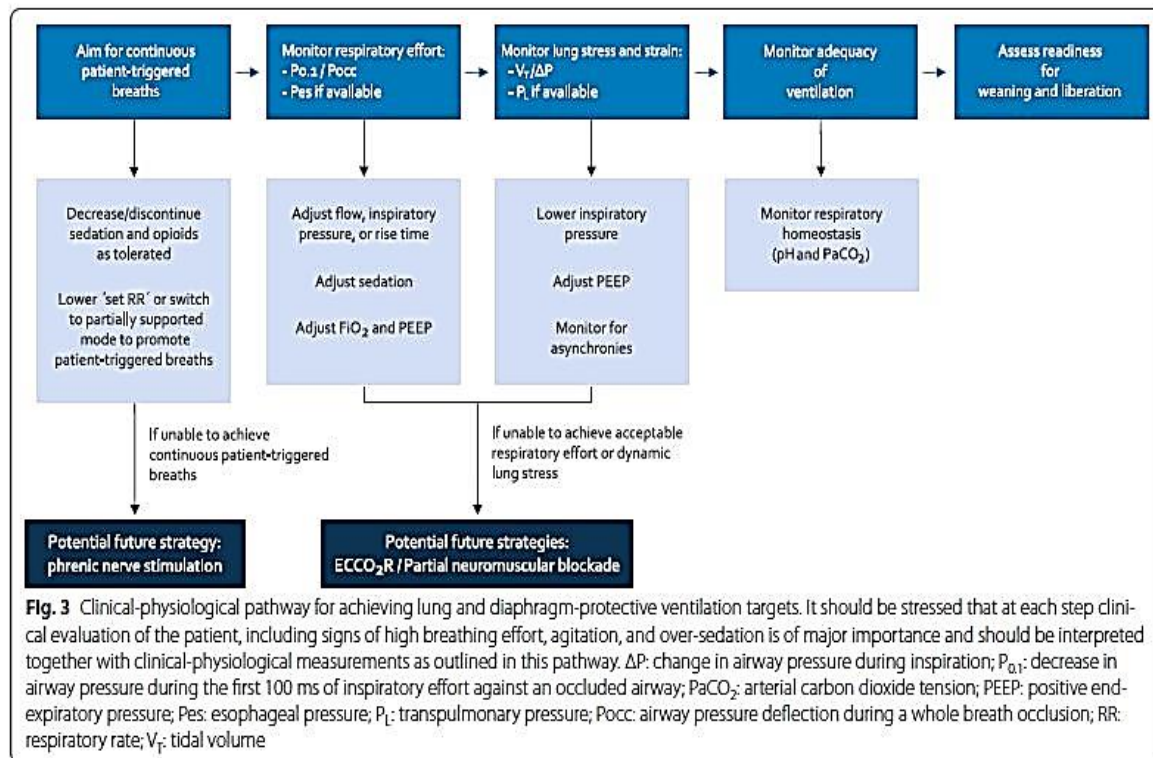
**Table 2 Effect of sedation on respiratory drive, effort and breathing pattern**

Drug class	Inspiratory effort and tidal volume	Respiratory rate	Ventilatory response to hypercapnia and hypoxemia	Effect on diaphragm function and patient-ventilator interaction
Benzodiazepines	↓	↔ or ↑ ↓ at high doses	↓	Delay restoration of diaphragm activity
Propofol	↓	↔ or ↑ ↓ at high doses	↓	May ↑ dyssynchrony (i.e., ineffective efforts because of lower respiratory effort)
Opioids	↔ or ↑	↓	↓	May ↓ dyssynchrony (i.e., fewer ineffective efforts because of slower, deeper respiratory efforts)
Dexmedetomidine	↔	↔	↔	↓ dyssynchrony by decreasing agitation/delirium

