

Lung- and Diaphragm-protective Ventilation in Acute Respiratory Distress Syndrome

Rationale and Challenges

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Mechanical ventilation can injure both the lung and the diaphragm, leading to substantial morbidity and mortality in ventilated patients. Whereas the importance of lung-protective ventilation is well established, the concept of diaphragm-protective ventilation is an important but unproven new paradigm in the field. A novel approach to mechanical ventilation in the intensive care unit integrating both diaphragm- and lung-protective measures has the potential to accelerate liberation from mechanical ventilation, prevent long-term disability, and increase survival after acute respiratory failure. In this review, we describe the evidence supporting this new paradigm and outline the basic approach to a lung- and diaphragm-protective ventilation strategy.

Ventilator-induced Lung Injury and Ventilator-induced Diaphragm Dysfunction: Evidence for Impact on Patient Outcomes

The recognition that mechanical ventilation can cause lung injury was a historic development in the field of mechanical ventilation. This injury, termed ventilator-induced lung injury, results from excessive global or regional lung stress and strain (volutrauma).¹ Further, if repetitive alveolar opening and closing occurs during mechanical ventilation, lung injury may result (atelectrauma). These mechanical stresses induce a local inflammatory response that can disseminate systemically, leading to multiple organ failure (biotrauma).² Ventilator-induced lung injury has been convincingly shown to markedly increase morbidity and mortality, and decades of intensive investigation in acute respiratory distress syndrome (ARDS) and ventilator-induced lung injury have yielded a variety of effective lung-protective ventilation strategies (e.g., low tidal volume [V_T] ventilation, prone positioning, neuromuscular blockade). These strategies all aim to reduce the mechanical stress placed on the injured lung either by the ventilator's action or by the patient's own respiratory muscle effort.³⁻⁶

More recently, the deleterious impact of mechanical ventilation on the diaphragm has come to light. The diaphragm and other respiratory muscles play a crucial role

in enabling patients to assume the full work of breathing upon recovery from respiratory failure. Respiratory muscle weakness, especially weakness of the diaphragm, prolongs ventilator dependence and predisposes to nosocomial complications and death.⁷⁻¹⁰ Diaphragm weakness is common among ventilated patients, affecting approximately 60% at the time of the first spontaneous breathing trial.¹¹ Furthermore, diaphragm weakness at the time of extubation is associated with an increased risk of intensive care unit readmission¹² and an increased risk of mortality within the year after intensive care unit discharge.¹³ Diaphragm function is therefore a crucial determinant of patient outcomes.

It is now well established that mechanical ventilation *per se* contributes to the diaphragm dysfunction observed in these patients, a phenomenon termed ventilator-induced diaphragm dysfunction.^{14,15} Both experimental and clinical data have shown that mechanical ventilation can cause diaphragm injury by a variety of mechanisms, principally disuse atrophy. The magnitude of diaphragm injury is correlated with the duration of mechanical ventilation.^{14,16-18} Nearly 50% of ventilated patients developed significant diaphragm atrophy within 3 to 4 days of mechanical ventilation, leading to impaired diaphragm strength. These changes in muscle thickness were associated with prolonged mechanical ventilation, prolonged intensive care unit admission, and a significant increase in the risk of complications during mechanical ventilation.¹⁹ Ventilator-induced diaphragm dysfunction thus constitutes a vicious cycle of ventilator dependence: acute respiratory failure renders the patient ventilator-dependent, and injurious mechanical ventilation weakens the respiratory muscles, thus perpetuating ventilator dependence.

Although the concept of lung-protective ventilation is well established, the concept of diaphragm-protective ventilation has only recently been proposed.^{19,20} The question arises whether both lung- and diaphragm-protective ventilation can be achieved concomitantly. Addressing this question requires a detailed understanding of the complex mechanisms driving lung and diaphragm injury in relation to spontaneous respiratory effort in acute hypoxemic respiratory failure.

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Patient Respiratory Effort in ARDS: Potential for Injury to the Lung and Diaphragm

Lung Injury

In ARDS, the lung volume (*i.e.*, number of alveolar units) available to participate in ventilation is markedly reduced—hence the ARDS lung is described as a “baby lung.”²¹ Consequently, V_T s in the usual range give rise to much greater mechanical stress and strain, potentially hyperinflating the already injured lung parenchyma.²² The forces causing hyperinflation and lung injury arise either from the ventilator (distending pressure inside the lung) or from the patient’s respiratory muscle effort (distending pressure outside the lung), or both. When these forces are excessive, ventilator-induced lung injury or (if high respiratory effort is present) “patient self-inflicted lung injury” may result.²³ Whether from ventilator or patient effort, the risk of injury is related to the magnitude of V_T and transpulmonary pressure applied to the lung.²⁴ Figure 1 details the different pressures involved.

