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Advances in Ventilator Management for Patients with Acute Respiratory Distress Syndrome

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KEYWORDS
- ARDS
- PEEP
- Prone positioning
- Neuromuscular blockers

KEY POINTS
- Despite decades of research, acute respiratory distress syndrome (ARDS) is not always recognized in ICU practice.
- Low-tidal-volume ventilation, plateau pressure limitations, driving pressure targets, and mechanical ventilation in the prone position for moderate–severe ARDS are strategies shown to minimize harm associated with mechanical ventilation.
- The risk–benefits of spontaneous breathing, optimal and individualized positive end-expiratory pressure titration, and oxygen therapy thresholds are areas of ARDS research that continue to evolve and likely have individualized targets for different phenotypes of patients with ARDS.

INTRODUCTION

The supportive care management of the acute respiratory distress syndrome (ARDS) has remained a cornerstone of therapy in critical care medicine for well over 50 years. Over time, we have seen an evolution in our understanding of the injured lung, its interaction with invasive mechanical ventilation and the optimal approach to supporting the lung while minimizing harm. Recent years have unveiled the heterogeneous nature of ARDS emphasizing the need to more accurately define sub-phenotypes. Given this, research is ongoing to better refine and individualized mechanical ventilatory support (eg, optimal selection of positive end-expiratory pressure [PEEP] and thresholds when spontaneous breathing efforts could be harmful). In this review, we highlight the current evidence-based ventilatory management practices for patients with ARDS and explore some experimental novel ventilation targets (Fig. 1).

What Is Acute Respiratory Distress Syndrome?

ARDS is the clinical syndrome consisting of acute hypoxemia, reduced lung compliance, and pulmonary infiltrates which was first described in 1967.\textsuperscript{1} The Berlin definition\textsuperscript{2} classifies ARDS as respiratory failure that occurs acutely (within 7 days) and is characterized by the onset of bilateral chest radiograph opacities not fully explained by cardiac failure. The severity of the syndrome is classified as mild, moderate, or severe according to the degree of hypoxemia defined by PaO\textsubscript{2}/FiO\textsubscript{2}. Importantly, this must be fulfilled with patients receiving at least 5 cm H\textsubscript{2}O of positive pressure.
The severity of ARDS correlates strongly with mortality. Contemporary estimates of ARDS mortality were recently described in the LUNGSAFE observational study, where investigators found approximately 25% mortality in mild ARDS and up to 45% in the severe subgroup. More recently and partially driven by the COVID-19 pandemic, there has been an interest in expanding the definition of ARDS, acknowledging the limitations of arterial blood gas measurements in resource-limited settings, and the consideration of high-flow nasal oxygen and noninvasive ventilation as equivalents of mechanical ventilation to satisfy diagnostic criteria.

Ventilator-Induced Lung Injury

The focus of mechanical ventilatory practices in ARDS centers around minimizing ventilator-induced lung injury (VILI). VILI is the consequence of trauma to the lungs secondary to high-tidal-volume ventilation (volutrauma), excessive ventilating pressure (barotrauma) and the cyclic opening and closing of alveoli during tidal ventilation (atelectrauma). These deforming and pathologic stresses to the lung architecture cause the release of inflammatory mediators into the systemic circulation (biotrauma). The translocation of these systemic inflammatory mediators has been implicated in the causal pathway leading to multisystemic organ failure and death that is associated with VILI and ARDS.

Ventilatory Management of Acute Respiratory Distress Syndrome

Lung-protective ventilation

The mainstay of lung-protective mechanical ventilation derives from the seminal ARDSnet trial in 2000. This randomized trial compared ventilating patients at 6 mL/kg of predicted body weight (PBW) 12 mL/kg. Compared with the higher tidal volume (VT) group, patients ventilated at 6 mL/kg PBW had improved survival, demonstrated important secondary objectives including shortened duration of mechanical ventilation, attenuated systemic inflammation, and reduced the incidence and amount of extrapulmonary organ failure.

