Objectives

- Understand the physiologic mechanisms of ventilator-induced lung injury (VILI)
- Understand initial ventilator management to prevent VILI in acute respiratory failure/acute lung injury
- Understand ongoing monitoring parameters and subsequent adjustments and adjunctive therapies to treat VILI

INTRODUCTION

Acute respiratory distress syndrome (ARDS) remains quite common and highly morbid, with an annual incidence of more than 170,000 cases in the United States alone and a mortality that is often greater than 30%. Although our understanding of ARDS pathophysiology has improved significantly, with pathways of injury, coagulation, and inflammation now elucidated, there remain no specific drug therapies. Supportive care with mechanical ventilation, therefore, remains the mainstay of therapy for ARDS. However, it is increasingly recognized that mechanical ventilation is an independent cause of lung injury and can worsen preexisting ARDS. Careful attention to management of the mechanical ventilator is therefore essential to reducing ARDS-associated morbidity and mortality.

ADULT CASE VIGNETTE

A 62-year-old woman with a history of morbid obesity and rheumatoid arthritis with associated interstitial lung disease presents with a four-day history of fever, myalgia, productive cough, and shortness of breath. In the emergency department, chest radiograph shows bilateral airspace infiltrates consistent with ARDS. Rapid diagnostic testing is positive for influenza. Broad-spectrum antibiotics and antiviral therapy are initiated. She remains hypoxemic despite the use of high-flow nasal cannula for oxygenation. Endotracheal intubation is performed urgently, and mechanical ventilation is initiated on volume control mode, with tidal volume (Vt) set at 6 mL/kg ideal body weight (IBW), rate 20 breaths/min, fraction of inspired oxygen (FiO₂) 1.0, and positive end-expiratory pressure (PEEP) 8 cm H₂O. Her measured end-inspiratory plateau pressure (Pplat) is 36 cm H₂O. She remains hypoxemic, with arterial partial pressure of oxygen (PaO₂) 48 mm Hg on FiO₂ 1.0.

Esophageal manometry is performed, revealing an end-expiratory transpulmonary pressure of −4 cm H₂O and...
end-inspiratory transpulmonary pressure of +13 cm H₂O. On a PEEP of 15 cm H₂O, her respiratory system compliance (Crs) was also noted to be optimized (stress index 1.03) compared to both higher and lower PEEP (stress index 1.19 and 0.78, respectively). Based on these measurements, the PEEP is increased to 15 cm H₂O. The patient is also administered neuromuscular blocking agents and placed in the prone position. With these interventions, subsequent improvements in oxygenation are noted. She is successfully extubated on day nine of intubation.

**PEDIATRIC CASE VIGNETTE**

A previously healthy eight-year-old girl presents to the emergency department with a two-day history of fever, cough, poor oral intake, and general malaise. Chest radiograph shows significant bilateral airspace disease without focal infiltrate. Rapid diagnostic testing is positive for influenza. Blood cultures are obtained, along with a respiratory polymerase chain reaction viral assay. Broad-spectrum antibiotics and antiviral therapy are initiated. She is admitted to the pediatric intensive care unit (ICU) on noninvasive ventilatory support. Over the next few hours, her work of breathing worsens, and the Fio₂ requirement increases. She is intubated and placed on synchronized intermittent mandatory ventilation in pressure control mode. The peak inspiratory pressure is set at 18 cm H₂O above PEEP (10 cm H₂O). The mean airway pressure is 14 cm H₂O. Vt, as measured by a pneumotachometer placed between the ventilator circuit and the endotracheal tube, is 6 mL/kg IBW. Ventilator rate is set at 24 breaths/min, and the Fio₂ is 1.0. The patient’s arterial blood gas analysis shows: pH 7.28, arterial partial pressure of carbon dioxide (Paco₂) 58 mm Hg, Pao₂ 60 mm Hg. The resultant oxygenation index is 23. The respiratory polymerase chain reaction viral study is positive for type A influenza. The patient is sedated with fentanyl and dexmedetomidine infusions but does not receive additional neuromuscular blockade (NMB) after an intubation dose.

Over the next 12 hours, she remains hypoxemic, with the Fio₂ weaned to only 0.80. The oxygenation index remains in the low 20s. A PEEP titration is performed while monitoring oxygenation, hemodynamics, and mixed venous lactate measurements. It is determined that optimal PEEP is 14 cm H₂O. Dynamic compliance improves with the peak inspiratory pressure remaining at 28 cm H₂O, despite the increased PEEP. Over the next four days, the patient’s respiratory process resolves, and she is uneventfully extubated on hospital day eight. She is discharged home four days later on no respiratory support.

