Lung and Diaphragm-Protective Ventilation

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Abstract (238 words)

Mechanical ventilation can cause acute diaphragm atrophy and injury and this is associated with poor clinical outcomes. While the importance and impact of lung-protective ventilation is widely appreciated and well-established, the concept of diaphragm-protective ventilation has recently emerged as a potential complementary therapeutic strategy. This Perspective, developed from discussions at a meeting of international experts convened by the Pleural Pressure Working Group of the European Society of Intensive Care Medicine, outlines a conceptual framework for an integrated lung and diaphragm-protective approach to mechanical ventilation based on growing evidence about mechanisms of injury. We propose targets for diaphragm protection based on respiratory effort and patient-ventilator synchrony. The potential for conflict between diaphragm protection and lung protection under certain conditions is discussed; we emphasize that where conflicts arise, lung protection must be prioritized over diaphragm protection. Monitoring respiratory effort is essential to concomitantly protect both the diaphragm and the lung during mechanical ventilation. To implement lung and diaphragm-protective ventilation, new approaches to monitoring, to setting the ventilator, and to titrating sedation will be required. Adjunctive interventions including extracorporeal life support techniques, phrenic nerve stimulation, and clinical decision support systems may also play an important role in selected patients in the future. Evaluating the clinical impact of this new paradigm will be challenging owing to the complexity of the intervention. The concept of lung and diaphragm-protective ventilation presents a compelling new opportunity to substantially improve clinical outcomes for critically ill patients.

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Introduction

The possibility that mechanical ventilation could cause iatrogenic injury to the lung was first appreciated in the 18th century (1); protection of the lung from injury has become a recognized priority. Iatrogenic injury to the diaphragm from mechanical ventilation was first described in the 1980s (2) but there is as yet no established approach to protecting the diaphragm during mechanical ventilation. In this Perspective, we discuss how the current approach to mechanical ventilation might be revised to prevent ventilator-induced diaphragm atrophy, injury, and resulting weakness while maintaining lung-protective ventilation, an approach we refer to as lung and diaphragm-protective ventilation. The mechanisms and clinical consequences of these issues are, in general, reasonably well-characterized, but it remains uncertain whether diaphragm atrophy and injury can be effectively prevented and whether this substantially improves clinical outcomes. This report proposes specific potential targets for diaphragm-protective ventilation and outlines a range of potential strategies for an integrated lung and diaphragm-protective approach to mechanical ventilation to be tested in future clinical trials.

Methodology for Quantifying Agreement Among Experts

This Perspective represents the views of a group of international experts in the field on how the complex—and sometimes competing—goals of protecting the lung and the diaphragm during mechanical ventilation might be integrated at the bedside. This was discussed at a two-day conference sponsored by the Pleural Pressure Working Group (PLUG, www.plugwgroup.org), a working group of the European Society of Intensive Care Medicine, held in Milan in May 2019. Panelists were selected from the membership of the Pleural Pressure Working Group based on prior publications and ongoing active research programs in relevant aspects of acute respiratory

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failure mechanical ventilation, lung injury, and diaphragm injury. Following the initial meeting, the conference writing committee (EG, MD, BP, SS, JB, IT, TY, KV, DLG, TS, GG, SS, LB) drafted and refined a series of statements intended to communicate areas of consensus and uncertainty. Input from the entire panel (n=31) was obtained before finalizing the statements. All conference panelists then communicated their level of agreement or disagreement for each statement through an online survey using the RAND/UCLA appropriateness rating method (rating scale from 1-9, 1 representing strong disagreement, 9 representing strong agreement). Support for each statement was defined according to the RAND/UCLA method as a score ≥ 7; opposition to each statement was defined as a scores ≤ 3. The proportion of panelists expressing support for each statement was used to characterize the level of expert agreement. The results are presented in **Table 1**. This Perspective outlines the key issues under discussion and the basis for agreement or disagreement among experts on various points.

Mechanisms of Injury

Mechanical ventilation can cause lung and diaphragm injury by a variety of putative interacting pathways (**Figure 1**). Several terms are employed to refer to these mechanisms and their consequences (**Table 2**). Lung injury is primarily mediated by mechanical stress and strain caused by the ventilator (ventilator-induced lung injury, VILI) or the respiratory muscles (patient self-inflicted lung injury, P-SILI). These mechanisms are discussed in detail elsewhere (3, 4) .

Diaphragm atrophy and injury (‘myotrauma’) may occur via several mechanisms (5). The most well-established mechanism is over-assistance myotrauma: excessive unloading of the diaphragm by ventilatory assistance abolishes or reduces inspiratory effort to very low levels resulting in disuse atrophy by a variety of cellular pathways (6); this phenomenon is well-

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documented in the clinical setting (7-9). Other likely mechanisms are supported primarily by experimental evidence as well as some recent clinical data (9, 10). Excessive diaphragm loading due to insufficient ventilator assistance can induce acute muscle inflammation and injury (under-assistance myotrauma) (11, 12), particularly in the context of sepsis and systemic inflammation which increase sarcolemmal fragility (13). The diaphragm is also subjected to potentially injurious eccentric (lengthening) loads when it contracts during the expiratory phase. Such eccentric contractions may occur during expiratory braking (14), non-synchronized bilevel ventilation (airway pressure release ventilation) (15), and specific forms of patient-ventilator dyssynchrony such as reverse triggering, premature cycling, and ineffective efforts (16-18). In laboratory animals, such eccentric loading is highly injurious (eccentric myotrauma) (19, 20). Finally, preliminary experimental observations suggest that maintaining the diaphragm at a relatively shorter length by the application of high PEEP may cause acute sarcomere dropout ('longitudinal atrophy') (21). This in turn could impair the length-tension of the muscle when PEEP is reduced during weaning (expiratory myotrauma).