In fact, for any given V_T , the inspiratory action of the respiratory muscles may be more injurious than that of the ventilator because of very high regional lung stress and strain.²⁵ Diaphragmatic force results from muscular shortening during contraction. The diaphragm shortens to a far greater extent in its dorsal aspect than in its ventral aspect.²⁶ Under normal conditions in health, the regional forces resulting from diaphragm shortening redistribute evenly throughout the lung, yielding a relatively homogeneous

distribution of transpulmonary pressure because the lung behaves like a fluid.^{26,27} In the presence of atelectasis, consolidation, edema, or injury, this fluid-like behavior is lost, and the lung behaves more like a solid—applied pressures are not evenly redistributed across the entire lung surface.²⁷ Vigorous inspiratory efforts will therefore produce large regional variations in transpulmonary pressure; because diaphragm shortening is greatest in the dorsal regions, the dorsal lung region is subjected to much greater mechanical stress than the ventral lung region (fig. 2).²⁸ In the presence of high inspiratory effort, spontaneous breathing can therefore cause lung injury even when global lung inflation (V_T) lies within accepted lung-protective limits. This phenomenon has been demonstrated convincingly experimentally²⁹; its prevalence and impact in the clinical setting remain uncertain.

Expiratory muscle effort may also contribute to lung injury. In the presence of high respiratory drive, the abdominal muscles are activated to contract vigorously in the expiratory phase.³⁰ Expiratory muscle contraction reduces lung volumes (derecruitment), “shrinking” the baby lung³¹; this in turn predisposes to greater mechanical stress and strain during inspiration (see above in this section). Expiratory effort can also worsen cyclic alveolar opening and closing.

Concerns over the injurious potential of spontaneous breathing in ARDS are supported by the improvements in outcome associated with suppressing respiratory muscle effort. Applying neuromuscular blockade in patients with moderate-to-severe ARDS (P_{aO_2} /fraction of inspired oxygen less than 150 mmHg) improves oxygenation, attenuates the systemic inflammatory response, and is associated with enhanced

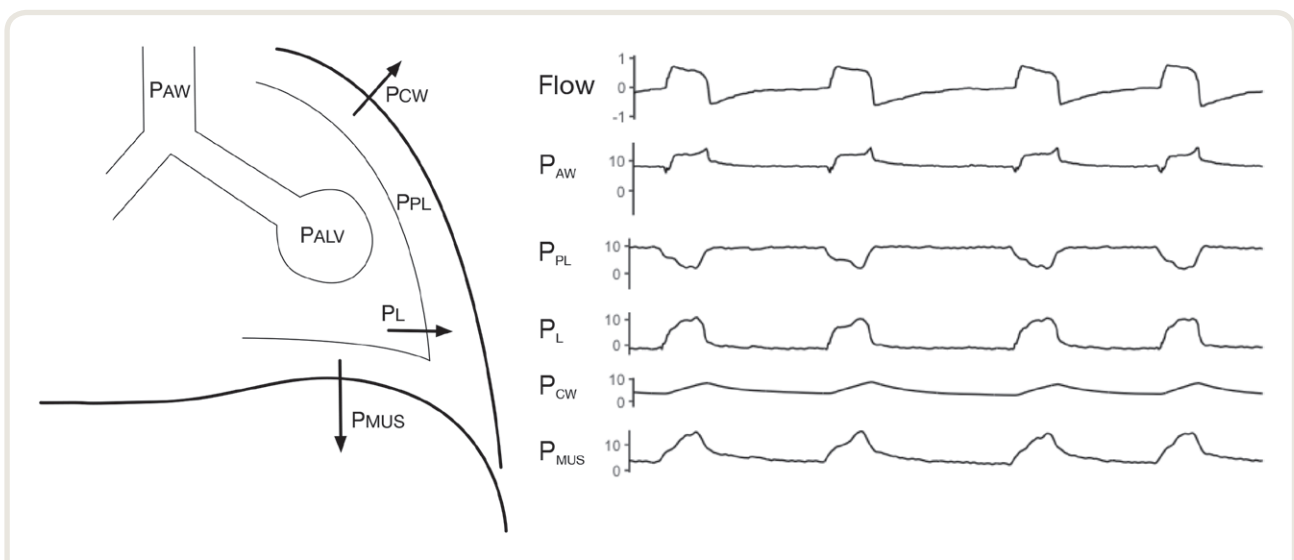


Fig. 1. Respiratory pressures relevant to spontaneous breathing during mechanical ventilation. The locations of relevant pressures are depicted on the *left*. Typical tracings of respiratory pressures under assisted mechanical ventilation are shown on the *right*. Pleural pressure is estimated by esophageal manometry. The respiratory muscle pressure is computed as the difference between observed chest wall elastic recoil pressure and pleural pressure swing. Chest wall elastic recoil pressure is estimated as the product of tidal volume and chest wall elastance (measured during passive ventilation). P_{ALV} , alveolar pressure; P_{AW} , airway pressure; P_{CW} , chest wall elastic recoil pressure; P_L , transpulmonary pressure ($P_{AW} - P_{PL}$); P_{MUS} , respiratory muscle pressure; P_{PL} , pleural pressure.