**DEFINITION OF ACUTE RESPIRATORY DISTRESS SYNDROME AND TYPES OF VENTILATOR-INDUCED LUNG INJURY**

ARDS is a clinical syndrome defined by the acute onset of bilateral pulmonary infiltrates and hypoxemia not solely attributable to cardiogenic pulmonary edema. The classic pathophysiology is defined by alveolar-capillary membrane breakdown with the subsequent influx of protein-rich plasma, formation of hyaline membranes, and loss of alveolar stability. ARDS can result from a variety of stimuli, including...
trauma, pulmonary or extrapulmonary infection, and other inflammatory conditions such as pancreatitis and blood product transfusion. Most patients require mechanical ventilatory support, either invasively or noninvasively, for hypoxemic respiratory failure.

Although mechanical ventilation can be lifesaving, the very act of ventilating someone via positive pressure can cause and propagate lung injury in a process broadly termed ventilator-induced lung injury (VILI) or ventilator-associated lung injury (VALI). The relative importance of VILI is increasingly recognized, particularly since studies have shown a mortality benefit to specific lung-protective ventilator strategies. Additionally, it is now recognized that VILI can result in ARDS in susceptible patients. As a result, and in the absence of specific drug therapies to prevent and treat ARDS, significant emphasis should be placed on ventilator strategies that protect the lung and minimize secondary damage and inflammation. The two primary theoretical mechanisms of VILI are excess stress, defined in physical terms as the force per unit area, and excess strain, defined as mechanical deformation (in the lung, volume change).

The primary mechanism of lung injury is thought to be overdistention and excess local strain; there is limited evidence that high pressure alone is injurious. However, because high airway pressures often reflect local overdistention, some lung injury is categorized as barotrauma, indicating injury from high pressures. Pneumothorax, pneumomediastinum, and subcutaneous emphysema are all examples of classical barotrauma. Although these are unlikely to occur without regional volume change, there are some sequelae of ventilation at high pressures that are true manifestations of high intrathoracic pressure. These include a potential decrease in cardiac output due to decreasing venous return and an increase in physiologic dead space as alveolar pressure exceeds pleural pressure.

The other large category of VILI is volutrauma, referring to excess volume change, either globally or regionally, that results in injury and increased circulating inflammatory mediators. Volutrauma can result either from the use of large tidal volumes or the delivery of smaller volumes into a heterogeneous lung, resulting in regional overdistention. The risk of volutrauma is particularly high in ARDS, in which there can be a significant reduction in the volume of aerated lung, or functional lung size, sometimes referred to as the "baby lung." There is strong evidence that limiting tidal volumes and scaling them to IBW improves outcomes in ARDS patients, but it remains difficult to measure regional overdistention. Therefore, a number of proxy measurements have been implemented to limit injurious overdistention including driving pressure ($\Delta P$), or $Vt/Crs$), which scales tidal volume to lung volume.

Two other categories of common VILI include atelectrauma and biotrauma. Atelectrauma results from the cyclic opening and closing of lung units, resulting in shear stress and strain in the form of cellular deformation. Although there is some debate about the degree of lung collapse versus the filling of lung units with fluid and cells, the movement of a column of
fluid in and out of alveoli could result in similar shear stress. Based on this theoretical mechanism of injury, and on the experimental observation that ventilation at a low PEEP promotes lung injury, significant attention is focused on preventing derecruitment, or loss of aerated lung volume, with the use of PEEP. Biotrauma refers to the inflammatory cascade that results from mechanical ventilation and that can propagate lung injury as well as other organ failure. It is notable that most patients who die of ARDS do not die from hypoxemia but rather from other organ failure, suggesting that normalizing blood gases may be an insufficient guideline for ventilator strategies.

Other commonly set ventilator parameters include $\text{FiO}_2$ and respiratory rate. Inhalation of hyperoxic gas over a prolonged period has been well demonstrated in animals to cause hyperoxic acute lung injury, and it is suspected that prolonged exposure to a high $\text{FiO}_2$ is injurious in humans as well. Hyperoxia is thought to cause lung injury via increased production of reactive oxygen species and increased oxidative stress. Hyperoxia has previously been demonstrated to cause alveolar epithelial cell death and capillary endothelial dysfunction. There also appears to be a synergistic effect between hyperoxia and strain in promoting lung injury. However, despite convincing animal data for the role of hyperoxia in lung injury, there have been no randomized studies of $\text{FiO}_2$ levels or levels of oxygen saturation in humans with ARDS. In prior studies, it has been difficult to distinguish whether patients worsened because of high $\text{FiO}_2$ or received high $\text{FiO}_2$ because of the severity of their illness. It is nevertheless reasonable to attempt to use the minimum necessary $\text{FiO}_2$ to maintain safe oxygenation ($\text{PaO}_2 > 55$ mm Hg).