Targets for Diaphragm Protection

Based on our evolving understanding of the mechanisms of diaphragm myotrauma, several diaphragm-protective ventilation targets can be proposed (**Table 3**).

Target 1: Maintain modest inspiratory effort (probably important)

An inspiratory effort level consistent with resting quiet breathing is likely to avoid both diaphragm atrophy and load-induced injury. Several lines of evidence support this target. The very low effort levels required to trigger ventilator triggering are not sufficient to prevent diaphragm atrophy (9, 22). Modest diaphragm contractions (e.g. during resting quiet breathing or

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intermittent diaphragm stimulation by phrenic nerve pacing) appear to be sufficient to attenuate diaphragm atrophy and restore diaphragm muscle bulk (23-25). On the other hand, avoiding excessive respiratory effort might prevent potential load-induced diaphragm injury (26).

The exact upper limit for acceptable respiratory effort is uncertain, though effort should probably be kept low enough to keep tension-time index values below 0.12-0.15 (tension-time index is a dimensionless index quantifying the magnitude and duration of load on the respiratory muscles relative to force-generating capacity and duty cycle) (27). This would imply esophageal pressure swings below 10-15 cm H2O (assuming the patient's maximal inspiratory pressure is 30-50 cm H2O and inspiratory time is approximately 50% of expiratory time). Patients successfully liberated from ventilation generally exhibit a relatively low inspiratory effort (esophageal pressure swings of 4-10 cm H_2O) during a T-piece trial (28) and after extubation (29), suggesting that this level of effort is sustainable and non-injurious. By contrast, patients who fail spontaneous breathing trials usually exhibit much higher levels of effort, suggesting that these levels are not sustainable (30). It is important to appreciate that the upper limit of effort associated with injury likely varies with diaphragm force-generating capacity, the presence of muscular inflammation, and muscle perfusion.

A diaphragm thickening fraction in the intermediate range of 15-30% (similar to that of healthy subjects breathing at rest) was associated with the shortest duration of mechanical ventilation in comparison to lower or higher thickening fraction values (10). Moreover, this association was mediated by changes in diaphragm thickness over time, corroborating (but not confirming) a causal pathway linking mechanical ventilation to insufficient or excessive respiratory effort, diaphragm atrophy and injury, and poor clinical outcomes (5). Although these clinical observations do not confirm a causal relationship, these data in combination with the

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large body of experimental evidence showing the deleterious effects of absent or excessive respiratory effort, suggest that modest inspiratory effort is probably the optimal target for diaphragm protection during mechanical ventilation. The panel reached strong consensus that maintaining a modest level of respiratory effort would prevent diaphragm atrophy; there was moderate consensus that avoiding excess respiratory effort would prevent load-induced injury.

Target 2: Maintain synchronous expiratory cycling (possibly important)

Eccentric contractions may occur with several forms of dyssynchrony (e.g., premature cycling, reverse triggering, ineffective efforts during expiration). When detected, these dyssynchronies can often be avoided by ensuring that the ventilator cycles into expiration at the same time as the patient's inspiratory effort ends. Close inspection of the airway pressure and flow waveforms suggests whether patient inspiratory effort ceases before or after the ventilator cycles into the expiratory phase (18). Detecting expiratory cycling dyssynchrony can be facilitated by directly monitoring respiratory effort with esophageal pressure or diaphragm electrical activity signals. It is possible that the amplitude of the effort is an important determinant for this risk of injury but the threshold determining this risk is currently unknown. There was moderate consensus for this target among panelists.

Target 3: Avoid excessive expiratory braking (possibly important)

Continued contractile activation of the diaphragm into the expiratory phase is referred to as 'expiratory braking' or 'post-inspiratory effort'. While expiratory braking may be present at low levels in healthy subjects, increased expiratory braking to maintain end-expiratory lung volume in the presence of significant atelectasis and increased lung elastance may result in a potentially substantial eccentric load to the diaphragm that can be attenuated by the application of sufficient

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PEEP (14). As yet, methods for detecting and monitoring expiratory braking at the bedside and determining whether post-inspiratory loading is excessive are not well-defined. This target remains largely theoretical; the magnitude of expiratory braking in patients with acute hypoxemic respiratory failure is unknown.

Protecting the Lung While Protecting the Diaphragm

In some patients, maintaining patient respiratory effort to protect the diaphragm can present challenges to also maintaining lung protection. The challenge of managing spontaneous breathing in patients with moderate or severe acute respiratory distress syndrome (ARDS) is widely appreciated (31). Indeed, patient respiratory drive and effort may be very high in ARDS because of dead space, metabolic acidosis, stimulation of pulmonary parenchymal receptors, brainstem inflammation, and cortical stimuli (32).

In this context, monitoring respiratory effort is important for maintaining lung protection. During spontaneous breathing, airway pressures displayed by the ventilator may significantly underestimate the true magnitude of cyclic lung stress (33); the pressure applied to the lung by the respiratory muscles must be considered (**Figure 2**). The risk of injurious regional cyclic stress and strain depends on the magnitude of respiratory effort (34). Therefore, lung protection during spontaneous breathing requires attention primarily to respiratory effort as well as tidal volume and global lung-distending (transpulmonary) pressure.