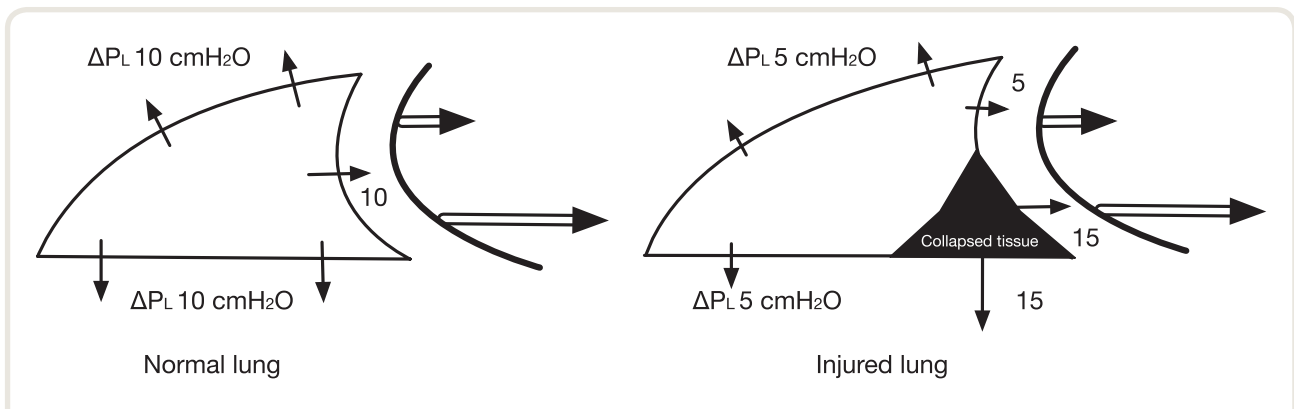


Fig. 2. Pressure transmission in a normal lung (*left*) versus an injured lung with dorsal atelectasis/consolidation (*right*). The posterior diaphragm shortens more than the anterior diaphragm (*double line arrows*). In the normal lung, the negative pleural pressures generated by diaphragmatic shortening during inspiration are distributed evenly across the whole lung surface because healthy lung tissue exhibits “fluid-like” behavior. In the presence of lung injury, injured lung regions exhibit “solid-like” behavior and do not transmit regional forces generated by diaphragm contraction to other parts of the lung. Consequently, injured regions are subjected to significantly greater regional stress in comparison with transpulmonary pressures experienced by the rest of the lung. PL, transpulmonary pressure. Adapted from Hraiech *et al.*²⁸ with permission from Wolters Kluwer Health.

survival, although it remains uncertain whether these benefits are entirely attributable to respiratory muscle relaxation.^{32–34} Patient–ventilator dyssynchrony and breath stacking because of vigorous inspiratory effort are associated with an increased risk of death and morbidity.^{35,36} These data suggest that excessive respiratory muscle effort makes a clinically significant contribution to ventilator-induced lung injury.

Oxygen Consumption

Respiratory muscle activity may consume a substantial proportion of total oxygen delivery. In cardiovascular shock states, this can reduce oxygen delivery to other critical organs such as the brain, kidneys, gut, and skeletal muscles, propagating ischemic injury and multiorgan dysfunction.³⁷ When the work of breathing is reduced by mechanical ventilation or neuromuscular blockade, blood flow and oxygen delivery to other organs improve.^{38,39} For this reason, permitting respiratory muscle effort in patients in cardiovascular shock requires caution and close attention to systemic perfusion.³⁸

Load-induced Diaphragm Injury

Two types of diaphragm loading can cause acute muscular injury. When the muscle contracts against an excessive load as it shortens (concentric loading) or as it lengthens (eccentric loading), acute diaphragm injury, inflammation, and weakness may result.^{39,40} Eccentric loading is generally more injurious than concentric loading.⁴¹ Eccentric loading may occur when the diaphragm activation persists into expiration to slow the rate of lung volume loss—a phenomenon known as “expiratory braking.”^{42,43} Eccentric loading may also occur during reverse triggering or ineffective efforts.^{44,45}

Histologic evidence of the injurious effects of both chronic and acute load-induced diaphragm injury has been documented in healthy human subjects and in patients with chronic obstructive pulmonary disease.³⁹ The risk of load-induced injury is heightened in critically ill patients, because sepsis and systemic inflammation render the myocyte cell membrane (sarcolemma) fragile. When subjected to high inspiratory loads, the inflamed sarcolemma can fracture, leading to myofibril edema, inflammation, and contractile dysfunction.^{40,46} Elevated inspiratory effort under mechanical ventilation is associated with a rapid increase in diaphragm thickness (visualized on ultrasound); this increase in thickness predicts both impaired diaphragm strength and prolonged ventilator dependence, suggesting that this increase in thickness may signify load-induced injury. Avoiding excessive loading of the diaphragm during septic shock has been shown experimentally to prevent myofibril membrane injury and diaphragm weakness.⁴⁷ Excess concentric loading likely occurs when the pressure and flow delivered by the ventilator are inadequate; excess eccentric loading may occur when the diaphragm is actively contracting during the mechanical expiratory phase, such as during significant expiratory braking⁴³ or during reverse triggering dyssynchrony.⁴⁴ The mechanisms linking inappropriately titrated mechanical ventilation to diaphragm and lung injury are summarized in figure 3.