When setting the respiratory rate on the ventilator, the primary concern should be maintenance of adequate minute ventilation, which may be a challenge with low Vt. There are not thought to be any adverse sequelae to the frequency of breathing normally used in mechanically ventilated patients (respiratory rate 10–35 breaths/min), although in patients with obstructive disease, a higher respiratory rate may result in more dynamic hyperinflation and the development of intrinsic PEEP. However, most patients with ARDS without underlying obstructive disease have normal airway resistance, and intrinsic PEEP is absent or minimal across a range of breathing frequencies.

The overall lung-protective strategy, therefore, focuses on minimizing regional and global overdistention and reducing cyclic opening and collapse while using the minimal necessary $\text{FiO}_2$. This lung-protective strategy, often summarized as an “open lung” approach, often comes at the cost of deep sedation, which is increasingly recognized to be associated with poor outcomes, including prolonged weakness (i.e. critical illness myopathy), impaired functional status, and adverse cognitive and psychological outcomes. However, there remains strong evidence for improved outcomes with lung-protective ventilator settings. For example, there is epidemiologic evidence for a decreased incidence of iatrogenic ARDS since the standardization of low Vt ventilation and a growing surgical litera-
ture suggesting a mortality benefit to low Vt ventilation even in those without preexisting lung injury. Strategies for reducing VILI, therefore, remain a cornerstone of therapy for patients with ARDS and other types of respiratory failure.

**INITIAL STRATEGIES TO REDUCE VENTILATOR-INDUCED LUNG INJURY**

**Low Tidal Volume Ventilation**

A landmark study from the ARDS Network (ARDSNet)\(^6\) in 2000 that was designed based on data from similar prior smaller studies, examined the use of low Vt (lung-protective) ventilation in patients with ARDS (\(P_{aO_2}/Fio_2\) ratio \(P/F < 300\) mm Hg). Conventional ventilation approaches traditionally used larger Vts of 10–15 mL/kg of body weight to ensure normalization of the \(P_{aco_2}\) and serum pH. The ARDSNet investigators theorized that these larger Vts, greater than those of healthy people (5–8 mL/kg of body weight), might contribute to excessive distention of the aerated portions of the lung (ie, volutrauma), leading to lung injury through a variety of mechanisms, as had previously been demonstrated in animal studies. Given the large non-aerated dependent portions of the injured ARDS lung, Vt targets might need to be even lower than in normal subjects.

In this double-blind, randomized, controlled trial of 861 patients, subjects in the experimental arm were assigned to an initial targeted Vt of 6 mL/kg (with a range of 4–8 mL/kg) IBW (based on height and gender) and a target Pplat of 30 cm H\(2\)O or less, while those in the control arm received an initial Vt of 12 mL/kg (with a range of 4–12 mL/kg) IBW and a target Pplat of 50 cm H\(2\)O or less. Compared with the control group, those in the lung-protective ventilation group had an absolute reduction of 9 percentage points in the rate of death before a patient was discharged home and was breathing without assistance (39.8% vs. 31.0%, \(p = 0.007\)). Ventilator-free days were also greater in the lung-protective group. Mean Vts were 11.8 mL/kg in the control group and 6.2 mL/kg in the lung-protective group, although there was a less substantial difference in mean Pplats (33 vs. 25 cm H\(2\)O, respectively).\(^6\)

Serum interleukin-6 concentrations (known to play a role in lung inflammation and injury via biotrauma) were lower in the lung-protective arm, despite higher PEEP and Fio\(_2\) requirements and lower P/F. The authors theorized that mortality benefit may have been mediated by a reduction in systemic inflammation and therefore fewer organ failures. The improved outcomes in this study are greater than the benefit seen with any single intervention in any other ARDS study. Lung-protective ventilation has since become the standard of care for patients with ARDS.

Improved outcomes have also been observed in surgical populations receiving lung-protective ventilation.\(^7\) Studies are ongoing to determine the effectiveness of low Vt ventilation in the prevention of ARDS in subjects without evidence of lung injury but with risk factors for its development. While most trials have been performed using volume control ventilation, other modes of ventilation, such as pressure control, may be used with lung-
protective ventilation, but close attention should be paid to the delivered Vt to ensure that it remains within the safe range of 4–8 mL/kg IBW.

In the pediatric population, low Vt ventilation has not been studied in a randomized, controlled fashion. The Pediatric Acute Lung Injury and Consensus Conference (PALICC) recommended the use of Vts in or below the range of physiologic Vts for age/IBW (ie, 5–8 mL/kg).13,14 PALICC further recommended that this range be adjusted based on the patient’s lung pathology and Crs with Vts of 3–6 mL/kg IBW for those pediatric patients with more severe ARDS.14,15 Until more definitive data are available for pediatric ARDS, it seems reasonable to follow the adult-based, low Vt data and the recommendations from PALICC.