In patients with relatively high respiratory drive and a low respiratory system time constant, the neural inspiration time may exceed the mechanical inflation (*premature cycling*). In such cases, the contraction of the inspiratory muscles continues during mechanical expiration and the diaphragm is forced to contract while lengthening (eccentric contraction). In volume-targeted modes, unmet high demands appear as ‘flow-starvation’, a downward curvature of inspiratory Paw, and the patient may experience dyspnea and distress, which can be resolved by increasing inspiratory flow rate using a decelerating flow pattern. Strong inspiratory efforts may result in *double-triggering*, *breath stacking* and, therefore, delivery of high tidal volumes. A better match of mechanical and neural inspiratory time can be achieved by increasing ventilator inspiratory time and using a decelerating flow pattern in volume-assist control mode, by decreasing the cycling-off criterion in pressure support mode, or using proportional modes of assist. Importantly, in patients with high respiratory drive, modification of inspiratory time may not suffice to resolve dyssynchrony. Increasing the level of assist to match the patient’s demands should be considered, but, if that results in an injurious high ventilation, other means to decrease the patient’s respiratory drive, such as sedation, may be required.

Another dyssynchrony occurring in patients with absent or low respiratory drive is *auto-triggering*, i.e., the delivery of a ventilator-assisted breath in the absence of patient effort. Auto-triggering due to strong cardiac oscillations transmitted to the Paw or airflow signal is more likely to occur when the respiratory system time constant is low, such as in ARDS. Air leaks and moisture in the ventilator circuit are also common causes of auto-triggering.

*Ineffective triggering* (or ineffective efforts) develops when a patient’s effort fails to trigger a ventilator-delivered breath. Ineffective triggering is generally the consequence of weak inspiratory efforts, either from low respiratory drive due to sedation, metabolic alkalosis or excessive ventilatory assist, or because of diaphragm weakness. When the respiratory system time constant is high, (i.e., obstructive lung disease), ventilator over-assistance results in delayed cycling, dynamic hyperinflation, and increased intrinsic PEEP, predisposing to ineffective triggering. Decreasing the level of assist can therefore alleviate ineffective efforts [57]. Over-assistance in assisted ventilation can also induce apneas during sleep. Interestingly, several studies have demonstrated that NAVA improves patient-ventilator interaction, especially reducing the risks of ineffective efforts and over-assist [39, 58]. Whether the reduced duration of mechanical ventilation reported in some NAVA trials [40, 41] results from improved patient-ventilator interaction remains to be investigated.



## Sedation strategies

Sedation can facilitate lung and diaphragm-protective ventilation by ameliorating, when present, excessive respiratory effort. Complete suppression of respiratory drive and effort with sedation can also contribute to diaphragm disuse atrophy. A judicious approach to sedation is key and monitoring of respiratory drive and effort may be helpful in selecting the sedation strategy that facilitates lung and diaphragm-protective ventilation. Before administering sedation to address excessive respiratory drive or ventilator dyssynchrony, ventilator settings should be adjusted and other factors increasing respiratory drive such as metabolic acidosis or pain should be addressed. Relying on sedation alone to enhance patient-ventilator interaction without addressing these issues can paradoxically exacerbate dyssynchrony, prolong mechanical ventilation, and exacerbate diaphragm dysfunction [59]. Recent clinical practice guidelines have recommended an “analgesia- first approach” to minimize the risk of excessive sedation as opioids during mechanical ventilation were associated with less dyssynchrony and depressed consciousness in comparison to sedative-based approaches [60].

Nevertheless, when elevated respiratory drive cannot otherwise be resolved, sedatives can attenuate the ventilatory response to hypoxemia and hypercapnia and cortical input to the respiratory centres [33] (Table 2). Propofol and benzodiazepines are gamma-aminobutyric acid (GABA) agonists known to cause respiratory depression, primarily by reducing the amplitude of respiratory effort [61–63]. Because benzodiazepines are associated with a high risk of delirium and prolonged mechanical ventilation [64], propofol is the preferred sedative of choice for controlling high respiratory drive. Because propofol or benzodiazepines reduce the amplitude of inspiratory effort, ineffective triggering may develop as sedation depth increases [61]. Inhalational sedation offers a potential alternative for controlling respiratory effort though clinical experience is limited to date [65]. To avoid excessive sedation,

strategies aimed at active titration of sedatives or daily interruption of sedation should be employed and respiratory drive and effort should be monitored closely.