Respiratory drive may be excessive and may give rise to high lung stress with or without high tidal volume. Even when tidal volume is adequately controlled (e.g., using volume-controlled ventilation), regional lung stress may be excessive in the presence of high respiratory effort (35). In addition, breath-stacking dyssynchrony from high respiratory drive also markedly increases

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lung stress (36). Adequate lung protection therefore sometimes requires suppression of respiratory muscle effort. In many patients respiratory drive and effort can be controlled to some extent with sedation; the adequacy of the effect of sedation on drive and effort should be closely monitored. In some patients, sedation alone cannot adequately reduce effort, and neuromuscular blockade should be considered. In this case, priority should be given to lung protection. Routine neuromuscular blockade in all patients with moderate/severe ARDS cannot be recommended based on the results of a recent clinical trial (37). Other strategies for controlling respiratory drive, such as adjusting ventilatory settings, may prove effective in this context (see below).

The risk of lung injury as a consequence of maintaining patient respiratory effort likely varies considerably between patients. Biological and pulmonary mechanical heterogeneity entail that the stress and strain required to generate lung injury varies (38); ARDS patients with pulmonary inflammation and significantly reduced functional residual capacity and lung compliance (and hence elevated driving pressures) are probably at highest risk (39). Conversely, maintaining spontaneous respiratory effort can sometimes lower cyclic lung stress and improve homogeneity of ventilation by recruiting atelectasis (40).

There was strong consensus amongst panelists that where conflicts arise, lung protection must take priority over diaphragm protection because of the established mortality benefit associated with lung-protective ventilation.

How can Lung and Diaphragm-Protective Ventilation be Implemented?

A conceptual approach to lung and diaphragm-protective ventilation is presented in **Figure 3**.

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Monitoring

Based on the mechanisms and targets presented above, the foundation of a diaphragm-protective ventilation strategy is close monitoring of patient respiratory effort. There was strong agreement amongst panelists that respiratory effort should be assessed routinely during mechanical ventilation (**Table 1**).

Respiratory rate is insensitive to changes in respiratory load and effort and should not be relied upon to monitor respiratory effort (41). Esophageal manometry provides direct measurements of patient respiratory effort and driving transpulmonary pressure (cyclic lung stress) and can directly guide ventilatory settings (**Figure 2**).

Three simple measurements can also be made on any ventilator without additional monitoring equipment to evaluate effort and drive and the resulting lung stress. First, respiratory drive can be quantified non-invasively using the airway occlusion pressure ($P_{0.1}$) (42). Second, the magnitude of the airway pressure swing during a single-breath expiratory occlusion (Pocc) can detect excess respiratory muscle effort and excess dynamic lung stress (33). Third, an end-inspiratory occlusion can be used to assess plateau pressure and driving pressure in pressure support, carefully assessing for expiratory muscle contraction (43), or in proportional modes (44, 45). These various measurements are represented in **Figure 2**.

Diaphragm electrical activity (EAdi) provides continuous monitoring of diaphragmatic activation. Because of marked interindividual variability in the signal, no specific target value for EAdi can be established (though values below 10 μV are nearly always abnormally low) (46). However, respiratory muscle pressure can be estimated from EAdi by measuring the ratio between Pocc and EAdi (47). Ultrasound has also proven to be an informative technique for the

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assessment of respiratory muscle activity and function (48). One particular mode of ventilation, PAV+, allows respiratory muscle effort to be estimated non-invasively (49).

The choice of technique may vary according to local expertise and preference. Importantly, all these techniques are now available in the clinical setting and are accessible to clinicians.

Mechanical ventilator settings

With respect to diaphragm protection, how a mode of ventilation is applied and monitored probably matters more than the selection of mode per se. In theory, proportional assistance modes should facilitate diaphragm-protective targets: asynchronies are reduced through improved patient-ventilator interaction and over-assistance is prevented because there is no guaranteed minimum tidal volume (50). NAVA was associated with improved diaphragm function in one study (51) but, in a clinical trial, no significant improvement in clinical outcome was observed, possibly because the mode was applied after diaphragm myotrauma had already developed (52).

In a lung and diaphragm-protective approach, inspiratory pressure, flow, and cycling would be set bearing in mind 1) the resulting patient inspiratory effort level, 2) the dynamic lung stress and, 3) adequacy of gas exchange. For clinicians, understanding the determinants of the patient's effort when setting the ventilator is essential. Inspiratory effort responds to changes in peak flow rate and pattern in volume-controlled ventilation (53) and to changes in inspiratory pressure and cycling in pressure-targeted modes. Increases in FiO_2 over relatively moderate ranges of PaO_2 can reduce respiratory drive in some patients without reaching hyperoxemia (54). Patient-ventilator dyssynchrony can often be resolved by adjustments to inspiratory trigger setting, present inspiratory time, or cycling criteria.

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Applying higher PEEP may reduce the risk of both lung and diaphragm injury in some patients: by recruiting atelectatic dependent lung regions to reduce global and regional cyclic lung stress, attenuating inspiratory effort (55), and alleviating expiratory braking (14), PEEP may have important protective effects. However, patients vary markedly in their response to PEEP and this setting requires careful individualized management.

Sedation

The effect of sedation on respiratory drive requires specific monitoring: sedation depth is poorly correlated with diaphragm activity (33) and cannot not be used as a surrogate for respiratory drive. If excessive respiratory effort persists despite adequate analgesia or ventilator titration, sedatives can be useful attenuate potentially injurious drive and effort.

The effects of different analgesics and sedatives on breathing pattern and drive should be familiar to clinicians: opioids primarily depress respiratory rate, increasing the risk of apnea under mechanical ventilation, propofol primarily decreases respiratory effort rather than respiratory rate (56). Benzodiazepines have a similar effect on respiratory pattern to propofol but confer a higher delirium risk and prolong mechanical ventilation (57, 58). Dexmedetomidine is a selective alpha-2 agonist which provides sedation, anxiolysis, and analgesia without reducing respiratory drive (59).