**High Versus Low Positive End-Expiratory Pressure**

VILI may occur through a variety of mechanisms, including atelectrauma, or large shear forces produced by repetitive recruitment (opening) and derecruitment (collapse) of alveoli. The functions of PEEP in mechanical ventilation include alveolar recruitment and the prevention of derecruitment, decreased cyclic airway opening and end-expiratory collapse improving ventilation homogeneity, redistribution of extravascular lung water, and protecting lung surfactant, thereby reducing alveolar surface tension. Higher levels of PEEP (greater than 12 cm H₂O) were traditionally avoided because of the risk of hemodynamic instability related to reduced venous return from higher intrathoracic pressure, along with the risk of barotrauma and pneumothorax with high airway pressures. However, the lung-protective ventilation group in the 2000 ARDSNet study6 received higher levels of PEEP and demonstrated no evidence of deleterious effects as a result.

Based on these data, another ARDSNet double-blind, randomized, controlled trial was designed, targeting a low versus high PEEP strategy in patients with early ARDS (P/F < 300 mm Hg).16 Both arms received lung-protective ventilation (Vt goal 6 mL/kg IBW, target Pplat < 30 cm H₂O), but oxygenation targets were obtained using different PEEP and Fio₂ tables. Mean (±SD) PEEP values were 8.3 ± 3.2 cm H₂O in the low PEEP arm and 13.2 ± 3.5 cm H₂O in the high PEEP arm, with no difference in adverse events noted between the groups. There was no difference in the primary outcome of death before discharge home while breathing without assistance (24.9% in the low PEEP arm, 27.5% in the high PEEP arm, p = 0.48). In addition, no difference was seen in the number of ventilator-free days between the groups.

Because this study included all patients with ARDS (mild, moderate, and severe),16 and given the theory that higher PEEP levels would be of greater benefit in those with more severe ARDS, a more recent meta-analysis of three randomized controlled trials of high versus low PEEP strategy, consisting of almost 2,300 patients with ARDS, was performed.17 In addition to
the 2004 ARDSNet study, this analysis included two additional trials, the Lung Open Ventilation trial and the Express study. In the Lung Open Ventilation trial, subjects in the experimental group were allowed a higher maximum Pplat of 40 cm H$_2$O and included recruitment maneuvers and higher PEEP targets than the control group. All subjects received low Vt ventilation. In the Express study, subjects also received low Vts but were randomized to low PEEP (5–9 cm H$_2$O) versus titrating PEEP to achieve a Pplat of 28–30 cm H$_2$O. While no overall difference was seen in hospital deaths between the low and high PEEP strategies in the meta-analysis, a beneficial effect for high PEEP was demonstrated in those with P/F $< 200$ mm Hg (previously defined as ARDS, with P/F 200–300 mm Hg defined as acute lung injury), with a rate of hospital death of 34.1% in the high PEEP group and 39.1% in the low PEEP group ($p = 0.049$). Rates of barotrauma and vasopressor use were similar in the two groups.

Similar to the situation with low Vt ventilation, definite data are lacking for PEEP management in pediatric ARDS patients. PALICC recommended "moderately" elevated levels of PEEP, defined as 10–15 cm H$_2$O, for patients with severe pediatric ARDS, titrated to the observed oxygenation and hemodynamic response. PALICC further recommended that PEEP levels higher than 15 cm H$_2$O may be needed for severe pediatric ARDS, with close attention paid to limiting the Pplat and monitoring markers of oxygen delivery, Crs, and hemodynamics.

### Personalized PEEP Titration

One suspected reason that comparisons of high versus low PEEP strategies have not shown benefit in large studies is that while some patients benefit from higher PEEP, others, with less recruitable lungs, may experience only the adverse effects of overdistention. One strategy to set PEEP in individual patients is, therefore, to identify a PEEP where physiologic parameters are optimized. There are multiple personalized PEEP titration approaches, including esophageal manometry, PEEP titration to best tidal compliance, calculated stress index, and titration of PEEP and Vt to a minimal driving pressure.

The optimal mode for bedside titration of PEEP has not been clearly established in the adult or pediatric population. In a novel, well-designed study conducted at two centers between 2008 and 2011, 51 adult subjects with ARDS received standardized ventilator management with the exception of randomization of the mode of bedside PEEP titration, along with computed tomography of the chest to determine the degree of lung recruitability. All subjects received NMB throughout the study as well as an initial recruitment maneuver followed by low Vt ventilation. Four different PEEP titration strategies were tested, including the oxygenation-based Lung Open Ventilation strategy PEEP/F$\text{IO}_2$ tables (using the higher PEEP table previously studied), esophageal manometry, increasing the PEEP until a Pplat of 28–30 cm H$_2$O was achieved (maintaining Vts at 6 mL/kg IBW), and adjusting PEEP according to the stress index.
Using the Lung Open Ventilation tables, PEEP was lower in those with mild ARDS and higher in those with severe ARDS (8 ± 2 vs. 15 ± 3 respectively, \( p < 0.05 \)), with a weak relationship to lung recruitability \((r^2 = 0.29, p < 0.0001)\). PEEP was similarly high regardless of ARDS severity when the other three strategies were used, with no relationship to lung recruitability.\(^{20}\) Until better data are available to guide the choice of PEEP titration method, the preferred method for any clinician should be based on available local expertise and technology.

