

# Optimal Ventilator Strategies in Acute Respiratory Distress Syndrome

Michael C. Sklar, MD<sup>1</sup> Bhakti K. Patel, MD<sup>2</sup> Jeremy R. Beitler, MD, MPH<sup>3</sup> Thomas Piraino, RRT<sup>4,5,6</sup>  
Ewan C. Goligher, MD, PhD<sup>1,7,8</sup>

<sup>1</sup> Interdepartmental Division of Critical Care Medicine, University of Toronto, Toronto, Ontario, Canada

<sup>2</sup> Section of Pulmonary and Critical Care, Department of Medicine, University of Chicago, Chicago, Illinois

<sup>3</sup> Center for Acute Respiratory Failure and Division of Pulmonary, Allergy, and Critical Care Medicine, Columbia University, New York, New York

<sup>4</sup> Keenan Centre for Biomedical Research, St. Michael's Hospital, Toronto, Ontario, Canada

<sup>5</sup> Division of Critical Care, Department of Anesthesia, McMaster University, Hamilton, Ontario, Canada

<sup>6</sup> Department of Respiratory Therapy, St. Michael's Hospital, Toronto, Ontario, Canada

<sup>7</sup> Toronto General Hospital Research Institute, Toronto, Ontario, Canada

<sup>8</sup> Department of Medicine, Division of Respiriology, University Health Network, Toronto, Ontario, Canada

Address for correspondence Ewan C. Goligher, MD, PhD, Toronto General Hospital, 585 University Ave, Peter Munk Building, 11th Floor, Room 192, Toronto, Ontario, Canada M5G 2N2  
(e-mail: Ewan.goligher@mail.utoronto.ca).

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## Abstract

Mechanical ventilation practices in patients with acute respiratory distress syndrome (ARDS) have progressed with a growing understanding of the disease pathophysiology. Paramount to the care of affected patients is the delivery of lung-protective mechanical ventilation which prioritizes tidal volume and plateau pressure limitation. Lung protection can probably be further enhanced by scaling target tidal volumes to the specific respiratory mechanics of individual patients. The best procedure for selecting optimal positive end-expiratory pressure (PEEP) in ARDS remains uncertain; several relevant issues must be considered when selecting PEEP, particularly lung recruitability. Noninvasive ventilation must be used with caution in ARDS as excessively high respiratory drive can further exacerbate lung injury; newer modes of delivery offer promising approaches in hypoxemic respiratory failure. Airway pressure release ventilation offers an alternative approach to maximize lung recruitment and oxygenation, but clinical trials have not demonstrated a survival benefit of this mode over conventional ventilation strategies. Rescue therapy with high-frequency oscillatory ventilation is an important option in refractory hypoxemia. Despite a disappointing lack of benefit (and possible harm) in patients with moderate or severe ARDS, possibly due to lung hyperdistention and right ventricular dysfunction, high-frequency oscillation may improve outcome in patients with very severe hypoxemia.

## Keywords

- ▶ acute respiratory distress syndrome
- ▶ mechanical ventilation
- ▶ positive end-expiratory pressure
- ▶ high-frequency oscillation
- ▶ noninvasive ventilation
- ▶ oxygen

Mechanical ventilation is the mainstay of therapy for acute respiratory distress syndrome (ARDS)—apart from mechanical ventilation, ARDS would likely not have been recognized. Recognizing the importance of avoiding lung injury and ensuring adequate gas exchange, optimal ventilator management in ARDS has been the subject of intensive research efforts for the

last several decades, and will continue to be such for decades to come. This review provides a state-of-the-art summary of several aspects of mechanical ventilator management in ARDS. Given the widespread appreciation for the heterogeneity of this syndrome, possibilities for optimization through personalization are emphasized throughout.

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## Optimizing Tidal Volume

Lower tidal volumes ( $V_T$ ) attenuate biophysical lung injury by several mechanisms. Preventing frank overdistension (volutrauma/barotrauma),<sup>1-3</sup> decreasing tidal shear strain in regions of mechanical heterogeneity,<sup>4,5</sup> and reducing cyclic opening and collapse of small airways/alveoli (atelectrauma)<sup>6-8</sup> all reduce cellular and extracellular matrix injury.<sup>9-11</sup> Multicenter trials have demonstrated that targeting  $V_T$  of 6 mL/kg predicted body weight (PBW), compared with 12 mL/kg PBW, expedites resolution of multiple organ failures, lessens systemic inflammation, and improves survival in patients with ARDS.<sup>1,2,12,13</sup>

However, while 6 is superior to 12 mL/kg PBW, the *ideal*  $V_T$  strategy in ARDS is unknown. Two mechanistic human studies have found lowering  $V_T$  below 6 mL/kg PBW by means of extracorporeal life support as needed to maintain adequate gas exchange may attenuate systemic inflammation in select patients with severe ARDS and poor respiratory system compliance.<sup>14,15</sup> The recently published EOLIA trial aimed to address this question by randomizing patients with severe ARDS to conventional mechanical ventilation (CMV) or extracorporeal membrane oxygenation.<sup>16</sup> This trial was stopped early by the data safety monitoring board and failed to demonstrate a statistical difference in the primary outcome of mortality at 60 days. Reanalysis of the EOLIA trial suggested that this biological signal with ultra-low  $V_T$  for very severe ARDS may translate to clinical benefit.<sup>16,17</sup> Readers are guided to the accompanying section on mechanical circulatory support for more details.