Although sedation is commonly used to treat dyssynchrony, the panel agreed that sedation administration to alleviate dyssynchrony is only appropriate when poor patient-ventilator interaction results from excessive respiratory drive and only after other sources of respiratory drive have been addressed (e.g. peak flow and pressure settings, PEEP, metabolic acidosis, pain

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etc.). Reverse triggering may be alleviated by lightening sedation to obtain a spontaneous respiratory rhythm (16).

Adjunctive therapies

Additional interventions may be required to control respiratory drive in more severely ill patients. Extracorporeal CO_2 removal can reduce respiratory drive and effort, potentially facilitating lung-protective ventilation during spontaneous breathing (60). Partial neuromuscular blockade can attenuate excess respiratory effort unresponsive to ventilator titration or sedation without entirely abolishing diaphragm activity (61), but the feasibility of maintaining partial neuromuscular blockade for prolonged periods is unknown. If sedation cannot be lifted to obtain spontaneous diaphragm activity, phrenic nerve stimulation permits controlled activation of the diaphragm when respiratory drive is minimal or absent (23).

Testing the Hypothesis

The effect of diaphragm-protective ventilation on patient-important outcomes requires evaluation, and this presents several substantial challenges. First, the effect of interventions to mitigate diaphragm atrophy and injury on outcomes may vary considerably between patients depending on the patient's risk of poor outcome, the individual risk of diaphragm atrophy or injury, the competing risk of lung injury, and the presence or absence of other competing mechanisms driving outcomes. For example, recent data suggest that diaphragm atrophy primarily occurs in patients with higher baseline diaphragm muscle mass (62). This problem of patient heterogeneity is a well-documented and widely discussed challenge for clinical trials in the ICU (63). Trials can account for this heterogeneity—provided it is adequately recognized—through patient selection and pre-specified subgroup analyses. Bayesian adaptive clinical trial

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designs may be well-suited to efficiently identifying patient subpopulations most likely to benefit from or be harmed by a diaphragm-protective ventilation strategy.

Second, diaphragm-protective ventilation is a paradigmatic example of a "complex intervention": it involves multiple interacting components (monitoring, ventilation, sedation, adjuncts), requires behavioural change on the part of multiple stakeholders (physicians, respiratory therapists, nurses, manufacturers), and entails extensive tailoring to the individual patient. Any trial of such an intervention is at high risk of failing to detect an important clinical benefit because of difficulties in implementation rather than true lack of benefit. The complex behavioural changes associated with the intervention may "contaminate" usual care, decreasing the apparent treatment effect. Standardization may be difficult and the intervention design may need to adapt to local ICU practices. These challenges are not new in the ICU; careful process evaluation and use of alternative trial designs such as cluster randomization or stepped wedge designs may help to surmount these challenges (64).

Third, it may well be time-consuming and difficult for busy clinicians to optimize ventilation and sedation along three dimensions (gas exchange, lung stress, and respiratory effort). Clinical decision support systems may facilitate lung and diaphragm-protective ventilation by providing real-time guidance for ventilator settings and sedation based on rule or model-based algorithms that integrate various clinical data points (65). These models can be tuned in individual patients using machine learning and artificial intelligence techniques (66). Such systems have already been designed to optimize mechanical ventilation; preliminary testing in the clinical setting offers promising results (67, 68) and randomized trials are ongoing (69).

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Conclusion

This paper outlines a lung and diaphragm-protective approach to mechanical ventilation focused on optimizing respiratory effort and synchrony to prevent diaphragm atrophy and injury while maintaining lung protection. Mounting evidence supports the contention that protecting the diaphragm (together with the lung) during mechanical ventilation might improve patient outcomes. In several instances, monitoring respiratory effort or drive can be beneficial for both lung protection and diaphragm protection. This approach presents new challenges for the bedside clinician and a broad program of research is required to explore the feasibility, safety, and benefit of this complex intervention, particularly in patients with a substantial competing risk of ventilation-induced lung injury. It remains to be shown whether lung and diaphragm-protective ventilation can be effectively implemented in the clinical setting and whether this approach improves outcomes for critically ill patients.

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Figure Legends

Figure 1. Mechanisms of injury to the lung and diaphragm during mechanical ventilation. Ventilator settings and sedation exert complex and interacting effects on the mechanisms of lung and diaphragm injury. Reducing ventilator-applied pressures may fail to protect the lung because of a resultant increase in respiratory effort when respiratory drive is intact. Suppressing respiratory drive to protect the lung by increasing sedation can lead to disuse atrophy. Conversely, maintaining respiratory drive to avoid diaphragm atrophy may result in patient self-inflicted lung injury and load-induced diaphragm injury if respiratory effort is excessive. Thus, a careful balancing act between excessive and insufficient ventilation and sedation may be required to protect both the lung and the diaphragm concomitantly. Similarly, positive end-expiratory pressure can exert complex and competing effects on the mechanisms of injury and all these effects may need to be considered when setting PEEP in individual patients. In all these cases, the risk of injury to the lung and diaphragm is likely "dose-dependent"—the injury risk depends on the magnitude of stress and strain in the baby lung and the magnitude of respiratory efforts generated during assisted breaths and asynchronies.