**Esophageal Manometry**

Two primary mechanisms of lung injury are volutrauma and atelectrauma, both of which should be reflected in derangements in transpulmonary pressure (defined as the difference between airway opening pressure and Pplat, the distending pressure of the lung). Critically ill patients, particularly those with volume overload, intra-abdominal hypertension, and obesity, can have unpredictable and often elevated pleural and abdominal pressures. This can lead to a net negative end-expiratory transpulmonary pressure, which signifies a net balance of pressures that promotes collapse and possibly atelectrauma. Conversely, if a patient has high end-inspiratory transpulmonary pressure, this signifies a high distending pressure of the lung and possible overdistention.

Esophageal manometry has been proposed as a surrogate for pleural pressure to aid in this decision-making process. Esophageal balloon measurements are limited in their accuracy by cardiac oscillations, esophageal contraction, and the position of the catheter in a gravitationally dependent position potentially under the weight of the mediastinum. Despite these limitations, previous animal and healthy human data suggest that its measurement might be beneficial in the management of mechanically ventilated critically ill patients. A single-center pilot study randomized adult subjects with ARDS to either conventional PEEP titration using ARDSNet tables versus PEEP titration according to esophageal manometry.\(^{18}\)

The trial was stopped after 61 subjects were enrolled because the primary end point of oxygenation at 72 hours was significantly better in the esophageal manometry arm (P/F 280 mm Hg for esophageal manometry, 191 mm Hg for conventional titration, \( p = 0.002 \)).\(^{21}\) Oxygenation was better in the esophageal manometry arm at all time points (24–72 hours), and PEEP was higher in the esophageal manometry group at 72 hours (18 ± 5 for the esophageal manometry group, 12 ± 5 for the conventional titration group, \( p < 0.001 \)). PEEP titration by esophageal balloon resulted in a net positive transpulmonary pressure. There were no signs of overdistention in the esophageal manometry group, despite the overall higher PEEP, and, in fact, Crs was increased in the esophageal manometry group (\( p = 0.01 \)), suggesting a net recruitment of lung. There was also a trend toward improved survival in the esophageal manometry group. Given these promising results, a multicenter randomized clinical trial is currently under way to better elucidate the utility of esophageal manometry in the titration of PEEP in patients.
with ARDS. Notably, the first study compared esophageal manometry to a low PEEP/Fio₂ table whereas the ongoing trial uses a higher PEEP/Fio₂ table for comparison. Unfortunately, similar data are not available in the pediatric population.

**Stress Index**

Stress index is a dimensionless coefficient that describes the slope of the time-pressure curve of the respiratory system. In essence, it describes whether, with a constant change in volume, the change in pressure per unit volume is constant, decreasing or increasing during the inhalation—ie, whether Crs remains stable, increases, or decreases. A value less than 1 indicates improving Crs over the breath, suggesting lung recruitment. A value greater than 1 indicates decreasing Crs over the breath, suggesting lung overdistention. A value equal to 1 reflects stable Crs with neither net recruitment nor net overdistention. In an animal model of lung injury in which a recruitment maneuver was followed by PEEP titration to a target stress index, the stress index values correlated significantly with tidal recruitment and tidal hyperinflation as measured by computed tomography evaluation of lung density (R = 0.917 and R = 0.911, p < 0.0001). The major limitation to this method of PEEP titration remains the availability of software to analyze the airway pressure-time curve.

**Best Tidal Compliance**

Since the goal is to increase PEEP only as long as it provides the benefit of recruitment and without overdistention, one strategy is to titrate PEEP directly to Crs, calculated as \(\text{Crs} = \frac{\text{Vt}}{(\text{PEEP} - \text{Pplat})}\). Using volume control ventilation mode, PEEP is titrated to optimal Crs, which has also been shown to optimize oxygen delivery and minimize shunt fraction and dead space. This strategy was first described decades ago but remains in clinical practice because of the ease of bedside measurements. However, it does require a fully passive patient to obtain reliable Pplat values.