Existing data indicate that no arbitrary  $V_T$  threshold, even if scaled to PBW, is universally protective for all patients.<sup>18-20</sup> Rather, an ideal  $V_T$  strategy likely must incorporate two related patient-specific factors: mechanics and biology.<sup>21</sup>

Several approaches have gained interest recently for adjusting  $V_T$  according to mechanics. Perhaps most immediately clinically accessible is airway driving pressure, defined as plateau pressure minus positive end-expiratory pressure (PEEP). Airway driving pressure is equivalent mathematically to  $V_T$  scaled to the individual patient's respiratory system compliance ( $V_T/C_{RS}$ ) (→ **Fig. 1**). It was highly correlated with mortality independent of  $V_T$  in a secondary analysis of multiple ARDS randomized trials.<sup>22</sup> Airway driving pressure also appears highly correlated with  $V_T$  scaled to lung compliance (transpulmonary driving pressure =  $V_T/C_L$ ).<sup>23</sup> Typical transpulmonary driving pressure is roughly 5 to 10 cm H<sub>2</sub>O with normal spontaneous breathing in healthy individuals,<sup>24,25</sup> indicating the usual amount of global stress experienced across the lung in health. However, transpulmonary driving pressure can be substantially higher in patients with ARDS due to changes in compliance of the injured lung.<sup>21,26</sup> Targeting healthy normal driving pressure during ARDS has intuitive appeal for this reason, but its role for enhancing lung protection remains to be tested directly in prospective clinical trials.

Volume-based strategies for individualizing  $V_T$  to mechanics include scaling  $V_T$  to either functional residual capacity (FRC) measured at end-expiration ( $V_T/FRC$ ) or inspiratory capacity (IC) measured during a maximal insufflation

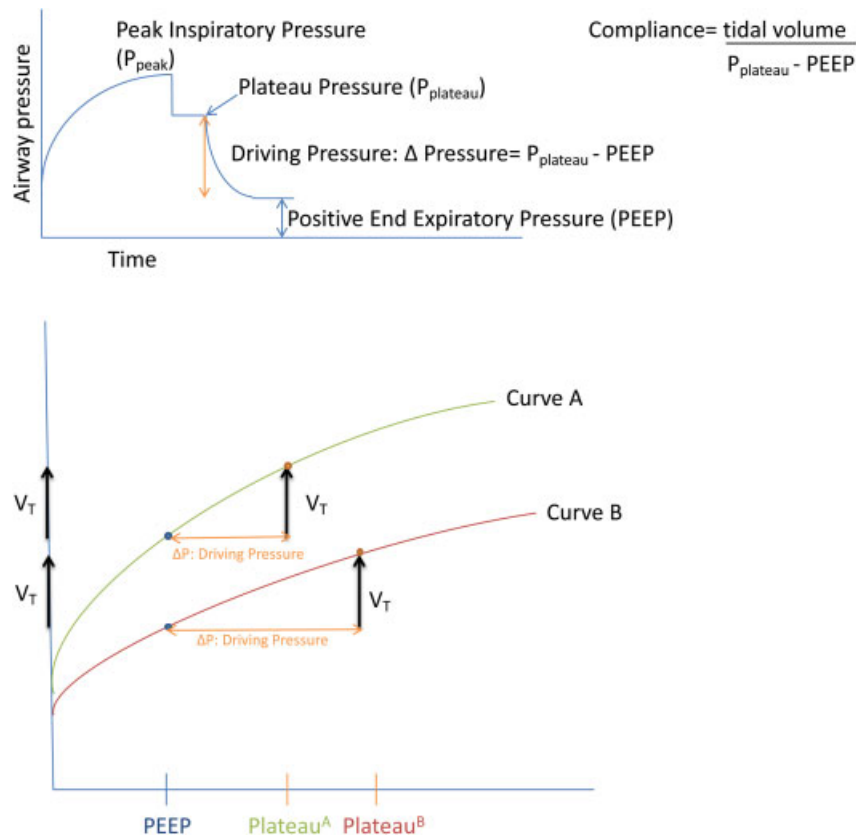
maneuver ( $V_T/IC$ ). FRC-based approaches use computed tomography imaging, nitrogen wash-out/wash-in, or helium dilution to measure end-expiratory lung volume,<sup>26-28</sup> after which  $V_T$  might be set to equal a certain percentage of that volume. Of course, FRC may change rapidly with any adjustment in ventilator pressures or volumes and with the evolution of ARDS, requiring frequent reassessment. While important research tools, feasibility and availability of the techniques may limit broad clinical application. Measuring IC can be done at bedside with any modern ventilator able to report volume change in response to change in pressure,<sup>23</sup> but lung recruitment and hyperinflation may complicate measurement, and limited data exist on this approach. As with driving pressure, no threshold has been proposed nor strategy tested prospectively for scaling  $V_T$  to these volume-based measures.

Indeed, it is likely that no universal threshold for lung protection exists regardless of how  $V_T$  is scaled to patient-specific mechanics. Rather, the extent to which a given  $V_T$  causes lung injury likely also depends on concomitant biological risk, including endothelial injury/activation, local/systemic inflammation, a primary alveolar epithelial insult, and heterogeneous distribution of injury patterns further confounding the ability to personalize lung protective ventilation.<sup>29-31</sup>

Currently, no clinically available, well-validated metric to assess risk of biophysical injury is available. Lung injury prediction scores from clinical data have not identified risk of ARDS with sufficient accuracy for clinical use,<sup>32,33</sup> and similar is likely true of risk of biophysical injury in established ARDS. Both instances likely require incorporating molecular markers of lung injury to assess patient-specific risk.<sup>34</sup> Two potential plasma markers of promise are soluble receptor for advanced glycation end-products (sRAGE), a marker of alveolar epithelial injury,<sup>35-38</sup> and angiotensin-2, a marker of vascular endothelial injury.<sup>39-41</sup> Whether these or other biomarkers, alone or in combination, identify risk of biophysical injury with sufficient reliability for clinical use remains to be tested.