Patient Respiratory Effort in ARDS: Potential for Benefit

Oxygenation and Hemodynamics

Spontaneous breathing in patients with ARDS may sometimes improve oxygenation^{29,48} or impair oxygenation,³² possibly

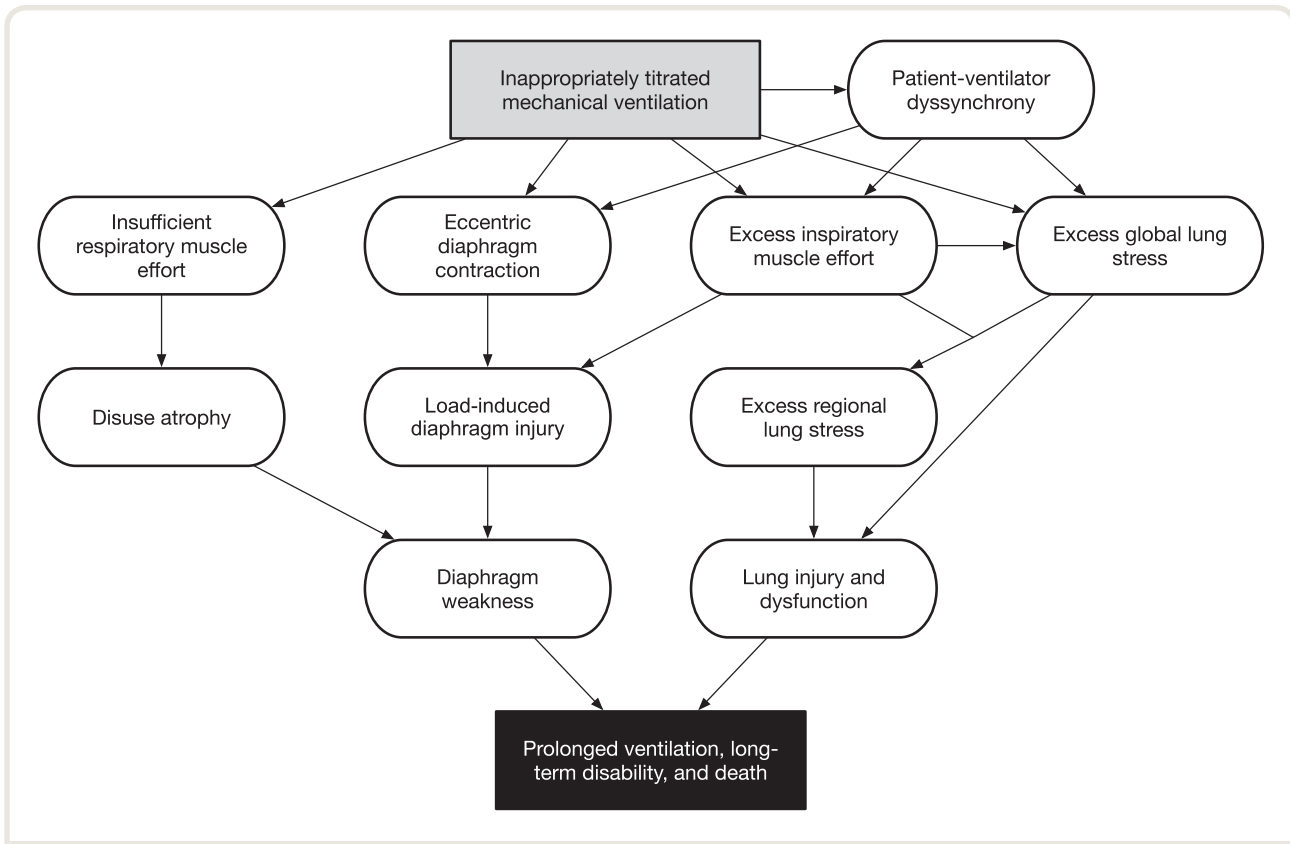


Fig. 3. Mechanisms linking inappropriately titrated mechanical ventilation to diaphragm and lung injury.

depending on the level of respiratory drive and the relative contributions of inspiratory and expiratory muscle effort. In brain-dead organ donors and in critically ill patients, diaphragmatic contractions recruit dorsal lung atelectasis, muscular inactivity rapidly initiates various proteolytic pathways (i.e., calpains, caspases, ubiquitin proteasome system), and diaphragm contractile efforts persisting into the expiratory phase (expiratory braking) mitigate atelectasis and mediate mitochondrial dysfunction, resulting in cellular oxidative stress and contractile dysfunction. Maintaining inspiratory effort during ventilation can be injurious to the lung, as discussed above in the section on Lung Injury.⁶⁰ Spontaneous breathing usually enhances hemodynamic performance. The inspiratory rise in intraabdominal pressure and the concomitant fall in intrapleural pressure during active inspiratory effort substantially increase venous return.⁵¹ Negative pleural swings during inspiratory effort are transmitted to the pulmonary capillary system, reducing right ventricular afterload. On the other hand, vigorous inspiratory effort may increase cardiac afterload and induce acute left ventricular failure.⁵²