Tidal Volume: More than just 6 mL/kg

Although 6 mL/kg of VT compared with 12 mL/kg has been demonstrated to be effective in
preventing VILI,\(^9\) the ideal \(V_T\) strategy in ARDS is unknown. In fact, even when \(V_T\) is normalized to a patient’s PBW, there is experimental evidence to suggest that this too does not guarantee lung protection.\(^{10,11}\) Conceivably, therefore, ventilating patients below 6 mL/kg may confer even greater lung protection. Two human studies in patients on extracorporeal life support for severe ARDS, in which \(V_T\) was below 6 mL/kg demonstrated a reduction in systemic inflammatory mediators.\(^{12,13}\) However, whether this translates to clinical benefit remains unclear. A recent trial employing the use of extracorporeal CO2 removal to facilitate lower tidal volume ventilation (≤3 mL/kg) did not confer a survival advantage compared with conventional ventilation and there were increased adverse events associated with the device. The trial was stopped early due to futility and feasibility following recommendations from the data safety monitoring committee. More research is needed to evaluate the population, approach, and potential utility to lowering tidal volumes less than 6 mL/kg.

**A physiologically derived ventilation target: Driving pressure**

A pressure- and volume-limited ventilation strategy neglects the individual respiratory pathophysiology and heterogeneity of ARDS patients. To account for this variability in respiratory mechanics across ARDS patients, investigators evaluated driving pressure (\(\Delta P\)) as a predictor variable for mortality in ARDS. Compared with set tidal volume, \(\Delta P\) is a tidal volume normalized to an individual patient’s lung compliance. \(\Delta P\) is measured as the difference between Pplat and total PEEP. There are a few caveats that should be mentioned to ensure the measurement of this value is accurate: the patient should be completely passive on the ventilator (either receiving neuromuscular blockade or deep sedation) and an end-expiratory occlusion maneuver should be performed to ensure there is no additional auto-PEEP.

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\Delta P = P_{\text{plat}} - P_{\text{PEEP total}}
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Amato and colleagues performed an individual patient meta-analysis of more than 3000 patients with ARDS from several randomized controlled trials (RCTs) to evaluate the association between \(\Delta P\) and survival in ARDS.\(^{14}\) Importantly, these investigators found that increases in \(\Delta P\), even in those patients receiving conventionally protective Pplat, were associated with increased mortality. Furthermore, \(\Delta P\) was found to be the strongest predictor associated with outcome in ARDS patients, potentially explained by the physiologic and individualized nature of this variable.\(^{14}\) In this analysis, there was an association toward increased mortality as \(\Delta P\) became greater than approximately 14 cmH\(_2\)O. A pilot, RCT was recently published which established that a \(\Delta P\)-targeted ventilation approach was safe, feasible, and laid the foundation for a future large-scale RCT.\(^{15,16}\)

**Positive End-Expiratory Pressure Titration and Lung Recruitment**

**Physiologic impact of positive end-expiratory pressure**

PEEP has been a cornerstone of ventilator management for ARDS since its first description.\(^{1,17}\) However, defining the optimal level of PEEP has been challenging.\(^{18}\) This is likely due to the fact that no one PEEP strategy is generalizable to all patients with ARDS. PEEP is used primarily to improve oxygenation and prevent atelectrauma (the cyclic opening and closing of alveoli that can occur during tidal ventilation) that contributes to VILI.\(^{5,19}\) Further mechanistic benefits of PEEP include recruiting collapsed alveoli, thereby improving overall gas exchange,\(^{20}\) reducing intrapulmonary shunt, and reducing stress and strain on the lung.\(^{21}\) By recruiting additional alveolar units to participate in gas exchange, this improves the homogeneity of ventilation and reduces VILI by mitigating the effects of stress multipliers on the lung.\(^{22}\)

PEEP can have a major effect on circulatory function and plays a key role in complex heart–lung interactions in mechanically ventilated patients. PEEP can affect both left and right heart function and depending on volume status and ventricular function can have either beneficial or detrimental effects on cardiovascular and respiratory function. With respect to the compromised left ventricle, PEEP can improve cardiac function by reducing afterload, although PEEP typically increases right ventricular afterload.\(^{23}\) Conversely, higher levels of applied PEEP via reduction in venous return and therefore preload can significantly reduce cardiac output.\(^{24}\)