Figure 2. Monitoring strategies for lung and diaphragm-protective ventilation. These tracings illustrate both the utility of semi-invasive monitoring by esophageal manometry and non-invasive monitoring strategies using respiratory maneuvers on the ventilator. Esophageal pressure swings (ΔPes) reflect patient respiratory effort. Transpulmonary pressure swings ($\Delta P_{L,dyn}$ – the difference between airway pressure (Paw) and Pes) directly assess dynamic lung stress. Airway driving pressure (ΔPaw) and transpulmonary driving pressure (ΔP_L) can be quantified even when patients make spontaneous respiratory efforts by applying an end-

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inspiratory occlusion to measuring plateau pressure (Pplat). Pplat may be higher than peak airway pressure when patients make spontaneous respiratory efforts (as shown) because the lung is inflated by respiratory muscle effort as well as positive pressure from the ventilator. The airway pressure swing during an expiratory occlusion (P_{occ}) can be used to predict both $\Delta P_{L,dyn}$ and respiratory effort (53). Airway occlusion pressure ($P_{0.1}$) can be used to detect insufficient or excessive respiratory drive.

Figure 3. Conceptual framework for lung and diaphragm-protective ventilation. Major goals (homeostasis, lung protection, diaphragm protection) are achieved by delivering mechanical ventilation according to proposed therapeutic targets. The goal of the strategy is not to restore normal physiology but to minimize risk of injury in order to optimize patient outcomes. QOL = quality of life.

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Table 1. Proposed principles for lung and diaphragm-protective ventilation

Topic	Statement	**Distribution of ratings (1-9)*** Median (IQR)	**Range of ratings** (Min – Max)	**Number of panelists expressing support** (Total n=31)
Monitoring	Respiratory effort should be assessed routinely during mechanical ventilation as part of the risk assessment for lung and diaphragm injury	9 (8-9)	4-9	28 (90%)
	Sedation depth is not a reliable surrogate for respiratory drive. When suppressing respiratory drive is a therapeutic objective, drive should be monitored directly.	8 (7-9)	5-9	28 (90%)
	Clinicians are encouraged to become skilled in the use of techniques for assessing respiratory effort including esophageal manometry, diaphragm electrical activity, diaphragm ultrasound, and airway occlusion pressure	9 (7-9)	3-9	25 (81%)
	Automated techniques should be developed to monitor effort and synchrony	8 (7-9)	5-9	25 (81%)
	The exhaled tidal volume should be monitored routinely during mechanical ventilation to ensure tidal volume delivered is as intended. Delivered tidal volume may exceed preset tidal volume in volume-controlled modes.	8 (7-9)	3-9	25 (81%)
	Esophageal manometry is the reference technique for monitoring in real-time both respiratory effort and global lung stress during mechanical ventilation.	8 (7-9)	5-9	24 (77%)
Diaphragm protection	There is no single universally applicable one-size-fits-all setting for optimal mechanical ventilation. Ventilator settings should be tailored to the individual patient's characteristics based on the clinician's assessment of the most pressing risks to the patient in any given situation, integrating best available clinical and experimental evidence with a sound mechanistic evaluation of the patient's condition.	9 (9-9)	7-9	31 (100%)

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	Avoiding excessively low respiratory effort during mechanical ventilation is likely to prevent disuse diaphragm atrophy (over-assistance myotrauma)	8 (7-9)	4-9	28 (90%)
	The mere presence of patient-triggered breaths during mechanical ventilation does not guarantee sufficient diaphragm activity to prevent diaphragm atrophy	8 (7-9)	2-9	25 (81%)
	Patient-ventilator dyssynchrony may injure the lung and the diaphragm, depending on the type of dyssynchrony and the magnitude and timing of the resulting lung stress and diaphragm loading.	8 (7-9)	3-9	24 (77%)
	Avoiding excessively high respiratory effort might prevent load-induced diaphragm injury (under-assistance myotrauma).	7 (6-8)	1-9	21 (68%)
	Proportional assistance modes have the potential to promote a lung and diaphragm-protective ventilator strategy.	7 (5-8)	2-9	16 (52%)
Lung protection versus diaphragm protection	Given currently available evidence, protecting the lung should be prioritized over protecting the diaphragm when necessary, though every effort should be made to protect both organs simultaneously	8 (7-9)	5-9	28 (90%)
	Even when tidal volume is acceptably low, respiratory efforts may induce regional lung overdistension.	8 (7-9)	3-9	27 (87%)
	When considering the application of a higher PEEP strategy, the integrated physiological response to an increase in PEEP (oxygenation, respiratory mechanics, hemodynamics) should be carefully assessed to determine evidence of lung recruitability	8 (7-9)	5-9	27 (87%)
	Targeting a tidal volume of 6 mL/kg predicted body weight is not universally protective against ventilator-induced lung injury. In some patients with severe acute respiratory distress syndrome, lower tidal volumes may be necessary to prevent clinically significant lung injury.	8 (8-9)	5-9	26 (84%)
	The dominant mechanism of ventilation-induced lung injury is excessive lung stress and strain during tidal ventilation (volutrauma) either from	8 (7-9)	3-9	26 (84%)

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	excessive delivered ventilator volume and pressure or from excessive patient respiratory effort.			
	Avoiding excessively high respiratory effort can prevent patient self-inflicted lung injury	8 (7-9)	5-9	25 (81%)
	In patients without acute respiratory distress syndrome, risk from higher tidal volumes may be offset by benefits of preserving spontaneous breathing, less analgosedation, and early mobilization.	7 (7-8)	3-9	24 (77%)
	Higher PEEP during spontaneous breathing may mitigate the risk of patient self-inflicted lung injury provided that it recruits collapsed lung and attenuates inspiratory effort. However, these potential benefits must be balanced with the risk of VILI from hyperinflation, particularly in the setting of breath stacking dyssynchrony.	7 (7-8)	3-9	23 (74%)
Sedation and diaphragm protection	Sedation should be administered to alleviate patient-ventilator dyssynchrony only when the dyssynchrony results from excessive drive to breathe and after attempting to optimize ventilator settings, correcting metabolic derangements, and treating pain and anxiety.	8 (7.5-9)	5-9	28 (90%)
	Propofol is more effective than opioid analgesics to reduce the amplitude of respiratory effort.	6 (5-8)	2-9	15 (48%)

*Each panelist rated each statement on a scale from 1-9, where 1-3 indicates opposition, 4-6 indicates uncertainty, and 7-9 indicates support.