24 to 48 h of ventilation has been demonstrated repeatedly in brain-dead organ donors and in critically ill patients.^{47,18} At the same time, diaphragm contractile efforts persisting into the expiratory phase (expiratory braking) mitigate atelectasis and mediate mitochondrial dysfunction, resulting in cellular oxidative stress and contractile dysfunction. Maintaining inspiratory effort during ventilation can be injurious to the lung, as discussed above in the section on Lung Injury.⁶⁰ Spontaneous breathing usually enhances hemodynamic performance. The inspiratory rise in intraabdominal pressure and the concomitant fall in intrapleural pressure during active inspiratory effort substantially increase venous return.⁵¹ Negative pleural swings during inspiratory effort are transmitted to the pulmonary capillary system, reducing right ventricular afterload. On the other hand, vigorous inspiratory effort may increase cardiac afterload and induce acute left ventricular failure.⁵²

Preventing Diaphragm Atrophy

Changes in diaphragm muscle mass and muscle fiber composition commence rapidly after instituting mechanical ventilation.⁵⁴⁻⁵⁷ Diaphragm atrophy developing after more than

Reduce Sedation Requirements and Facilitate Mobilization

Patients with ARDS often exhibit high levels of respiratory drive; heavy sedation and/or neuromuscular blockade are often required to suppress respiratory muscle effort.

Permitting spontaneous breathing during ARDS may therefore allow clinicians to lighten sedation, as demonstrated in a randomized clinical trial of airway pressure release ventilation for ARDS and in a large cohort study. This in turn may facilitate early mobilization and mitigate the risk of delirium, resulting in better functional outcomes at hospital discharge.

Integrating the Concepts of Ventilation Targets in a Lung- and Diaphragm-protective Ventilation Strategy

Having outlined the basic mechanisms responsible for lung and diaphragm injury in relation to the presence or absence of spontaneous breathing (Fig. 3), we proceed to set out key targets for a strategy aiming to avoid both forms of injury with the ultimate goal of improving survival and accelerating liberation from mechanical ventilation. The strategy is summarized in Figure 4. The approach proposed aims to strike a careful balance between potentially injurious insufficient respiratory effort and potentially injurious excessive effort while maintaining the overarching goal of ventilation to support homeostasis and recovery.

those employed in trials of lung-protective ventilation: pH higher than 7.20 to 7.25 and P_{aO_2} of 55 to 80 mmHg. Importantly, in awake or lightly anesthetized patients, deranged gas exchange will modulate the control of breathing, contributing to excessive respiratory drive and effort. A ventilation strategy that permits spontaneous breathing must therefore respond to the influence of pH, P_{aO_2} and P_{aCO_2} on patient respiratory effort; these ventilation targets may need to be adjusted to achieve the other goals of the strategy. Additionally, hyperoxia should be avoided. An accumulating body of high-quality evidence from clinical trials demonstrates that liberal oxygen therapy (targeting oxygen saturation measured by pulse oximetry of more than 96%) is associated with substantially increased risk of death. The mechanisms responsible for this clinical effect are uncertain—oxidative stress and inflammation resulting from hyperoxia can potentially injure the lungs, heart, and central nervous system. Nevertheless, a modern protective ventilation strategy should assiduously aim to avoid hyperoxia and maintain arterial oxygen saturation ideally in the range of 88 to 95%.

Goal 2: Protect the Lung by Minimizing Global Dynamic Lung Stress

Goal 1: Maintain Adequate Gas Exchange

The immediate purpose of ventilation is to support acid–base homeostasis and oxygen delivery in the face of this life-threatening critical illness. This does not entail that arterial blood gases should be “normalized”—intensivists have learned to accept a certain degree of physiological derangement to avoid harming the patient.

Limiting V_T s and airway pressures has been the mainstay of lung-protective ventilation for two decades, since the publication of National Heart, Lung, and Blood Institute (Bethesda, Maryland) Acute Respiratory Distress Syndrome Network low tidal volume ventilation trial and related trials.^{3,67,70,71} Recent guidelines specify widely accepted lung-protective targets: V_T of 6ml/kg of predicted body weight and airway plateau pressure less than 30 cmH₂O. Nevertheless, the cyclic tidal stress applied to the lung at 6ml/kg may still be excessive and injurious, depending on

The ventilation targets of a lung- and diaphragm-protective ventilation strategy might therefore be similar to