**Recruitment maneuvers**

Predicated on the physiologic basis that atelectasis is a major contributor to VILI, an “open lung” approach has been advocated for the management of patients with ARDS.\(^{25}\) One such way to maximally open the lung units is to perform a “recruitment” maneuver. Using a sustained increase in airway pressure, alveolar units are opened, and then a certain amount of applied PEEP is maintained to keep the lungs “open.”\(^{26}\) Two commonly described approaches to delivering a recruitment maneuver involve a sustained inflation and “staircase” increase in positive
pressure. Typically, a sustained inflation recruitment maneuver may be executed as a set applied PEEP for a fixed time (30 cm H₂O for 30 seconds). The staircase maneuver involves progressive increased airway pressure while maintaining a constant driving pressure up to peak airway pressure of approximately 40 to 60 cm H₂O. Although recruitment maneuvers may serve to open atelectatic lung units to improve oxygenation, they may also lead to overdistension or compromise in cardiac output. The overall benefit achieved (improving oxygenation vs overdistension and decrease in cardiac output) depends on the overall recruitable ability of the lung. Being able to predict which patients will have a favorable response is sometimes difficult to determine at the bedside.

**Clinical evidence guiding recruitment maneuvers and positive end-expiratory pressure**

Although it has been at least a decade since the publication of RCTs evaluating high versus low PEEP strategies, there is still no clear evidence for the guidance of PEEP in the contemporary management of ARDS. The ALVEOLI trial enrolled 549 patients to receive either high PEEP (mean PEEP 13.2 ± 3.5 cm H₂O) or low PEEP (mean PEEP 8.3 ± 3.2 cm H₂O) in patients with ARDS. The lung open ventilation study (LOVS) enrolled 983 patients randomized to high (mean day 1 PEEP 15.6 ± 3.9 cm H₂O) or low (mean day 1 PEEP 10.1 ± 3.0 cm H₂O) PEEP strategy. Finally, the EXPRESS trial randomized 767 patients to a moderate PEEP strategy (5–9 cm H₂O) or titrated PEEP to reach a Pplat of 28 to 30 cm H₂O (mean PEEP 15.8 ± 2.9 cm H₂O). All studies individually found no difference in mortality between higher and lower PEEP strategies. However, in a 2299 meta-analysis, high PEEP to 30 cm H₂O (mean PEEP 15.8) or titrated PEEP to reach a Pplat of 28 to 30 cm H₂O (mean PEEP 15.8 ± 2.9 cm H₂O). All studies individually found no difference in mortality between higher and lower PEEP strategies. However, in a 2299 meta-analysis, high PEEP was associated with a mortality benefit across the subgroup of patients with moderate–severe ARDS. An RCT of high-intensity recruitment maneuvers, the ART trial, was published in 2017. This trial randomized 1010 patients with moderate or severe ARDS to either a control arm of low PEEP or an experimental arm of lung recruitment maneuvers followed by a decremental PEEP trial incorporating compliance measurements to determine optimal PEEP. The primary outcome of 28-day mortality was higher in the experimental (55%) compared with the control group (49%) contrary to the original hypothesis.

It has been theorized that the excess mortality rate in the experimental arm may be explained by at least two physiologic processes. First, the recruitment maneuvers in the protocol may have been both excessive and prolonged. Peak pressures upwards of 60 cm H₂O and total recruitment maneuver time for as long as 25 minutes may have contributed to barotrauma and VILI, leading to the increased mortality rates. The second concern in this trial was the high proportion of patient–ventilator dyssynchrony in the experimental group. These dyssynchronies have the potential to lead to breath stacking and double triggering, which, effectively, can double tidal volume and/or peak pressures and precipitate further lung injury.

Finally, a reevaluation of high versus low PEEP strategies categorized patients with moderate-to-severe ARDS into hyperinflammatory versus non-hyperinflammatory subphenotypes. The impact of PEEP strategy differed by phenotype for mortality, ventilator-free days, and organ-failure-free days.

Although several questions remain on the contemporary application of PEEP in ARDS, there are several emerging, physiologically based methods proposed to enable clinicians to apply individualized PEEP to their patients.