Ideally, biomarker(s) might facilitate risk stratification for biophysical injury and allow the clinician to weigh risks/benefits of adjusting  $V_T$ . Even if threshold mechanical and biological measures are established, lung protection is not the sole goal in titrating  $V_T$ . Maintaining lower sub-physiologic  $V_T$  requires escalating cointerventions that carry their own risks. Deeper sedation and/or neuromuscular blockade may be required to facilitate patient tolerance and suppress ventilatory drive, which in turn increase risk of delirium and disuse atrophy of the diaphragm and other skeletal muscle.<sup>42-45</sup> Extreme lowering of  $V_T$  (e.g., 3 mL/kg PBW) may require extracorporeal life support to facilitate adequate gas exchange, which may heighten risk of hemorrhage, hematological, and neurological complications.<sup>46</sup>

To truly individualize  $V_T$  for patient-centered benefit will require (1) identifying who is at risk of biophysical injury, (2) developing an approach for titrating  $V_T$  to risk, and (3) weighing clinically the tradeoff between further lung protection and escalating cointerventions required for lowering  $V_T$ . Research in lung mechanics and biology is advancing toward that goal at an increasingly rapid pace, with clinical protocols ready for testing on the horizon.



**Fig. 1** Driving pressure and compliance. Top panel: respiratory pressures generated during a volume-controlled ventilation breath with an end-inspiratory pause. After generation of the peak inspiratory pressure, a pause allows for static conditions and the measurement of plateau pressure. The difference between the plateau and end-expiratory pressure is the airway driving pressure. Respiratory system compliance is the tidal volume divided by the driving pressure. Bottom panel: the effect of compliance on driving pressure. On this pressure–volume graph, compared with curve B, curve A illustrates a patient with increased respiratory system compliance and as a result at a given tidal volume there is reduced driving pressure.

## Positive End-Expiratory Pressure and Lung Recruitment

Since the first description of ARDS by Ashbaugh and colleagues, PEEP has been integral to the management of hypoxemia in ARDS.<sup>47,48</sup> More recently, the use of higher PEEP has been studied as a possible strategy to avoid lung injury. While several strategies for optimizing PEEP have been tested, none have yet shown a mortality benefit and one strategy was even associated with harm in ARDS patients. Consequently, PEEP titration remains a controversial area of ventilator management and great care must be taken when applying PEEP at the bedside.

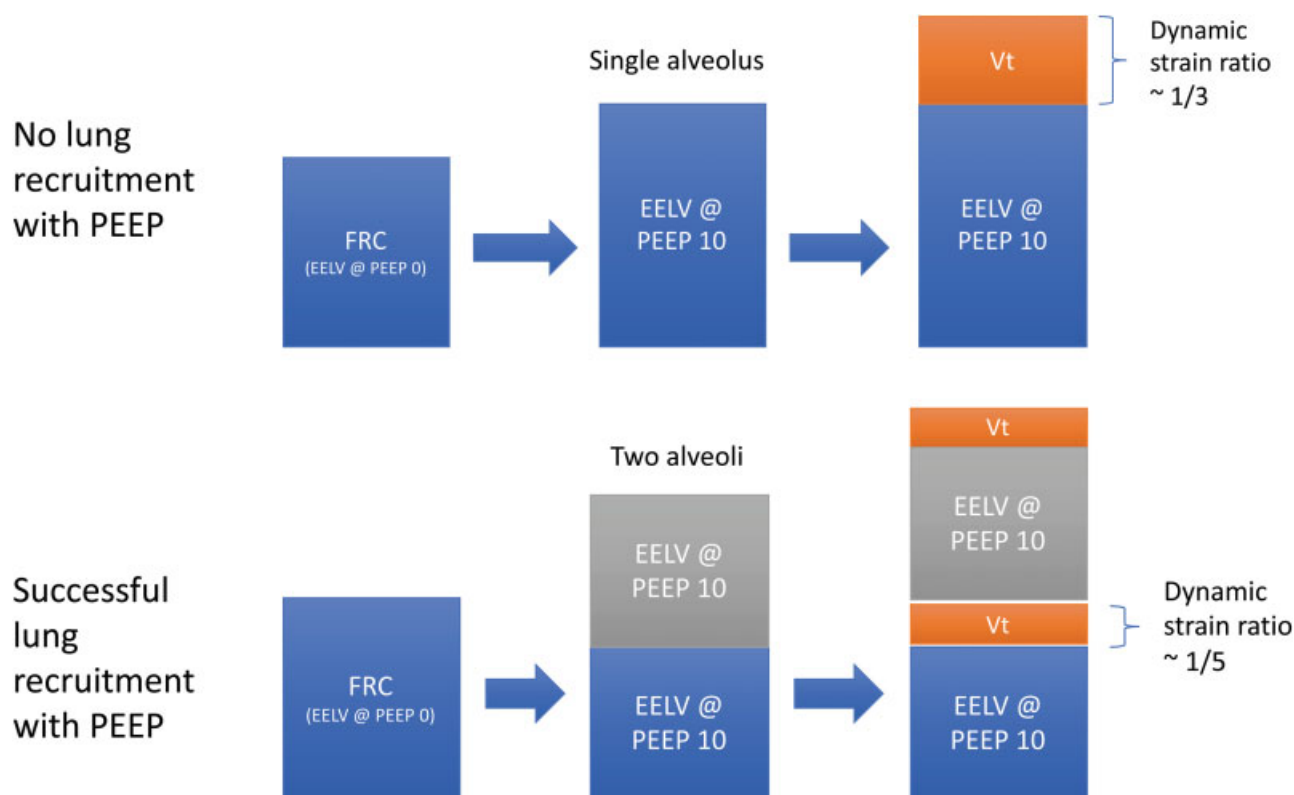
### Physiological Basis for Titrating PEEP