For patients without excessive breathing effort (Table 2), a multimodal analgesia approach that minimizes opiate use is recommended to avoid diaphragm inactivity. Dexmedetomidine is a selective alpha-2 agonist which, in contrast to propofol and benzodiazepines, provides sedation, anxiolysis, and analgesia without respiratory depression [66]. This property makes it an interesting drug of choice to preserve awareness and diaphragm contractility and at the same time limiting excess delirium risk in agitated patients without elevated respiratory drive.

### **Prone positioning**

The prone position has been used for decades in early ARDS to improve oxygenation and over time an appreciation for the lung-protective benefit of prone positioning has emerged [67]. As the amount of lung tissue is larger in dorsal lung regions, gravitational forces generate more dependent atelectasis in the supine position compared to prone position. Therefore, ventilation-perfusion matching is improved in the prone position and, more importantly, the energy applied to the lung by mechanical ventilation is distributed among more (non-atelectatic) alveoli, reducing lung stress. This is the putative basis for the observed mortality benefit of prone positioning in patients with ARDS [68]. The mechanistic benefits of prone positioning may also apply under assisted ventilation with spontaneous breathing, because the lung recruitment accrued by prone positioning may attenuate ‘solid-like’ lung behaviour and reduce effort-dependent regional lung stress. Prone positioning improves oxygenation in spontaneously breathing patients with COVID- 19 pneumonia [69]; it is possible that prone positioning could also reduce the risk of patient self-inflicted lung injury [70]. Thus, prone positioning might facilitate safe spontaneous breathing and diaphragm-protective ventilation as well as lung protection.

### **Future approaches to lung and respiratory muscle-protective ventilation**

#### ***Extracorporeal carbon dioxide removal***

Eliminating CO<sub>2</sub> is the primary purpose of alveolar ventilation. ECCO<sub>2</sub>R reduces the ventilatory demands, decreasing the respiratory effort, and thus may ameliorate dynamic lung stress. ECCO<sub>2</sub>R is feasible and effective in reducing tidal volume, driving pressure, and mechanical power in patients with ARDS [71]. In spontaneously breathing patients, ECCO<sub>2</sub>R can dampen respiratory drive and effort [72], theoretically reducing the requirement for ventilatory support or sedation to control respiratory effort. Karagiannidis et al. showed that increasing sweep gas flow, increasing CO<sub>2</sub> elimination, in ARDS patients undergoing extracorporeal membrane oxygenation (ECMO) reduced respiratory drive, estimated by EAdi [73]. Mauri et al. [7] also showed that higher ECCO<sub>2</sub>R support reduced P<sub>0.1</sub>, respiratory muscle effort, and transpulmonary pressure in spontaneously breathing patients recovering from severe ARDS [74]. Pilot clinical studies have explored the extreme possibility of extubating severe ARDS patients early after intubation by means of ECCO<sub>2</sub>R: preliminary results were encouraging but they also recognized the need to identify the subgroup of patients with a high probability of success [75–77].

Despite the appeal and physiological rationale of this strategy, there are relevant limitations. First, in some patients, non-chemoreceptive stimuli (pain, agitation, discomfort, metabolic acidosis, lung mechanical stimuli) may predominate and high respiratory drive may persist



despite ECCO2R [78]. Second, ECCO2R requires full anticoagulation and the risk of bleeding is not insubstantial [79]. Third, the application of ECCO2R may exacerbate hypoxemia by various mechanisms [80].