**The future: Personalized positive end-expiratory pressure selection**

**Esophageal pressure**

Contemporary ventilator management and guidelines for mechanical ventilation target airway Pplat as surrogates for alveolar distending pressure. Airway pressure, however, reflects the sum of the distending pressures of the lungs and the chest wall. The use of esophageal pressure (Pes) manometer allows for the estimation of pleural pressure and therefore allows for the partitioning of lung and chest wall distending pressures.

Measurement of Pes during mechanical ventilation has been a technique commonly used in the research setting but has had sparse clinical uptake. Pes estimates the changes in pleural pressure and therefore allows estimation of transpulmonary pressure, calculated as the difference between Pplat and Pes. Pes tracings can be used to individually understand and titrate mechanical ventilatory support in patients with ARDS.

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P_{\text{tp}} = P_{\text{aw}} - P_{\text{es}}
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The most commonly known method to estimate pleural pressure and calculate transpulmonary pressure is by directly estimating pleural pressure from absolute values of Pes. The absolute value of the Pes method relies on the assumption that Pes is a direct estimate of pleural pressure. A pig and human cadaver study found that absolute measured Pes accurately reflects local pleural pressure in the mid to dependent lung regions, where atelectasis and lung
collapse typically occur in ARDS. Thus, titrating PEEP to absolute Pes is physiologically sound, and two RCTs of this approach demonstrated physiologic benefits, but did not demonstrate survival advantage in ARDS patients.

An alternative approach is using airway Pplat and the elastance ratio of chest wall to the respiratory system. The ratio of chest wall to respiratory system elastance determines the fraction of airway driving pressure consumed to inflate the chest wall, thought to be non-harmful to the lungs. An experimental study found that transpulmonary pressure calculated from the elastance ratio reasonably reflects transpulmonary pressure in the nondependent “baby” lung where it is most vulnerable to VILI.

Perhaps applying both approaches in prospective trials may translate into improved outcomes in patients with ARDS. Pes measurements also have a role in the ARDS recovery phase to monitor spontaneous breathing and the assessment of patient–ventilatory asynchronies.

Recruitment-to-inflation ratio A novel, single-breath maneuver, termed the recruitment-to-inflation (R/I) ratio to assess lung recruitment, was recently described in non-COVID ARDS. Using a drop in PEEP over a single-breath maneuver, investigators measured recruited lung volume over the given range of PEEP change. Mathematically, the R/I ratio represents the proportion of volume distributed to the recruited lung compared with that volume distributed to the baby lung with changes in PEEP. In other terms, the R/I ratio can help clinicians separate patients who may benefit from higher PEEP (recruitment of collapsed alveoli) versus over-distending lung units that are already open (potentially injuring the baby lung). A small prospective study in 24 patients with COVID-related ARDS supported this finding. A multicenter, prospective RCT comparing traditional PEEP titration with PEEP–FiO2 tables versus PEEP based on the R/I ratio in both COVID and non-COVID ARDS is currently recruiting patients (NCT03963622).

High-frequency oscillation High-frequency oscillatory ventilation was a strategy previously evaluated across patients with moderate–severe ARDS. It was hypothesized that an approach that focuses on optimal lung recruitment with minimal tidal volumes may be the most “lung-protective” approach to ventilation. In two large randomized trials across patients with moderate–severe ARDS, high-frequency oscillation, compared to the standard of care (conventional ventilation targets or an open lung ventilatory strategy), did not improve mortality. In an individual patient meta-analysis, however, at a \( \text{Pao}_2/\text{FiO}_2 \) threshold below 64mm Hg, there was a signal toward benefit with the use of high-frequency oscillation.

To Open the Lung or Not

Strategies aimed at fully recruiting or “opening” the lung through recruitment maneuvers, oscillatory ventilation, or higher PEEP strategies have consistently lacked translation to clinically meaningful improvements in patient outcomes. However, many of these studies adopted an approach to opening the lung independent of patient’s individual ARDS physiology. Maximal inflation across all patients with ARDS may not be the right approach for all patients. Emerging evidence suggests that the collapsed lung may not be always harmful and may in certain settings be associated less inflammatory compared with aerated lung units.