**Driving Pressure**

Since the two determinants of pulmonary overdistention are PEEP and Vt, one method to minimize pulmonary overdistention is a combined titration of both parameters to Crs. One retrospective study of nine adult ARDS trials examined whether driving pressure (\(\Delta P\)), defined as Vt divided by Crs, was associated with outcome. In patients not making spontaneous breathing efforts, \(\Delta P\) is calculated as Pplat minus PEEP. This study demonstrated that, among ventilation variables (PEEP, Pplat, and \(\Delta P\)), \(\Delta P\) was most strongly associated with survival. Elevated \(\Delta P\), even in the context of “protective” Vt and Pplats, was associated with increased mortality. Additionally, changes in PEEP or Vt were correlated with outcomes only if \(\Delta P\) changed as well. The authors theorized that \(\Delta P\) was so strongly predictive of outcomes because it incorporates both the net effect of PEEP (recruitment vs. overdistention) and a measure of whether Vt is appropriately scaled to the proportion of lung available to ventilation or functional lung.
Recruitment Maneuvers

Recruitment maneuvers involve temporarily inducing a higher transpulmonary pressure than that seen with tidal breathing. Similar to PEEP titration, the major limitation to recruitment maneuvers is the risk of barotrauma/pneumothorax and hemodynamic instability (ie, hypotension) related to an elevated mean intrathoracic pressure. There is no standardized approach to conducting a recruitment maneuver. Variations in duration, maximum pressure, and end-expiratory pressure have been reported. This variability, combined with the fact that these maneuvers are usually studied as part of a broader ventilator management strategy, has limited the ability of investigators to detect a clear signal as to their utility for adult or pediatric ARDS patients. In general, the maneuver usually consists of providing approximately 20–60 seconds of 30–40 cm H₂O continuous positive airway pressure before returning to prior tidal ventilation. Some of the studies to date have placed limitations on Vt and Pplat, while others have not.

A 2009 Cochrane review assessed a total of seven trials comprising 1,170 subjects. All seven trials included a recruitment maneuver for the management of mechanically ventilated patients with ARDS. Two of the trials included an alternative ventilator management strategy in addition to the recruitment maneuver (as compared with standard of care). There was no significant difference in 28-day mortality in those who received a recruitment maneuver. Importantly, there was also no difference in rates of barotrauma or hypotension in these pooled data. There were insufficient data on outcomes, such as duration of mechanical ventilation and hospital stay, in the pooled data, but individual studies did not demonstrate a benefit with regard to mortality or duration of mechanical ventilation or hospitalization. In those studies that measured changes in oxygenation following these maneuvers, there was a temporary (maximum time measured from maneuver was 24 hours) improvement in arterial oxygenation. The significance of this change is not clear, since the recruitment maneuver not only may have recruited alveoli for ventilation but also may have caused overdistention and subsequent VILI that became evident more than 24 hours after the maneuver.

Additionally, if a recruitment maneuver is performed without subsequent appropriate PEEP titration, then lung recruitment may be temporary. Additional studies are needed before recruitment maneuvers can be recommended as part of a standardized approach to the ventilator management of adult or pediatric patients with ARDS. It remains unclear whether recruitment maneuvers offer benefit over the more standard approaches to PEEP titration. It also remains unknown whether short-term high transpulmonary pressures may contribute to VILI and whether any such injurious effects outweigh improvements in oxygenation.

High-Frequency Oscillatory Ventilation

Based on the knowledge that repetitive overdistention and alveolar collapse contribute to VILI, a strategy of high-frequency
oscillatory ventilation (HFOV) has been studied in a number of trials. HFOV uses very small Vts (usually 1–2 mL/kg) delivered at very high rates (5–15 breaths/sec). In the past, it had been used as a rescue strategy for those patients with severe ARDS who did not respond to conventional ventilation strategies. A number of early small trials compared HFOV with conventional ventilation (which did not use low Vt ventilation strategies), finding some degree of benefit.

A multicenter, randomized, controlled trial (OSCILLATE)\textsuperscript{25} was conducted in which adult patients with early moderate to severe ARDS (P/F \( < 200 \text{ mm Hg} \)) were assigned to HFOV or lung-protective ventilation, with those in the conventional arm having the ability to cross over to HFOV for salvage therapy. The trial was stopped early on the recommendation of the data-monitoring committee after 548 of the planned 1,200 subjects had been enrolled. The two study groups were well matched, and 12\% of those assigned to conventional ventilation crossed over to receive HFOV. In-hospital mortality was 47\% in the HFOV group and 35\% in the conventional ventilation group, with a relative risk for HFOV of 1.33 (95\% CI, 1.09–1.64, \( p = 0.005 \)).\textsuperscript{25} Higher rates of sedative, NMB, and vasopressor use were noted in the HFOV group. HFOV frequency was maximized to minimize Vts, and mean airway pressures were higher in the HFOV group, potentially providing some explanation for the increased mortality. Based on this and other similar negative studies, HFOV cannot be recommended for first-line treatment of moderate to severe ARDS in the adult population.\textsuperscript{3,26}

The use of HFOV for pediatric ARDS remains controversial. Some pediatric intensivists critique the OSCILLATE study for the high number of patients with sepsis, the relative inexperience with HFOV of many clinicians in the multiple sites, and the significant need for vasoactive agents in the HFOV group. The inclusion of such patients and the use of a high mean airway strategy may explain the increased risk of mortality with HFOV in this adult population.