### ***Partial neuromuscular blockade***

Complete neuromuscular blockade may increase the risk for diaphragm disuse atrophy and increases sedation requirements. Low-dose neuromuscular blockers (“partial neuromuscular blockade”) is an interesting compromise between total paralysis and strenuous breathing efforts, particularly when respiratory effort does inadequately respond to titration of ventilatory support or sedation. The feasibility of partial neuromuscular blockade has been evaluated in a proof of concept study in patients with moderate ARDS and high respiratory drive on partially supported modes [81]. Titration of rocuronium decreased tidal volume from approximately 9 mL/kg to approximately 6 mL/kg while maintaining Pdi at approximately 5 cm H2O (within the physiological range for diaphragm activity in healthy subjects). These preliminary findings suggest that partial neuromuscular blockade could be a feasible approach to achieving lung and diaphragm-protective ventilation targets in patients with high respiratory effort. Importantly, partial neuromuscular blockade does not reduce respiratory drive, but only the mechanical consequences of high drive. This dissociation between central drive and respiratory muscle mechanical output may result in dyspnea [33]; adequate relief of dyspnea and distress must be ensured by judicious application of sedatives and opioids. Future clinical studies should confirm the safety and efficacy of prolonged partial neuromuscular blockade in ventilated patients.

### ***Neuromuscular stimulation***

Neuromuscular stimulation (“pacing”) uses electrical currents to generate muscle contraction in the absence of volitional efforts, making it an attractive intervention in incapacitated critically ill patients. There is growing interest in neuromuscular stimulation as a novel strategy to preserve or restore respiratory muscle activity and, in turn, to prevent or treat ICU-acquired diaphragm weakness. In addition, by inducing diaphragm contractions, neuromuscular stimulation may improve lung aeration of dependent lung regions [82]. Pacing must be synchronized with the ventilator and potentially injurious inspiratory efforts must be avoided. There is as yet no clinical evidence of benefit from diaphragm pacing in ICU patients. Direct stimulation of the phrenic nerves by surgically implanted electrodes has been employed to restore spontaneous ventilation in patients with high-level spinal cord injury and central hypoventilation syndrome [83]. The feasibility of direct pacing using temporary implanted electrodes for the prevention of diaphragm dysfunction is currently under investigation in cardiac surgery patients identified to be at risk for prolonged mechanical ventilation (NCT04309123). Preclinical work showed that this technique could reduce the development of diaphragm type II fiber atrophy [84, 85]. Recently, Reynolds et al. presented a first-in-human series of temporary transvenous phrenic nerve pacing in surgical patients and showed that this technology delivered safe and effective diaphragm contractions [86]. This strategy is currently being studied as potential intervention for improving diaphragm strength in difficult-to-wean patients (NCT03096639). The role of transvenous phrenic nerve pacing for the prevention of diaphragm disuse atrophy remains to be investigated. Neuromuscular stimulation strategies targeting the expiratory muscles of ICU patients are less well studied. This is surprising, as stimulation of the expiratory abdominal wall muscles can be employed noninvasively via surface electrodes placed over the abdominal wall. Feasibility of a breath-synchronized expiratory muscle stimulation technique during the early phase of mechanical



ventilation was recently demonstrated with promising results [87] and its efficacy is under investigation (NCT03453944).

## Summary and future directions

Clinicians caring for mechanically ventilated patients are generally well aware of the risk of causing barotrauma, volutrauma, and atelectrauma. Given the mounting evidence of clinically important diaphragm atrophy and injury, consideration must also be given to protecting the diaphragm. Based on the foregoing discussion about ventilation and sedation, a basic algorithm and approach to lung and diaphragm-protective ventilation is presented in Fig. 3. Clinical trials testing new ventilation algorithms and sedation strategies targeted at optimizing respiratory effort are required to confirm the benefit of the lung and diaphragm-protective approach outlined in this paper. The benefit of adjunctive strategies such as ECCO2R, partial neuromuscular blockade and phrenic nerve stimulation requires further evaluation, in particular to identify the subpopulations of patients most likely to benefit from these more costly and invasive interventions. For the present, we encourage clinicians to incorporate routine monitoring of respiratory drive and effort in their clinical practice and to adjust the ventilator to achieve a physiological level of effort where possible while carefully attending to the effect on lung stress.

## Compliance with ethical standards

## Conflicts of interest

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