Future research evaluating optimal mechanisms of opening/recruiting the lung needs to focus on the identification of which patients would benefit from an open lung strategy and pragmatic methods to execute this at the bedside.

Oxygen Titration

Optimal oxygen thresholds in the setting of ARDS have emerged as a topic receiving much attention in recent years. Liberal oxygen targets (hyperoxia/hyperoxemia), conservative oxygen targets, and permissive hypoxia have all been evaluated yielding conflicting results. The inconsistent findings are likely related to heterogeneous populations being evaluated with different intensities of illness and organ injuries present.

Hyperoxia and hyperoxemia have been associated with local and systemic toxicities. Excess oxygen can result in the development of reactive oxygen species which can precipitate apoptosis, vasoconstriction, inflammation, and multisystem failure. The specific oxygen thresholds and durations at which this may induce harm have yet to be determined. In the OXYGEN-ICU trial of 480 critically ill patients (66%–68% mechanically ventilated), lower oxygen targets (94%–98%, \( \text{PaO}_2 \) 70–100) were associated with lower mortality compared with a liberal oxygen strategy (97%–100%; \( \text{PaO}_2 \) up to 150 mm Hg). However, this study was not restricted to patients with ARDS and it was stopped early raising concerns about the potential overestimation of treatment effect. In the ICU-ROX trial, 965 mechanically ventilated patients were randomized to a conservative oxygen strategy (91%–96%) compared with a liberal approach (91%–100%). With the exception of patients admitted with anoxic brain injury following
cardiac arrest (who did worse overall), there was no difference in mortality or ventilator-free days across the conversative versus liberal strategies. The hypothesis behind the greater harm in the anoxic brain injury group may be related to conservative oxygen-reducing secondary brain injury compared with a more liberal approach. Limitations of the study include concern for heterogeneity of treatment effect across the mechanically ventilated population (ie, potential harm of liberal oxygen in the anoxic encephalopathy cohort vs potential benefit in the septic cohort). It is also important to note that the “liberal arm” of the ICU-ROX trial was not one of “hyperoxia.” Furthermore, these trials did not focus on patients with ARDS.10

The HOT-ICU trial randomized 2928 critically ill patients with hypoxic respiratory failure (57%–59% invasive ventilation, 13% ARDS) to a lower oxygen target (Pao2 60 mm Hg) versus a higher oxygen target (Pao2 90 mm Hg).54 Neither difference was found in 90-day mortality nor any of the secondary outcomes evaluated. This was in contrast to the LOCO2 trial where 201 patients with ARDS were randomized to a conservative oxygen target (Pao2 between 55 and 70 mm Hg) compared with a liberal target (90–105 mm Hg).55 There was no difference in 28-day mortality; however, the trial was stopped early (201/850 original sample size) because of an increased incidence of mesenteric ischemia in the conservative group (5 vs 0). They theorized that pulse oximetry may not be precise enough to avoid unrecognized hypoxic events in those most at risk. There was also a lower incidence of prone positioning in the treatment group which has been shown to improve mortality in ARDS. The trial was also terminated early which might have led to inaccurate estimations of treatment effect.

The ongoing MEGA-ROX trial (NCT01642498) is a platform trial that attempts to further evaluate the question of safe oxygen thresholds and address treatment effects across different populations of critically ill patients. As the evidence continues to evolve, given the totality of the evidence thus far, hyperoxia and hyperoxemia should be avoided, a lower limit saturation of 90% to 91% is likely acceptable and targeting a Pao2 between 70 and 100 mmHg has been demonstrated to be safe across patients with ARDS.

**Adjunct Therapies to Optimize Mechanical Ventilation**

**Prone positioning**

Prone positioning is one of the few interventions with mortality benefit in patients with moderate–severe ARDS (Fig. 2).56 Prone positioning can improve both oxygenation and ventilation (CO2 clearance through a variety of mechanisms. Oxygenation is improved principally through improvement in the homogeneity of ventilation and perfusion matching, alveolar recruitment, and alterations in the physical mechanics of the chest wall.57 Alveolar ventilation may improve with prone positioning because of the above mechanisms as well, which would manifest in a reduction in Paco2.