PALICC recommended that HFOV should be considered as an alternative approach for acute hypoxemic respiratory failure in pediatric patients with moderate to severe ARDS in whom the Pplat exceeds 28 cm H\textsubscript{2}O in the absence of reduced chest wall compliance.\textsuperscript{13,14} Subsequent to the PALICC publication, Bateman et al\textsuperscript{15} reported in a secondary analysis of data from the Randomized Evaluation of Sedation Titration for Respiratory Failure (RESTORE) trial that early HFOV use for pediatric ARDS was associated with a longer duration of mechanical ventilation but without a significant difference in mortality. This study raises the question of whether HFOV per se led to the longer length of ventilation or whether the issue is the current approach to the management of HFOV. Until a randomized, controlled trial is performed in the pediatric ARDS population, the use of HFOV in pediatrics will likely continue to be debated.
Adjunctive Therapies

Prone Positioning

ARDS is a disease characterized by heterogeneous lung parenchyma, with the majority of patients having a vertical and anatomic ventilation gradient with decreasing ventilation both in the nondependent-to-dependent axis and in the cephalad-to-caudad axis. Studies have demonstrated that up to 70% of patients with ARDS placed in the prone position have improvements in oxygenation with this intervention. Proposed explanations for this phenomenon include increased end-expiratory lung volume, better ventilation-perfusion matching, improved regional ventilation, and less compressive effect of the mass of the heart on the lower lobes. However, multiple previous randomized trials and meta-analyses failed to consistently show an improvement in mortality with prone positioning.

In a 2013 multicenter, randomized, controlled trial (Proning Severe ARDS Patients [PROSEVA]) of patients with early (less than 36 hours), moderate to severe (P/F < 150 mm Hg) ARDS, 466 subjects were assigned to undergo prone positioning for at least 16 hours per day versus remaining supine throughout their course. Both groups received a lung-protective ventilation strategy, and standard ICU beds were used for all patients. Prone treatment was stopped based on improvements in oxygenation and/or complications that occurred during prone positioning that necessitated immediate stoppage. The groups were well matched at baseline. Twenty-eight-day mortality was 16.0% in the prone group and 32.8% in the supine group ($p < 0.001$), with a hazard ratio of 0.39. Similar improvements in mortality were noted at 90 days. Patients in the prone group were extubated sooner and had more ventilator-free days than those in the supine group. Importantly, rates of adverse events such as unintended extubation or removal of catheters were similar in the two groups, with the supine arm actually having an increased rate of cardiac arrest compared with the prone arm. Potential explanations for the unprecedented mortality benefit in this study include selection of sicker patients, a threshold effect of longer prone positioning duration per day, and the use of prone positioning as an early intervention instead of a rescue therapy. Based on this trial and the physiologic rationale for its use, prone positioning should be strongly considered in patients with severe, early ARDS, particularly in those with significant heterogeneity of lung involvement.

The situation for prone positioning for pediatric ARDS is less clear. In 2005, Curley et al published a randomized, controlled trial of prone positioning for infants and children with acute lung injury. The study was stopped at a planned interim analysis due to futility. It should be noted that the degree of ARDS was less in the Curley study than in the PROSEVA trial. PALICC stated that prone positioning cannot be recommended as routine therapy for children with ARDS; however, it should be considered as an option for pediatric patients with severe ARDS. Further study is clearly needed for pediatric ARDS.
Neuromuscular Blockade

NMB can be used in the care of adult and pediatric patients with severe hypoxemia and ARDS, particularly those who continue to exhibit signs of ventilator-patient dyssynchrony despite appropriate pharmacologic sedation and appropriate ventilatory management. In a multicenter, randomized, controlled trial,340 adult subjects with moderate to severe ARDS (P/F < 150 mm Hg), with ARDS onset within the previous 48 hours, were randomized to receive 48 hours of NMB with cisatracurium versus placebo. Open-label boluses of cisatracurium were allowed in both arms in response to high end-expiratory Pplats. Lung-protective ventilation strategies were used for both groups.

While the study was underpowered, the hazard ratio for death at 90 days in the cisatracurium group was 0.68 (95% CI, 0.48–0.98; \( p = 0.04 \)) after adjustment for severity of illness. Crude mortality at 90 days was 31.6% in the NMB group versus 40.7% in the placebo group (\( p = 0.08 \)). Mortality at 28 days was 23.7% in the NMB group versus 33.3% in the placebo group (\( p = 0.05 \)). Ventilator-free days, ICU-free days, and rates of barotrauma were also lower in the cisatracurium arm. Equally important, rates of ICU-acquired paresis, felt to be a significant risk in the use of NMB and known to contribute to long-term ICU outcomes, was similar between the two arms despite the high infusion rate and cumulative dose of cisatracurium administered. A replication study powered to confirm the mortality benefit is currently underway as part of the Prevention and Early Treatment of Acute Lung Injury (PETAL) network.