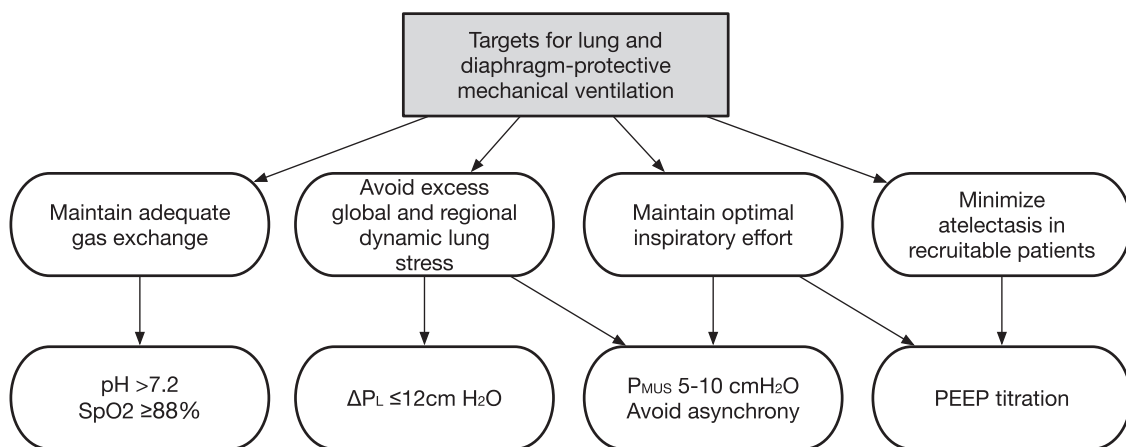


Fig. 4. Summary of proposed different targets for a combined lung- and diaphragm-protective ventilation strategy. PEEP, positive end-expiratory pressure; ΔP_L , tidal driving transpulmonary pressure; P_{mus} , respiratory muscle pressure; SpO₂, oxygen saturation measured by pulse oximetry.

the size of the baby lung.⁷⁵ Because the size of the baby lung determines respiratory system compliance, normalizing V_T to respiratory system compliance may more accurately reflect the stress applied to the lung by a given volume. Recent data suggest that the ratio of ΔP and respiratory system compliance, referred to as the driving pressure, is the best predictor of ventilator-induced lung injury—probably because it more accurately reflects dynamic lung stress. The utility of this parameter can be further enhanced by accounting for the elastic recoil pressure of the chest wall (which does not contribute to lung injury) by measuring the driving transpulmonary pressure (the tidal swing in the pressure gradient between the airway and pleural space, estimated by esophageal manometry; Fig. 1). This quantity provides the most accurate measure of the global dynamic stress experienced by the lung in response to tidal ventilation. Although other factors such as static strain and respiratory frequency may contribute to ventilator-induced lung injury,⁷⁷ both experimental and clinical data and physiologic considerations suggest that dynamic strain is by far the most important determinant of lung injury.^{76,78,79} The main target for lung-protective ventilation is therefore to achieve acceptable levels of driving transpulmonary pressure.

The focus on pressure over volume is crucial to the lung- and diaphragm-protective approach: targeting driving transpulmonary pressure will require lower V_T in patients with a smaller baby lung and permit larger V_T in patients with a larger baby lung. This has important implications for a strategy that maintains some level of spontaneous breathing. First, spontaneous breathing uncouples the relationship between V_T and airway pressure; plateau pressure is no longer a reliable surrogate of lung protection. Second, achieving 6 ml/kg predicted body weight sometimes requires suppression of respiratory effort; this may not be necessary if driving transpulmonary pressure remains within acceptable limits, even if V_T reaches 8 or 9 ml/kg predicted body weight. Interestingly, patients with ARDS transitioned from assist-controlled ventilation to proportional assist ventilation behave in precisely this way: V_T rose or fell in proportion to respiratory compliance to maintain the transpulmonary pressure at approximately 15 cm H₂O or lower.⁸⁰

What should be accepted limits for driving transpulmonary pressure? Quasi-static transpulmonary driving pressure swings of 12 cm H₂O or lower are advised. This threshold is supported by two considerations. First, airway driving pressure swings less than 15 cm H₂O were associated with significant improvements in clinical outcome—this would be equivalent to driving transpulmonary pressure of approximately 12 cm H₂O given the typical ratio of lung elastance to total respiratory elastance in ARDS (~70 to 80%). Second, because the specific elastance of the baby lung is approximately 13 cm H₂O/l, limiting rises in transpulmonary pressures to 12 cm H₂O or less ensures that tidal insufflation does not increase lung strain above a value of 2.0 (the risk of injury increases considerably once strain reaches 2.5).

Goal 3: Protect the Diaphragm by Maintaining Adequate Inspiratory Effort while Avoiding Excessive Inspiratory Effort

As discussed above, diaphragm injury may result from either excessive or insufficient inspiratory effort during ventilation. The patient's inspiratory effort can be modified in a number of ways, e.g., by manipulating inspiratory pressure and flow, changing the ventilation mode, or altering the type and dose of sedation. However, the optimal level of inspiratory effort to target during assisted mechanical ventilation has been uncertain because of the many competing considerations summarized above in the Patient Respiratory Effort in ARDS section.

We propose that the optimal target range for inspiratory effort is similar to that of healthy subjects breathing at rest (respiratory muscle pressure of 5 to 10 cm H₂O; Fig. 1). Several theoretical and empirical considerations favor this target. First, at this effort level, respiratory muscle blood flow and oxygen consumption are quite low and would not compete significantly with other organs for blood flow and oxygen delivery. Second, it is likely that excess regional stress and strain arising in the presence of spontaneous breathing and solid-like lung behavior require relatively high levels of effort; such injury would be relatively minimized at lower levels of effort provided that global lung stress is also within acceptable limits. Third, patients who are successfully liberated from ventilation display this range of effort level during their weaning trials, suggesting that this level of effort is sustainable and safe after extubation. Fourth, decreases or increases in diaphragm thickness (likely indicative of either atrophy or load-induced injury, respectively) occurred when inspiratory effort falls below or above that of healthy subjects at rest. Thus, an intermediate level of effort can avoid both diaphragm atrophy and load-induced injury, potentially navigating “a patient's safe passage between the Scylla of excessive patient effort and the Charybdis of excessive respiratory muscle effort.”