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Table 2. Definitions of terminology

Atelectrauma	Shear stress injury in the small airways and alveoli as a consequence of repetitive opening and closing of atelectatic lung regions during tidal ventilation
Barotrauma	Gross morphologic injury to the lung (manifesting as pneumothorax, pneumomediastinum, subcutaneous emphysema, etc.) as a consequence of excessive inspiratory pressures
Biotrauma	Systemic inflammation generated by pulmonary inflammation from volutrauma and atelectrauma; leads to inflammation and injury in other organs (brain, kidneys, etc.) leading to multi-organ failure
Critical illness-associated diaphragm weakness	A loss of diaphragmatic force-generating capacity developing during critical illness regardless of the cause and timing
Diaphragm-protective ventilation	Theoretical ventilation strategy designed to avert or mitigate the various forms of myotrauma to preserve diaphragm function and accelerate liberation from mechanical ventilation
Dyssynchrony (also termed, Asynchrony)	Dissociation between the patient's neural respiratory rhythm and the mechanical ventilator's respiratory timing, occurring at the onset of neural inspiration or the onset of neural expiration (or both). Often also referred to as 'asynchrony.' Dyssynchrony is also sometimes used to refer to a mismatch between patient ventilatory demands and delivered flow and pressure (i.e. 'flow starvation' dyssynchrony)
Eccentric myotrauma	Deleterious changes in the diaphragm resulting from diaphragm contractile loads applied under eccentric (lengthening) conditions; possible contributor to VIDD
Lung strain	The deformation experienced by the lungs during inflation relative to the lung's resting volume (under zero stress). Strain is approximated by the ratio of tidal volume to functional residual capacity.
Lung stress	The mechanical force applied to the lung to inflate the lung and generate tidal volume (under zero flow conditions, the stress on the whole lung is quantified by transpulmonary pressure)
Lung-protective ventilation	Ventilation strategy aiming to reduce the mechanical stress placed on the injured lung to prevent further lung injury and accelerate recovery
Over-assistance myotrauma	Deleterious changes in the diaphragm (including disuse atrophy, myofibrillar proteolysis, autophagy) resulting from suppression of respiratory effort due to excess pressure and flow delivered by the ventilator; common cause of VIDD
Patient self-inflicted lung injury	Adverse structural and functional changes in the lung arising from excessive global or regional lung stress and strain as a consequence of respiratory muscle action
Under-assistance myotrauma	Deleterious changes in the diaphragm (sarcolemmal disruption, inflammatory infiltrates, sarcomeric disarray) resulting from inadequate unloading of respiratory muscles due to insufficient pressure and flow delivered by the ventilator; probable contributor to VIDD

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Ventilator-induced diaphragm dysfunction (VIDD)	A loss of diaphragmatic force-generating capacity specifically attributable to exposure to mechanical ventilation
Ventilator-induced lung injury	Adverse structural and functional changes in the lung due to pulmonary injury and inflammation from excessive global or regional lung stress and strain during mechanical ventilation
Volutrauma	Increased alveolar-capillary membrane permeability and alveolar inflammation as a consequence of excessive cyclic alveolar stress and strain

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Table 3. Potential therapeutic targets for diaphragm protection

Goal	Potential therapeutic target*
Prevent over-assistance myotrauma	Any 1 of: $P_{mus} \geq$ 3 to 5 cm H_2O $\Delta P_{di} \geq$ 3 to 5 cm H_2O $\Delta P_{es} \leq$ -2 to -3 cm H_2O $P_{0.1} >$ 1 to 1.5 cm H_2O $TF_{di} \geq$ 15% $EA_{di} \geq$ target value selected based on pressure-EAdi index and above targets
Prevent under-assistance myotrauma	Any 1 of: $P_{mus} \leq$ 10 to 15 cm H_2O $\Delta P_{di} \leq$ 10 to 15 cm H_2O $\Delta P_{es} \geq$ -8 to -12 cm H_2O $P_{occ} \geq$ -15 to -20 cm H_2O $P_{0.1} <$ 3.5 to 5 cm H_2O $TF_{di} \leq$ 30 to 40% EAdi $\leq$ limit value selected based on pressure-EAdi index and above pressure targets
Prevent eccentric myotrauma	Avoid ineffective triggering and reverse triggering Avoid premature cycling Minimize expiratory braking

Abbreviations: ΔP_{aw}, airway driving pressure; $\Delta P_{L,dyn}$, dynamic transpulmonary driving pressure; P_{mus}, the pressure generated by the respiratory muscles to inflate both the lung and the chest wall; P_L, transpulmonary pressure; ΔP_{di}, inspiratory swing in transdiaphragmatic pressure; ΔP_{es}, inspiratory swing in esophageal pressure; $P_{0.1}$, airway occlusion pressure; P_{occ}, occlusion pressure; TF_{di}, diaphragm thickening fraction

*The specification of ranges for the target values reflects uncertainty on the part of the authors about the safe upper limit for inspiratory effort; values specified represent suggested targets best on available physiological and clinical evidence