Although several small trials and physiologic observations supported the concept of prone positioning, the seminal trial informing practice today was PROSEVA. The PROSEVA trial randomized 474 patients with moderate–severe ARDS (P/F < 150 mm Hg) to prone positioning for at least 16 hours per session or to be continuously ventilated in the supine position. Both 28 day and 90 day mortality rates were significantly reduced in the prone positioning group (the 28-day mortality was 16.0% in the prone group and 32.8% in the supine group [P < 0.001]; 90-day mortality was 23.6% in the prone group versus 41.0% in the supine group [P < 0.001]).56 Despite these results, clinical implementation of prone positioning remains poor, as demonstrated in the LUNGSAFE study, where only 16% of patients received prone positioning.57 Despite concerns of complications58 (pressure sores, loss of central lines, or endotracheal tubes), there was no such observed difference in the PROSEVA trial.56

Prone positioning in spontaneous breathing, non-intubated patients has gained popularity in the context of the COVID-19 pandemic. One clinical trial of 1126 patients requiring HFNC assessed whether prone positioning improved treatment failure as defined as intubation or mortality by 28 days.59 The primary outcome of interest in this trial was death or intubation at 28 days. Treatment failure (mainly driven by intubation) occurred in 223 (40%) of 564 patients assigned to awake prone positioning and HFNC and 257 (46%) of 557 patients assigned to standard care with HFNC (relative risk 0.86 [95% CI 0.75–0.98]). Physiologic variables (respiratory rate, ROX index, and oxygenation) all improved when moving from the supine to prone position. Importantly, the rates of adverse events were not different between the two groups. More trials are underway evaluating the criteria for consideration of prone positioning and thresholds for intubation.

**Neuromuscular blocking agents to facilitate lung-protective ventilation**

The contemporary role of neuromuscular blocking agents (NMBAs) in ARDS is evolving. Now more than a decade since its publication, the
ACURASYS trial was the first major RCT which demonstrated a mortality benefit with the use of NMBAs in early ARDS. It randomized 340 patients with moderate–severe ARDS (P/F < 150 mm Hg) to 48 hours of NMBA infusion with cisatracurium versus placebo. Importantly, both groups received deep sedation. Investigators demonstrated improved 90 day survival in the NMBA group (23.6% in the prone group vs 41.0% in the supine group \(P < 0.001\)).

The postulated physiologic and survival benefit of NMBA administration are centered around the reduction of patient–ventilator dyssynchrony. It is hypothesized that patient–ventilator dyssynchrony can precipitate VILI due to variable V̇T and alveolar distending pressure, with increased risk of breath-stacking. This can lead to further barotrauma, atelectrauma, and biotrauma, resulting in a release of inflammatory mediators and end-organ dysfunction. Other physiologic benefits may include reduced respiratory and skeletal muscle oxygen consumption, leading to an increase in mixed venous oxygen and, possibly, anti-inflammatory effects. Despite this sound physiologic rationale and RCT evidence, the clinical use of continuous NMBA in ARDS is not widespread. The LUNGSAFE study demonstrated that NMBA was used in approximately 7%, 18%, and 38% of patients with mild, moderate, and severe ARDS, respectively. Reservation surrounding adoption may be attributable to concerns of deep sedation in the control arm, which one may argue does not reflect more contemporary sedation targets.

More recently, and based on evolving clinical practices since the publication of ACURASYS, the reevaluation of systemic early neuromuscular blockade (ROSE) trial was performed with a similar intervention arm as ACURASYS. It differed significantly from ACURASYS, however, in the in the timing of enrollment and the design of the control arm. Patients with moderate–severe ARDS (P/F < 150 mm Hg) were randomized to either a deep-sedation arm with 48 hours of NMBA or a light sedation strategy arm. Contrary to ACURASYS, ROSE did not demonstrate a benefit in 90 day survival with routine and early application of NMBA. One possible explanation for the differences in the study findings is that deep sedation without paralysis may precipitate patient–ventilator dyssynchrony, which would not be present under conditions of paralysis, and may be significantly less in cases of light-sedation.
was shorter compared with ACURASYS suggesting that patients in ACURASYS may represent a subset with more “persistent” ARDS. Current guidelines recommend against the routine use of NMBA across all patients; however, NMBA can be considered when paralytics are deemed necessary to facilitate lung-protective ventilation, address refractory hypoxia or hypercapnia, in the setting of ventilator asynchrony.  