Applied at the correct level, PEEP might mitigate the risk of ventilator-induced lung injury (VILI). By preventing end-expiratory collapse of alveoli and small airways during tidal ventilation, PEEP prevents the shear stresses resulting from cyclic opening and closing of alveolar units—“atelectrauma.”<sup>49,50</sup> PEEP effectively reduces intrapulmonary shunt and improves oxygenation by opening collapsed lung units to participate in gas exchange.<sup>51</sup> Increasing the number of aerated lung units participating in ventilation reduces the dynamic tidal strain and stress applied to the lung<sup>52,53</sup> (→ Fig. 2). Finally, lung recruitment by PEEP results in more homogeneous inflation of the

lung; this can significantly reduce mechanical stress resulting from local inhomogeneities in the lung, which act as stress multipliers.<sup>4</sup>

At the same time, PEEP has important cardiorespiratory interactions which can limit the aforementioned physiological benefit. Depending on the underlying left ventricular function PEEP may improve cardiac output by a relative reduction in afterload.<sup>54</sup> At higher levels of PEEP, however, the increased intrathoracic pressure can be deleterious by elevating right atrial pressure, decreasing the gradient for venous return,<sup>55,56</sup> and reducing left ventricular preload—ultimately reducing cardiac output.<sup>56,57</sup> PEEP may also influence right ventricular performance indirectly by increasing pulmonary vascular resistance.<sup>58</sup> This occurs as elevated pressures occlude the alveolar septal vasculature,<sup>59</sup> thereby increasing right ventricular afterload and reducing cardiac output.<sup>58,59</sup>

From a pulmonary parenchymal perspective, PEEP may contribute to VILI by over-distending aerated lung units. Given that the ARDS lung is functionally a “baby lung,”<sup>60</sup> applied PEEP that fails to open collapsed alveoli will injuriously overinflate residual lung units propagating lung inflammation and injury, similar to the effects of excess tidal volume. Therefore, the benefit and harm of PEEP on the patient’s overall physiological condition will depend on how much lung can be recruited and on hemodynamic conditions.<sup>48</sup>



**Fig. 2** The effect of PEEP on dynamic strain depends on recruitability of the lungs. In the top panel, applying PEEP to the lung increases lung volume but because no additional alveoli are recruited, tidal ventilation is applied to the single alveolar unit and this unit experiences all of the dynamic strain. The amount of strain applied to the lung is determined by the ratio of tidal volume to end-expiratory lung volume ( $V_t/EELV$ ) at a given PEEP and FRC. In this theoretical (and simplified) representation, dynamic strain is approximately one-third in the nonrecruitable lung. In the bottom panel, applying PEEP to the lung increases lung volume and recruits an additional previously collapsed alveolus to participate in tidal ventilation. The same tidal volume is now distributed between two alveolar units, hence decreasing the dynamic strain experienced by each individual unit. This is the mechanism by which lung recruitment from PEEP is thought to decrease dynamic stress and strain. EELV, end-expiratory lung volume; FRC, functional residual capacity; PEEP, positive end-expiratory pressure.

### Recruitment Maneuvers and the Open Lung Approach

In view of concerns about the injurious effects of atelectasis and potential benefits of PEEP, the “open lung approach” gained favor.<sup>61</sup> Opening pressures in alveolar units often exceed 35 cm H<sub>2</sub>O (the accepted safe upper limit of plateau pressure)<sup>62</sup> while the PEEP required to maintain patency after opening is lower. Thus, various “recruitment” maneuvers for maximally inflating the lung to optimize lung recruitment have been studied. A recruitment maneuver is a sustained increase in airway pressure with the goal to open collapsed alveoli, after which sufficient PEEP is applied to keep the lungs open.<sup>63</sup> A sustained inflation is the most commonly employed maneuver: the ventilator is set to continuous positive airway pressure (CPAP) mode and pressures are increased to 30 to 40 cm H<sub>2</sub>O for 30 to 40 seconds.<sup>63</sup> An alternate approach is the “staircase” maneuver involving progressive increases in PEEP while maintaining a constant airway driving pressure until a maximum peak pressure of 50 to 60 cm H<sub>2</sub>O is achieved.<sup>62</sup> The physiological effects of recruitment maneuvers are transient and depend on the concomitant PEEP strategy.<sup>64</sup> The effects of a recruitment maneuver on lung injury are unclear, and hemodynamic instability (hypotension and/or bradycardia) can occur during maneuvers. The benefits of lung recruitment depend on

lung recruitability, but these maneuvers can be used as a diagnostic test to assess for recruitability.<sup>65</sup>

### Clinical Evidence Guiding the Delivery of PEEP

In patients with ARDS, no clinical trial has definitively concluded whether a high or low PEEP strategy is associated with improved outcomes. The ALVEOLI,<sup>66</sup> LOVS,<sup>67</sup> EXPRESS,<sup>68</sup> and ART trials<sup>69</sup> provide the highest quality evidence to answer the high versus low PEEP question. The LOVS and ALVEOLI trials were both randomized controlled clinical trials that compared high to low PEEP/FiO<sub>2</sub> tables in the ventilation management of patients with ARDS. In both of these trials, the higher PEEP arms resulted in increased mean arterial oxygen tensions<sup>66,67</sup> but neither trial was able to demonstrate a mortality benefit of a particular strategy. The French EXPRESS trial, though designed with a plateau pressure limit of 28 to 30 cm H<sub>2</sub>O, also failed to show a mortality benefit.<sup>68</sup>