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Figure 1

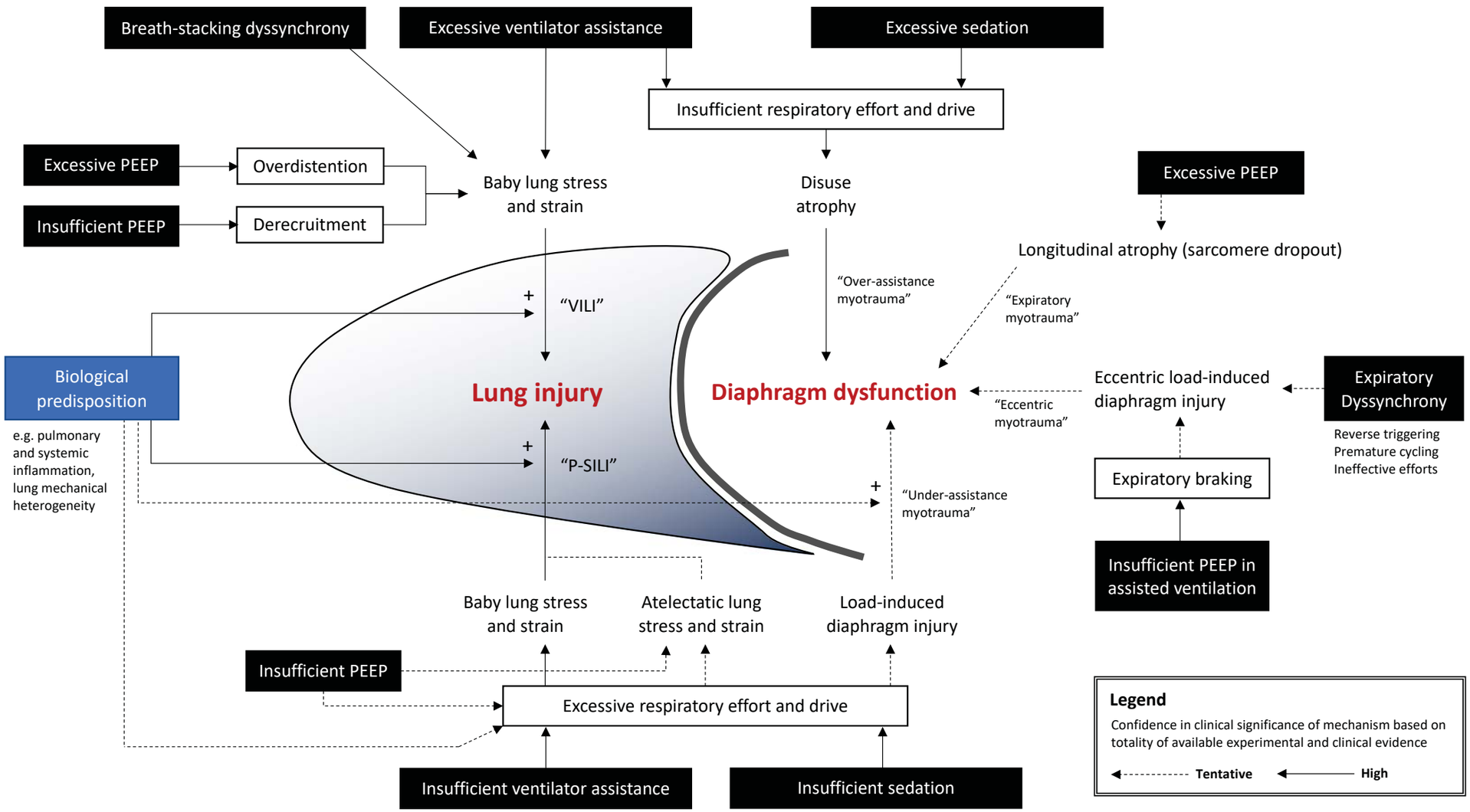

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Figure 2