There are many potential explanations for the benefit of NMB in the ARDS population. Pharmacologic paralysis ensures more accurate ventilator mechanics measurements, thereby possibly adjusting settings that cause regional overdistention and/or cyclic alveolar collapse. Specifically, in patients who are dyssynchronous or even making spontaneous breath efforts in concert with the ventilator, pleural pressure may be significantly negative and transpulmonary pressure therefore unexpectedly high. Lower circulating cytokine levels in the paralysis group supports the theory that prevention of VILI and not improved oxygenation was the mechanism of benefit29 and suggests a reduction in systemic inflammation, or biotrauma. The separation in the survival curves in this study also occurred relatively late in patients’ course, implying that the benefit may be caused by the prevention of biotrauma and subsequent multisystem organ failure. Lastly, reduced oxygen demand by skeletal muscle may also play a role.

Although the mechanism for benefit of NMB remains speculative, early administration of cisatracurium is recommended in adult patients with severe ARDS, especially if there is evidence of ventilator-patient dyssynchrony despite deep adequate sedation.

Because there has not been a randomized, controlled trial of NMB in pediatrics, a definitive statement is not possible. PALICC recommended that, if sedation alone is not adequate to achieve “effective
mechanical ventilation,” NMB should be considered. Without more definitive data, the pediatric intensivist is again left with relying on expert opinion, such as PALICC, or extrapolating the available data from the adult population.

**Noninvasive Ventilation and Oxygenation**

Studies have examined the role of noninvasive positive pressure ventilation (NIV) in patients with acute respiratory failure with the goal of avoiding intubation and the risks associated with invasive positive pressure ventilation. Positive results were seen for adults with cardiogenic pulmonary edema and chronic obstructive pulmonary disease. However, studies have failed to demonstrate a benefit of noninvasive ventilation for those with other causes of respiratory failure, such as pneumonia or ARDS.

More recently, high-flow nasal cannula (HFNC) with heated/humidified gas flow of > 30 L/min has been proposed as a treatment for patients with non-hypercapnic acute hypoxemic respiratory failure that cannot be reversed with lower oxygen flows. In a cohort of adult patients with non-cardiogenic acute hypoxemic respiratory failure (P/F < 300 mm Hg), more than 75% of whom had bilateral pulmonary infiltrates, subjects were randomized equally to HFNC, NIV, or standard oxygen therapy delivered through a mask. The primary outcome was the rate of intubation at 28 days. In the overall study population, there was no significant difference in rates of intubation between the three groups (p = 0.18 for all comparisons). However, in a subgroup analysis of those with P/F < 200 mm Hg, intubation rates were lower in those who received HFNC. More ventilator-free days were seen in the HFNC group, and the hazard ratio for death at 90 days favored HFNC as compared with NIV or standard oxygen therapy.

While HFNC is unlikely to have a significant impact on Vts, NIV uses applied inspiratory and expiratory pressure, which can have a significant effect on Vts and increase the risk for VILI, especially in patients with preserved respiratory drive. This may be especially important in the early phase of ARDS. In a prospective multisite cohort study of adult ARDS patients, investigators studied the association of ICU mortality both with initial Vt during mechanical ventilation and with Vt change over time. Approximately two-thirds of subjects had initial Vts greater than 6.5 mL/kg IBW. They found that an increase of 1 mL/kg IBW in initial Vt conferred a 23% increase in ICU mortality risk (adjusted hazard ratio 1.23, p = 0.008). Additionally, a subsequent increase in Vt of 1 mL/kg IBW beyond the initial Vt was associated with a 15% increase in mortality risk (adjusted hazard ratio 1.15, p = 0.019). This study further stresses the importance of timely initiation of lung-protective ventilation in ARDS patients to prevent VILI, regardless of whether the positive pressure is applied invasively or noninvasively. Therapies such as NIV and HFNC may contribute to VILI because of the inability to accurately predict or control Vts. This risk must be balanced against the risks of invasive mechanical ventilation. Additional studies are needed to determine the roles of NIV and HFNC in both the adult and pediatric ARDS populations.
KEY POINTS

- ARDS is a clinical syndrome defined by the acute onset of bilateral pulmonary infiltrates and hypoxemia not attributable to cardiogenic pulmonary edema.
- Despite being well studied in the adult population, the only management approach that has been shown to improve outcomes is low tidal volume ventilation.
- Other approaches with supportive data for those with severe ARDS include prone positioning and neuromuscular blockade.
- In pediatrics, definitive data are lacking. Clinicians are often left with expert opinion, such as the Pediatric Acute Lung Injury and Consensus Conference (PALICC), and/or extrapolation of data from the adult ARDS population.

REFERENCES