The relationship between inspiratory effort during the early course of ventilation and clinical outcome was recently described for the first time. The duration of ventilation, length of intensive care unit stay, and risk of complications of respiratory failure (prolonged ventilation, reintubation, tracheostomy, or death) were minimized in patients whose diaphragm thickening fraction (a surrogate measure of inspiratory effort) averaged 15 to 30%—similar to that of healthy subjects breathing at rest—during the first 3 days of ventilation.¹⁹ These outcome data strongly corroborate this proposed target for lung- and diaphragm-protective ventilation.

Goal 4: Protect the Lungs and Diaphragm by Recruiting “Recruitable” Lung

Few aspects of mechanical ventilation are as complex as the selection of best positive end-expiratory pressure (PEEP). To date, no single higher PEEP ventilation strategy has

been shown to improve outcomes^{67,86–88}; indeed, some electrical activity, suggesting that contractile activation during muscle lengthening was greatly reduced. aggressive recruitment maneuvers with higher PEEP or Caution is warranted; the optimal PEEP to reduce spon- high-frequency oscillation found that the open-lung strat- taneous breathing injury while also avoiding hyperin ation egy was associated with increased mortality. rational and hemodynamic impairment will vary considerably from PEEP titration strategy must take into account several crea- patient to patient. Variation in lung recruitability between tial mechanistic considerations: right ventricular function, patients must be carefully evaluated when considering the variable rightward shifts in pressure–volume curves during use of higher PEEP. Furthermore, new data suggest that critical illness, and the wide variation in lung recruitability the diaphragm muscle actually shortens (by sarcomere between patients.⁸⁹ For example, focal ARDS differs sub- dropout) signi cantly when higher lung volumes are main- stantially from nonfocal ARDS in several respects. Markers tained for a short period of time; this may impair diaphragm of epithelial injury are much higher in patients with nonfo- length–tension relations when PEEP is reduced. The over- cal ARDS compared to those with focal ARDS. In patients all bene ts of higher PEEP in the context of a lung- and with focal ARDS, consolidated lung areas coexist with non- diaphragm-protective strategy, taking into consideration mal lung aeration and interstitial injury in nondependent relevant patient characteristics such as lung morphology lung regions, whereas nonfocal ARDS is characterized by and recruitability, require careful clinical evaluation. di use epithelial injury and massive loss of aeration.

Patients with focal loss of lung aeration generally obtain significantly less lung recruitment than patients with dif- fuse loss of lung aeration,^{90,95} and the resulting hyperin ation may predispose them to worse outcomes.⁹⁶ There is therefore widespread appreciation that the PEEP titration strategy should be personalized according to patient charac- teristics. A trial that evaluates the effect of a ventilation strat- egy adapted to ARDS morphology is currently ongoing.

Although the aforementioned trials generally focused on the early period of ARDS, in which patients are passively ventilated, the same considerations apply in the context of spontaneous breathing. Emerging evidence suggests that PEEP has specific physiologic effects that promote both lung and diaphragm protection in the context of sponta- neous breathing. First, if PEEP successfully recruits the lung, it increases the lung volume available to participate in ven- tilation, reducing the stress experienced by the lung for a given \dot{V} . Second, if lung is successfully recruited, it reduces solid-like lung behavior and attenuates regional variation in stress and strain. Third, it can reduce the pleural pressure swings generated by diaphragm contraction, both reducing global and regional lung stress and mitigating the risk of load-induced diaphragm injury. A recent experimental study in animal models and in a small group of patients provided a preliminary demonstration of these putatively beneficial effects.⁹⁸ In this study, higher PEEP attenuated lung in- flammation and injury because of vigorous spontaneous breathing by (1) substantially reducing pleural pressure swings; (2) reducing global dynamic lung stress; and (3) attenuat- ing the regional maldistribution of lung stress. Importantly, these experimental findings should be regarded with cau- tion, because they employed a highly recruitable experimen- tal model of ARDS in this study.

Higher PEEP can also reduce the risk of eccentric load-induced diaphragm injury by attenuating the expira- tory braking phenomenon. Pellegrini et al^{43–45} showed that higher continuous positive airway pressure levels reduced respiratory drive and altered the rate of decay in diaphragm

Achieving Lung- and Diaphragm-protective Ventilation Targets: Practical Challenges

Clinical Monitoring

The conceptual approach to lung- and diaphragm-protective ventilation stipulates several different simultaneous targets for ventilation. Clinicians are familiar with adeptly managing oft-competing targets for acid–base homeostasis, oxygenation, and lung protection. Into this mix we have proposed to add yet another target: respiratory effort. Just as developments in arterial blood gas monitoring and respi- ratory mechanics were instrumental to progress in positive pressure ventilation and lung protection, the widespread utilization of accurate and feasible techniques for monitor- ing respiratory muscle effort will be crucial to the devel- opment of lung- and diaphragm-protective ventilation strategies.