The recently published ART trial was a multicenter randomized controlled trial (RCT) including just over 1,000 patients with moderate-to-severe ARDS randomized to a lower PEEP or higher PEEP arm with aggressive lung recruitment maneuvers.<sup>69</sup> Surprisingly, and different from previous trials, the 28-day mortality rate was significantly higher in the higher PEEP

plus recruitment maneuver group compared with the control arm (55 vs. 49%, respectively). Several methodological criticisms were raised about this trial.<sup>70</sup> One major concern was that the duration and amplitude of the lung recruitment maneuver in the experimental arm were excessive, increasing the risk of respiratory acidosis and barotrauma.<sup>70</sup> Peak recruitment pressures of 60 cm H<sub>2</sub>O and a recruitment time process of 24 minutes without ensuring adequate volume resuscitation might have explained in part the three cardiac arrests and seven pneumothoraces documented during recruitment.<sup>69</sup> A high proportion of patient-ventilator asynchrony in the experimental arm raised further concerns for significant VILI during controlled ventilation.<sup>70,71</sup> Some of these issues may explain this trial's disappointing result. Of note, a recent pilot RCT which also involved recruitment maneuvers and a decremental PEEP trial identifying the PEEP level associated with the maximum dynamic compliance demonstrated that an open lung approach improved oxygenation and respiratory system mechanics without detrimental effects on 60-day mortality, ventilator-free days, or barotrauma<sup>72</sup> and set the stage for a larger trial.<sup>69</sup>

It is important to note that none of the trials to date have explicitly considered lung recruitability as a criterion for enrolment or as a prespecified factor for stratifying analysis of the primary end-point. Given the foregoing physiological considerations, lung recruitability is likely a key determinant of benefit or harm from PEEP.<sup>73</sup> The importance of considering recruitability is supported by the observations that the oxygenation response to increased PEEP predicts mortality<sup>74</sup> and that the effect of PEEP on mortality appears to be mediated by its effect on driving pressure<sup>22</sup> (since both favorable oxygenation responses and mechanical responses will reflect lung recruitment).

### Optimal PEEP Management

In the contemporary management of patients with ARDS, the optimal approach to titrating PEEP remains unclear. It is clear that no strategy should attempt to apply a "one-size-fits-all" approach and individual variation in lung recruitability must be considered. The biological phenotype of ARDS may also be a crucially important consideration.<sup>75</sup> A variety of strategies for titrating PEEP are under investigation such as oxygen response to PEEP,<sup>74</sup> computed tomography,<sup>76</sup> driving pressure,<sup>22</sup> pressure-volume loops,<sup>77</sup> stress index,<sup>78</sup> esophageal manometry,<sup>79</sup> and electrical impedance tomography.<sup>80</sup> After 20 years of investigation, PEEP remains a challenging and important area of clinical investigation.

### Noninvasive Ventilation for ARDS

The role of noninvasive ventilation (NIV) in the management of ARDS is controversial and evolving. Although the benefits of NIV for acute exacerbations of chronic obstructive pulmonary disease<sup>81</sup> and cardiogenic pulmonary edema are substantial,<sup>82</sup> evidence supporting the use of NIV in ARDS is limited. The potential to avoid invasive mechanical ventilation in patients with ARDS is intriguing given the known complications linked to invasive mechanical ventilation,

deep sedation, neuromuscular blockade, and immobility.<sup>83</sup> Despite the paucity of evidence, NIV in ARDS is commonly used as an initial supportive therapy for ARDS<sup>84,85</sup> and was formally recognized as a therapeutic approach in the Berlin Criteria<sup>86</sup> defining ARDS.

### Physiological Considerations

NIV has specific physiological effects in acute lung injury. PEEP can recruit lung to improve oxygenation but improves work of breathing to only a minor degree. Applying additional inspiratory pressure support further reduces work of breathing and dyspnea.<sup>87</sup> Given the high respiratory drive of patients with ARDS,<sup>88</sup> the use of pressure support to unload the respiratory muscles can lead to excessive tidal volumes, which are associated with NIV failure<sup>89</sup> and may exacerbate lung injury.<sup>90</sup> The concern for excessive tidal volume and inability to support the high respiratory drive of patients with ARDS was confirmed in the LUNG SAFE study.<sup>91</sup> This prospective multicenter observational study demonstrated that 15.5% of patients with ARDS are managed with NIV as an initial approach. Interestingly, NIV was applied at similar rates across all ARDS severity categories. Patients managed with NIV had lower levels of PEEP and higher respiratory rates and tidal volumes in comparison to invasively mechanically ventilated patients, highlighting the challenge of controlling respiratory drive with a noninvasive approach.<sup>91</sup> Furthermore, the inspiratory pressures required to improve the work of breathing may worsen mask leaks, gastric distension, and patient tolerance.<sup>87</sup>

### Evidence Base

Notwithstanding the technical challenges of NIV titration in ARDS, there are data indicating some success with this approach. Antonelli and colleagues<sup>84</sup> investigated NIV as a first-line approach to patients with ARDS and found that endotracheal intubations were prevented 54% of the time. Correspondingly, avoiding endotracheal intubation was associated with less ventilator-associated pneumonia and decreased intensive care unit (ICU) mortality. A meta-analysis of randomized and observational studies which included 540 patients similarly indicated that NIV is successful in ARDS approximately 50% of the time.<sup>92</sup> However, the heterogeneity of the studies prevented interpretation on the effect of NIV on other outcomes such as mortality.