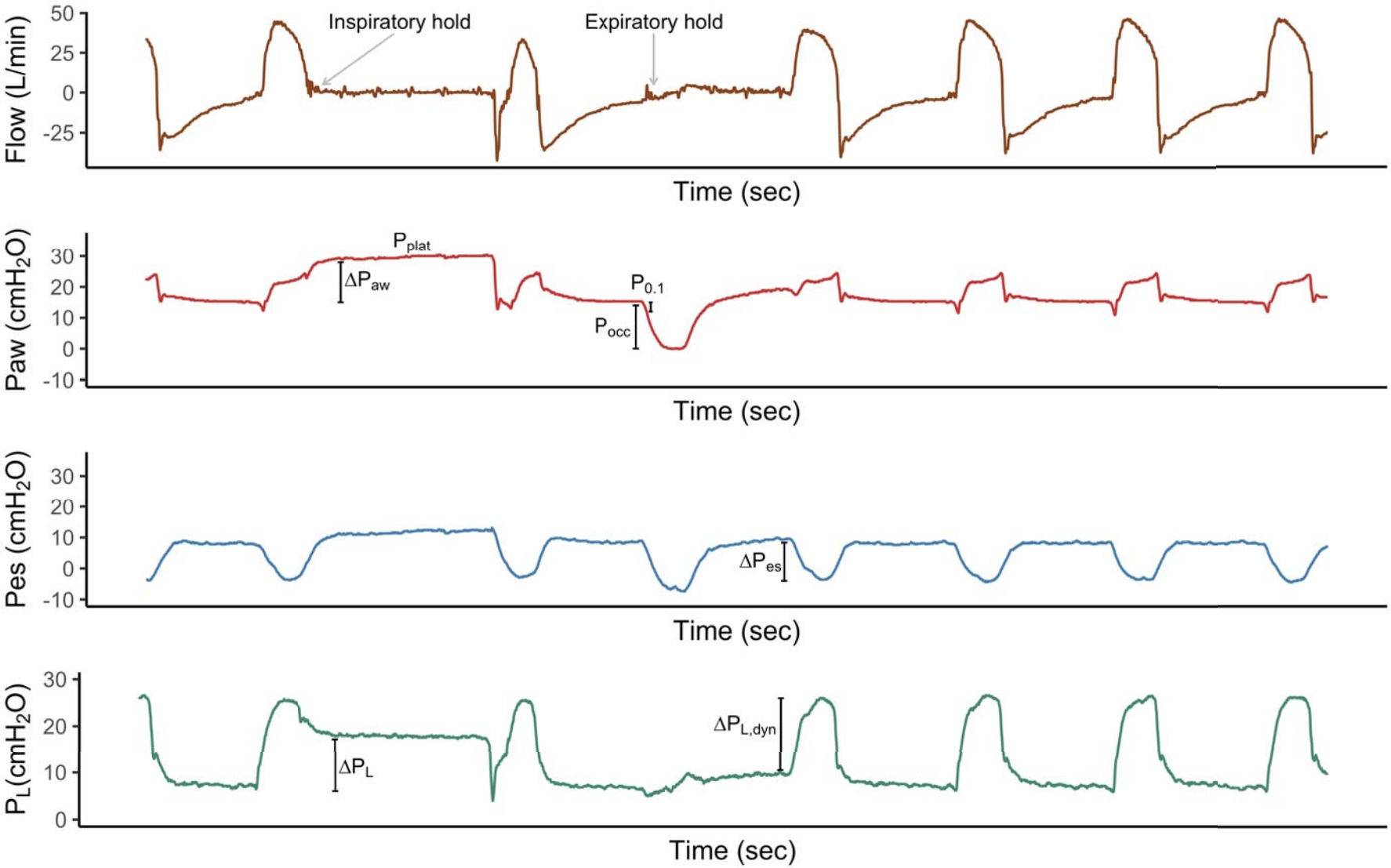

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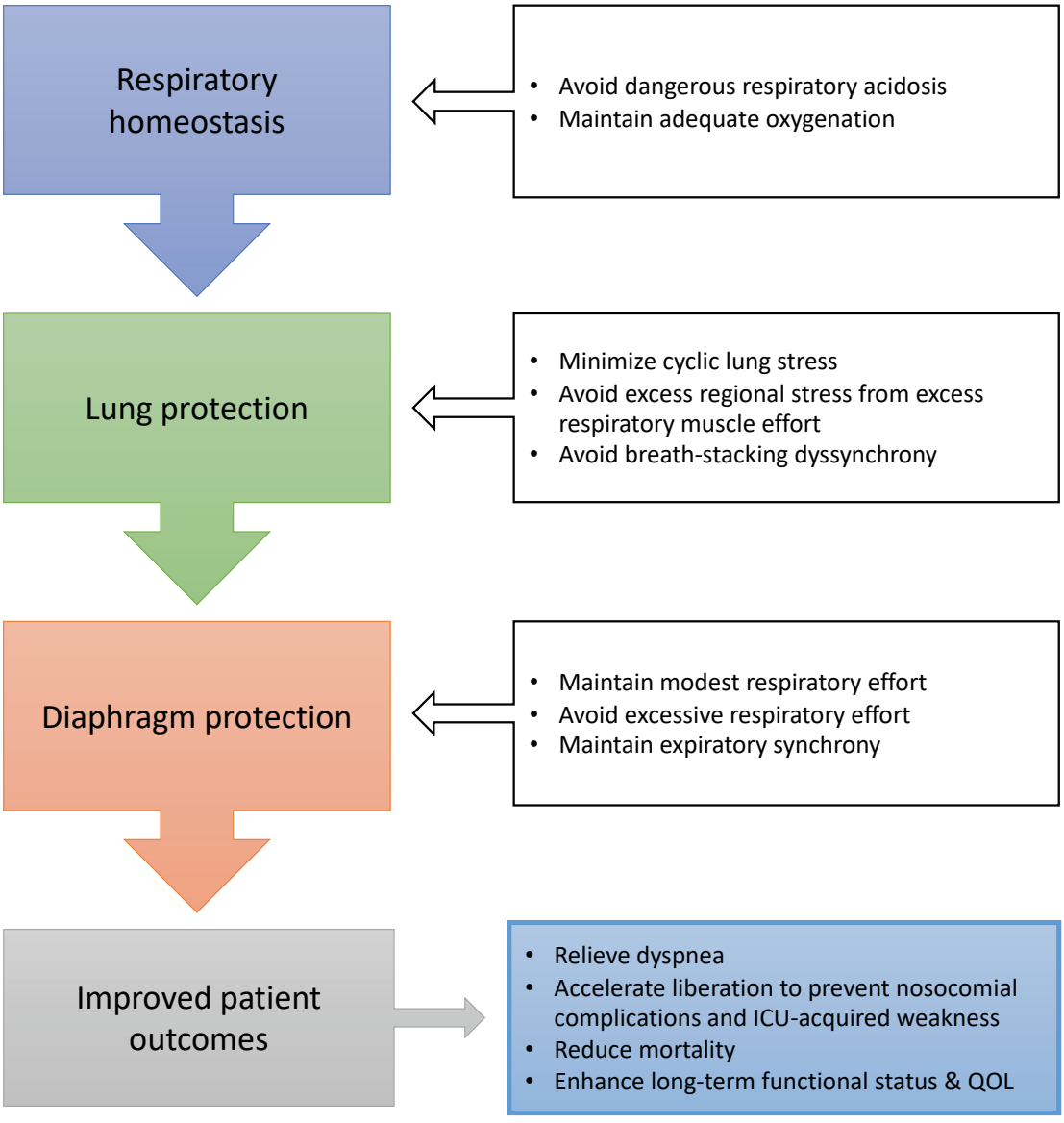
Figure 3



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