**Spontaneous Breathing in Patients with Acute Respiratory Distress Syndrome**

**Risks and benefits of spontaneous breathing**

Early in the course of ARDS, MV, supported by sedation, and sometimes NMBA will completely suppress patient respiratory drive and effort. Passively ventilated patients in this context are at increased risk of atelectasis and complications of deep sedation including diaphragm and respiratory muscle disuse and atrophy.66–68 Promoting spontaneous ventilation may mitigate these risks.

However, there may be a threshold of spontaneous ventilation that becomes injurious. Spontaneous ventilation that is excessive can propagate patient self-inflicted lung injury (P-SILI).69 The mechanisms underlying this have some similarities to VILI.70 Vigorous spontaneous breathing with large VT can elevate global and regional lung stress, which precipitates the risk of volutrauma.71 Importantly, even if VT is limited by using volume-controlled ventilation, spontaneous effort can still induce injury by increasing local lung stress and overdistension.72,73 These vigorous efforts can simultaneously induce diaphragm and respiratory muscle injury,68 which can delay liberation from mechanical ventilation and lead to adverse clinical outcomes.66,67 Finally, exaggerated spontaneous breathing effort can lead to, or worsen patient–ventilator dyssynchrony, as a consequence of double triggering or flow starvation.74 It is therefore increasingly recognized that monitoring of patient effort during mechanical ventilation is important to identify the risk of P-SILI.74

**Monitoring patient effort during mechanical ventilation**

Basic interpretation of ventilator waveforms is insufficient in detecting potentially injurious patient efforts for a variety of reasons.74 For example, airway pressure and flow provide limited direct information about inspiratory effort, but close inspection of flow deformations may be suggestive of patient effort.71 Furthermore, airway pressure, particularly in the presence of respiratory effort, may underestimate the increased transpulmonary pressure generated by negative pleural pressure swings from the contraction of the inspiratory muscles.75

Pes measurements can be used to assess respiratory intensity of spontaneously breathing patients.42 Unfortunately, Pes measurement is not routinely used at the bedside due to technical challenges, interpretation, and time-constraints.71 Two simpler techniques have been described to estimate patient drive and effort. First, the airway occlusion pressure (P0.1) is the drop in airway pressure in the first 100 milliseconds after the onset of inspiration during an end-expiratory occlusion of the airway.76 This measurement has gained recent interest as it is not affected by patient’s response to the occlusion, it is independent of respiratory mechanics and not impacted by some degree of respiratory muscle weakness.77 Although thresholds vary, a P0.1 between 1 and 4 cm H2O may be considered a safe drive, and below or above these values may be reflective of excessively low or high drive to breathe, respectively.78 Second, an end-expiratory occlusion maneuver (Pocc) in spontaneously breathing patients can be used to estimate the pressure generated by the respiratory muscles.71 Pocc can also be used to estimate dynamic transpulmonary driving pressure, which is a measure of the dynamic mechanical stress applied to the lung during inspiration.79 Although these measurements require prospective analysis, at the bedside, applying a simple end-expiratory hold maneuver, it may be reasonable to consider an estimated muscular pressure > 15 cm H2O and estimated dynamic transpulmonary driving pressure > 20 cm H2O as potentially markers of excessive and potentially injurious efforts.79 There is active ongoing research into prospectively evaluating these measurements (P0.1 and Pocc) to titrate ventilation and sedation to achieve safe spontaneous breathing in mechanically ventilated adults.

**SUMMARY**

ARDS supportive care has evolved over the past few decades as our understanding of injurious interactions between the ventilator and the lung has improved. Increasingly, the heterogeneous nature of ARDS and individualized lung physiology has proven that a single ventilatory strategy (eg, PEEP, recruitment) is not generalizable to all patients. The future of ARDS ventilatory practice will center around more individualized treatment strategies and targets taking into consideration the subtype of ARDS and evolution of physiology over the course of the disease.

**DISCLOSURE**

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