Several techniques are already available for clinical use, as described in detail elsewhere.^{49,99} These techniques include esophageal manometry, diaphragm electrical activity mon- itoring, diaphragm ultrasound, and noninvasive airway pressure measurements. The pros and cons of each of these techniques are summarized in table 1. Some of these tech- niques require training and great care in their utilization. For example, esophageal manometry requires attention to balloon lling, catheter positioning, and reliable signal acquisition. Excellent reviews on the esophageal manome- try technique are available.¹⁰¹

One monitoring technique that has been employed widely in clinical research but has yet to see routine clinical use is electrical impedance tomography. Electrical impedance tomography provides sophisticated and pow- erful real-time imaging data on the spatial distribution of ventilation; using this technique, it is possible to “see” the maldistribution of stress and strain caused by sponta- neous respiratory effort at the bedside. Electrical imped- ance tomography has the potential to aid clinicians in

Table 1. Monitoring Tools to Ensure Lung- and Diaphragm-protective Conditions during Mechanical Ventilation

Ventilation Parameter	Technique	Description	Pros	Cons
Inspiratory effort	Esophageal and/or gastric manometry	Monitoring esophageal pressure and transdiaphragmatic pressure to directly estimate pressures generated by respiratory muscles	Continuous monitoring	Requires some technical training and specialized equipment (or specific ventilators) for signal acquisition
	Diaphragm electrical activity	Crural diaphragm electromyography to monitor diaphragm activation during mechanical ventilation	Continuous monitoring; easy to place catheter and acquire signal with appropriate training and ventilator	Cannot directly infer pressure generation from electrical activity signal; no established normal values because of interpatient variability
	Diaphragm ultrasound	Direct visualization and measurement of diaphragm thickening	Feasible, point-of-care ultrasound equipment widely available in ICUs	Requires some initial training to acquire competency; provides intermittent rather than continuous monitoring data; a few minutes are required to set up ultrasound and obtain measurement
Global lung stress	Esophageal manometry	The inspiratory increase in the difference between the airway and esophageal pressures (transpulmonary pressure) reflects dynamic lung stress during tidal ventilation	Continuous monitoring	Requires some technical training and specialized equipment (or specific ventilators) for signal acquisition
Regional lung stress	Electrical impedance tomography	Visualizes and quantifies regional differences in ventilation to detect pendelluft and maldistribution of stress and strain within the lung	Continuous monitoring with excellent temporal resolution	Spatial resolution does not approximate that of conventional cross-sectional imaging such as CT; requires availability of EIT monitor

CT, computed tomography; EIT, electrical impedance tomography; ICU, intensive care unit.

tailoring protective mechanical ventilation to each individual patient.⁹² A variety of devices is available; ensuring the safety of spontaneous breathing may be an important clinical application for this technology.

Fine-Tuning Respiratory Control by Manipulating Ventilation and Sedation

Achieving lung- and diaphragm-protective targets simultaneously requires the ability to fine-tune respiratory effort so that it is neither absent nor excessive. This may be accomplished in part by manipulating ventilatory support: however, increases in support (to decrease effort) may lead to excessive lung stress, whereas decreases in support (to increase effort) may lead to insufficient ventilation. The other key variable to consider is sedation: depending on the drug and dose used, sedation can significantly impact respiratory effort and pattern and may modify the effect of ventilation on respiratory effort.^{94,105} Sedation strategies generally do not take patient inspiratory effort into account; more research is required to characterize the optimal drug and titration strategy to fine-tune respiratory effort level in combination with ventilator support.

Summary and Future Perspective

Mechanical ventilation can injure the lung and the diaphragm, resulting in substantial morbidity and mortality in critically ill patients. The evidence base underpinning

our mechanistic understanding of these forms of iatrogenic injury suggests that a novel approach to ventilation, integrating both lung-protective and diaphragm-protective considerations, is required. This combined lung- and diaphragm-protective ventilation has the potential to impact the length of ventilation, prevent long-term disability, and increase survival after acute respiratory failure. A lung- and diaphragm-protective strategy will need to ensure safe limits for global lung stress, avoid ventilation inhomogeneity and excessive regional stress, preserve an optimal range of inspiratory effort, and integrate individualized lung recruitment and PEEP titration, all while maintaining adequate gas exchange. Measuring the effects of all elements of this strategy on the diaphragm and the lung requires an important new set of respiratory monitoring tools and new insights into the manipulation of respiratory effort during mechanical ventilation. Monitoring respiratory muscle effort will be essential in the skill set of the intensive care unit physician of the future. Future trials are required to explore whether this novel approach is feasible and effective.

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Competing Interests

The authors declare no competing interests.

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Address correspondence to Dr. Goligher: Toronto General Hospital, 585 University Avenue, Peter Munk Building, 11th Floor, Room 192, Toronto, Ontario, Canada M5G 2N2. ewan.goligher@utoronto.ca. Information on purchasing reprints may be found at www.anesthesiology.org or on the masthead page at the beginning of this issue. ANESTHESIOLOGY's articles are made freely accessible to all readers, for personal use only, 6 months from the cover date of the issue.

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