Thus, as clinicians grapple with applying these limited data for clinical care, there are a few points to consider. First, the success of NIV for ARDS varies based on severity of hypoxemia.<sup>93</sup> The rates of NIV failure double as severity of ARDS increases from mild to moderate or severe, increasing from 22.2 to 42.3 and 47.1%, respectively.<sup>91</sup> This has led some to recommend that NIV in ARDS be restricted to patients with mild-moderate severity, defined as P<sub>a</sub>O<sub>2</sub>/FiO<sub>2</sub> ≥ 150 mm Hg.<sup>93</sup> Second, NIV failure is associated with worse outcomes,<sup>94</sup> which may reflect a higher severity of illness or possibly suggest that delays in intubation can be deleterious. Therefore, risk factors associated with NIV failure such as lack of improvement of the P<sub>a</sub>O<sub>2</sub>/FiO<sub>2</sub> ratio and shock<sup>84,95</sup> should be considered to optimize patient selection. In



parallel, close observation for early signs of failure is needed to prevent delays in endotracheal intubation. A new bedside tool, the HACOR score (heart rate, acidosis, consciousness, oxygenation, and respiratory rate) has been developed and validated to predict NIV failure in hypoxemic patients with high accuracy at 1 hour of NIV to prevent intubation delays.<sup>96</sup> Finally, although there are data indicating possible harm with NIV in ARDS, it is important to consider the clinical context. A randomized clinical trial comparing the efficacy of standard oxygen, high-flow nasal cannula (HFNC), and NIV in patients with hypoxemic respiratory failure suggested increased mortality in the NIV group.<sup>97</sup> However, patients in the NIV group received NIV only for 8 hours a day for 2 days. Given that the physiological effects of NIV dissipate quickly after discontinuation, it is unclear if the NIV protocol mediated these findings as opposed to NIV per se.

The capacity to apply prolonged NIV at higher pressures may mediate success. One small single-center clinical trial examined the effect of the NIV interface on its success in ARDS.<sup>98</sup> The authors postulated that the helmet, a transparent hood that encompasses the entire head of the patient and has a seal at the neck, would enhance titration of positive pressure and be better tolerated in comparison to the traditional facemask. Endotracheal intubation rates were reduced from 62% in the facemask group to 18% in the helmet group. In addition, 90-day mortality was reduced by 22% with helmet NIV. In a 1-year follow-up study, the authors also demonstrated that the avoidance of endotracheal intubation was associated with improved long-term neuromuscular and functional outcomes in ARDS survivors.<sup>99</sup> Early termination of the clinical trial may have exaggerated the magnitude of the findings and these data need to be replicated in larger multicenter trials prior to widespread adoption.

There are no definitive recommendations for or against the use of NIV for ARDS due to the paucity of high-level evidence.<sup>100</sup> Invasive mechanical ventilation remains the mainstay of supportive care for ARDS. However, NIV may obviate the need for endotracheal intubation in carefully selected and closely monitored patients. Clinicians must weigh the risk of complications with invasive mechanical ventilation against the potential harm of NIV due to delays in

endotracheal intubation or exacerbation of lung injury. As the debate between controlled invasive mechanical ventilation versus spontaneous breathing in ARDS continues, more research is warranted to identify subgroups of patients who may benefit from NIV, understand the effect of NIV interface on the physiology and outcomes of lung injury, and compare NIV to other respiratory support devices such as HFNC.

## Airway Pressure Release Ventilation

Airway pressure release ventilation (APRV) was originally described over 30 years ago by Stock et al as a mode of ventilation that maintained an elevated pressure for most of the respiratory cycle (inverse I:E ratio) with periods of “release” to a lower CPAP to facilitate elimination of CO<sub>2</sub>.<sup>101</sup> The mode is purely time-cycled, shifting between high-pressure and low-pressure settings at set time intervals while allowing unrestricted breathing by the patient at any time during ventilation. There are four settings that set APRV apart from other modes; high pressure ( $P_{\text{high}}$ ) and the length of time  $P_{\text{high}}$  is maintained ( $T_{\text{high}}$ ), low pressure ( $P_{\text{low}}$ ) and the length of time  $P_{\text{low}}$  is maintained ( $T_{\text{low}}$ ). However, the literature contains major differences in how these settings are used and in the ventilation strategies used as comparators in trials.<sup>102</sup> Older studies of APRV titrated  $P_{\text{low}}$  to prevent alveolar collapse, whereas a more modern approach adjusts  $T_{\text{low}}$  based on expiratory flow to maintain auto-PEEP to prevent alveolar collapse. Additionally, there are minor differences between studies of similar methods that may be important, such as the  $P_{\text{low}}$  settings used, or how much expiratory flow is limited with  $T_{\text{low}}$ <sup>103</sup> (→ Table 1).

### Setting $P_{\text{low}}$

The traditional method of APRV was to set a  $P_{\text{low}}$  level and allow exhalation to that level prior to returning to  $P_{\text{high}}$ .<sup>101</sup> In older studies,  $P_{\text{low}}$  was set according to the lower inflection point of the pressure–volume curve and control groups had PEEP set by the same method.<sup>104–106</sup> One of the most widely cited studies using this method was a crossover study of trauma patients by Putensen et al that randomly assigned 30 patients to receive APRV or pressure-controlled ventilation.

**Table 1** Differences between studies of APRV

Study	$P_{\text{low}}$	$T_{\text{low}}$	Primary outcome	Considerations
Putensen et al <sup>104</sup>	$P$ - $V$	Full exhalation	Cardiorespiratory function; better for APRV	Control group paralyzed for 72 h then switched to APRV for the rest of the time on the ventilator
Varpula et al <sup>106</sup>	$P$ - $V$	1 s	VFD; no difference	Used high $V_T$
Maxwell et al <sup>107</sup>	0	Exp flow 75–25%	VD; no difference	First study to target 6 mL/kg, but not exclusively ARDS patients
Zhou et al <sup>108</sup>	5 cm H <sub>2</sub> O	Exp flow > 50%	VFD; more for APRV	Sedation protocol differences; no spontaneous mode used in control group; unsuccessful extubation rate not explained
Lalgudi Ganesan et al <sup>110</sup>	0	Exp flow 75%	VFD; no difference	Higher mortality for APRV

Abbreviations: APRV, airway pressure release ventilation;  $P_{\text{low}}$ , pressure low;  $P$ - $V$ , pressure–volume curve;  $T_{\text{low}}$ , time low; VD, ventilator days; VFD, ventilator-free days.

They reported lower inotropic support requirements, fewer ventilator days, and a shorter length of ICU stay in patients that were initially managed with APRV.<sup>104</sup> However, the control group was paralyzed for the first 72 hours then switched to APRV; it is possible that the observed benefit of APRV was attributable to the protocol design rather than the mode per se. Subsequently, Varpula et al published the first RCT of APRV in ARDS patients using a  $T_{\text{high}}$  of 4 seconds and a  $T_{\text{low}}$  set to 1 second.<sup>106</sup> Similar to the Putensen et al,  $P_{\text{low}}$  values during APRV and PEEP in the control group were set according to the lower inflection point of the pressure-volume curve. They originally planned to enroll 80 patients but stopped early for futility after an interim analysis of the first 58 patients. They found no significant difference in the primary outcome of ventilator-free days (13.4 vs. 12.2 with APRV and synchronized intermittent mandatory ventilation [SIMV], respectively). Of note, tidal volumes were high in both groups (between 8 and 10 mL/kg).

### Limiting Expiratory Flow

In more recent years, studies of APRV have used a different approach where  $T_{\text{low}}$  is set short enough to limit expiratory flow deceleration. With this method, auto-PEEP rather than  $P_{\text{low}}$  is used to prevent alveolar collapse. This approach has now been used in three randomized trials (two adult and one pediatric study), with minor differences between them related to setting  $P_{\text{low}}$  and the allowable limit of expiratory flow. In an RCT by Maxwell et al, APRV was compared with low  $V_T$  ventilation (using SIMV) in 63 trauma patients.<sup>107</sup> They set  $P_{\text{low}}$  to 0 cm H<sub>2</sub>O with  $T_{\text{low}}$  set to terminate exhalation when the expiratory flow fell between 75 and 25% of peak expiratory flow. The outcomes were similar in both groups despite worse baseline physiological scores (APACHE II) in the APRV group. Sedation requirements were similar, and the duration of ventilation was not significantly different.

Recently Zhou et al conducted an RCT comparing APRV to conventional low tidal volume ventilation using the ARDS-Net trial protocol in 138 patients meeting criteria for ARDS.<sup>108</sup> This was the first RCT comparing APRV to low  $V_T$  specifically in ARDS. They set  $P_{\text{low}}$  to 5 cm H<sub>2</sub>O and set  $T_{\text{low}}$  to prevent expiratory flow from falling below 50% of the peak expiratory flow. They reported a significant improvement in the primary outcome of ventilator-free days using APRV compared with low  $V_T$  ventilation (19 vs. 2;  $p < 0.0001$ ). In contrast to Maxwell et al, they included spontaneous breathing trials in the protocols of both groups. However, the results may be confounded by several interventions: sedatives were significantly reduced in APRV patients by protocol design and spontaneous modes were not used in the control arm (patient-ventilator interaction was not assessed or considered). Furthermore, it was a single-center study limiting generalizability, baseline characteristics were not well balanced between groups (more patients with comorbidities were enrolled in the control arm), and there was an abnormally high rate of unsuccessful extubations and tracheostomies in the low  $V_T$  group.<sup>103,109</sup> Shortly after the Zhou et al publication, an RCT

of pediatric ARDS patients comparing APRV with low  $V_T$  was stopped early after 50% enrollment ( $n = 52$ ) when an interim analysis demonstrated higher mortality in the APRV group.<sup>110</sup>

### APRV with Shorter $P_{\text{high}}$

Another method to use the APRV mode is often referred to as biphasic positive airway pressure. This method uses  $P_{\text{high}}$  and  $P_{\text{low}}$  pressures comparable to conventional ventilation with  $T_{\text{high}}$  and  $T_{\text{low}}$  ratios similar to conventional pressure control (1:1 or greater), in contrast to the typical inverse ratio in most APRV studies.<sup>102</sup> The mode simply allows the patient to breathe freely without the need to be synchronous (ventilator breaths are delivered based solely on time and not patient effort). The primary goal of this approach is to limit transpulmonary pressure swings by inducing dyssynchrony (rather than trying to avoid dyssynchrony).<sup>111</sup> This method was recently applied in the largest study to date using the APRV mode, but the results have not been published at the time of this writing [NCT01862016]. Nonetheless, it will address a different question as it deals more with the question of synchrony rather than alveolar recruitment and an open lung approach.

The ability to generate higher mean airway pressure at lower peak airway pressures is the reason why APRV has been discussed in the context of managing ARDS, similar to the story of high-frequency oscillatory ventilation (HFOV).<sup>112</sup> However, in recent years the use of HFOV has fallen out of favor in the management of ARDS due to lack of effect and even potential harm.<sup>113,114</sup> Other “open lung” approaches using recruitment maneuvers and setting PEEP according to respiratory system compliance have also seen troubling results demonstrating potential for harm.<sup>69</sup> A major concern with widespread adoption of APRV is that it has not been studied nearly as well as these other approaches, which have all produced disappointing and concerning results in recent trials. Clinicians should be cautious in assuming that an open lung approach using APRV would yield different results. Currently the data are insufficient to recommend its use outside of a clinical trial.

## High Frequency Oscillatory Ventilation

HFOV is a unique mode of mechanical ventilation that utilizes nonconventional gas exchange mechanisms to deliver ventilation at very low tidal volumes and high frequencies. The rationale and clinical evidence are briefly reviewed here; interested readers are guided to a recently published comprehensive review of this topic.<sup>115</sup>

### Rationale for Use in ARDS

As described earlier, VILI is thought to result from excess tidal volume and pressure applied to the lung and the recurrent recruitment and collapse of lung units (atelectrauma).<sup>116</sup> HFOV is theoretically ideal for avoiding VILI because it delivers small (sub-dead space)  $V_T$  while preventing atelectasis with a consistently elevated mean airway pressure ( $mP_{\text{aw}}$ ).<sup>117</sup>

### Working Principles and Physiology

The oscillator circuit is relatively simple, with heated and humidified bias flow gas traversing a rapidly oscillating membrane. The set oscillatory frequency typically ranges from 3 to 15 Hz. This rapid oscillatory motion generates  $V_T$  lower than anatomic dead space, generally in the range of 1 to 3 mL/kg PBW. During HFOV, oxygenation and ventilation are independently controlled, with the former determined by the fraction of inspired oxygen and  $mP_{aw}$ , while the latter is influenced by the frequency, amplitude of oscillations, and inspiratory time.<sup>118</sup>

During HFOV, ventilation ( $CO_2$  clearance) is achieved despite the delivery of  $V_T$  below physiological dead space through several theorized mechanisms.<sup>119–124</sup> Convective bulk flow is a major mechanism of gas exchange. Typically, bulk flow is most pronounced in the proximal gas exchange units.<sup>121</sup> Here, convection is possible due to the asymmetric velocity profiles of inspired and expired gasses creating opposing convection currents—a phenomenon where gas exchange is even more pronounced at airway bifurcations.<sup>125</sup> Other mechanisms of gas exchange during HFOV include pendelluft<sup>126</sup> and cardiac oscillations.<sup>127</sup> The movement of gas between lung units with differing time constants for inflation and deflation (pendelluft) promotes gas exchange<sup>128</sup> and cardiac contractions cause a percussive movement of gas molecules allowing gas exchange to occur.<sup>129</sup>

### Current Evidence Base

Several RCTs have compared HFOV to CMV.<sup>74,113,114,130–132</sup> Early trials in ARDS patients were underpowered to detect clinically relevant differences in mortality and demonstrated nonsignificant effects in opposing directions.<sup>74,130,131</sup> When employed intermittently as a strategy to mimic a recruitment maneuver, HFOV was associated with significant improvements in oxygenation, lung compliance, and mortality (risk ratio [RR]: 0.59; 95% confidence interval [CI]: 0.41–0.85).<sup>132</sup>

Meta-analysis of these early trials found that the risks of complications such as barotrauma and hemodynamic instability were not different between HFOV and CMV, and suggested that mortality was significantly lower with

HFOV.<sup>133</sup> One must cautiously interpret these findings given that many of these trials were published before the wide adoption of plateau pressure and tidal-volume-limited CMV.

The large multicenter RCTs OSCAR<sup>114</sup> and OSCILLATE<sup>113</sup> were designed to definitively elucidate the role of HFOV in early ARDS. In the OSCILLATE trial, HFOV was applied using recruitment maneuvers and relatively high  $mP_{aw}$  and titrated according to the severity of hypoxemia. The CMV arm employed a low  $V_T$  and a high PEEP strategy.<sup>67</sup> OSCILLATE was stopped early after enrolling just under half of a planned 1,200 patients because mortality was significantly higher in the HFOV group compared with CMV (47 vs. 35%; RR: 1.33; 95% CI: 1.09–1.64). Vasopressor use and net fluid balance were higher in the HFOV arm, suggesting that HFOV may have significantly impaired hemodynamics, possibly contributing to the worsened outcome.

The OSCAR trial included almost 800 patients with moderate–severe ARDS, with HFOV titrated similarly to OSCILLATE. In contrast, however,  $mP_{aw}$  was generally lower in OSCAR and employed a lower PEEP strategy in the CMV arm. Mortality was no different between the trial arms (41.7% in HFOV vs. 41.1% in CMV; RR: 1.02; 95% CI: 0.86–1.20) and no significant difference in vasopressor requirements. A detailed comparison of these two trials is depicted in ►Table 2.

An individual patient meta-analysis was then performed on 1,552 patients across four trials of HFOV versus CMV,<sup>134</sup> demonstrating that HFOV was associated with worse outcomes in less severe ARDS, while possibly exerting a mortality benefit in very severe hypoxemia ( $P/F$  ratio  $\leq 65$  mm Hg). These findings suggest HFOV could have a limited role in very severe ARDS, reserved as a rescue strategy as reflected in current guidelines for ARDS management.<sup>135</sup>

### Risks of HFOV

Despite low  $V_T$  as delivered with HFOV, experimental studies suggest that high respiratory rates can cause cellular injury by influencing the elastic and frictional properties of pulmonary epithelium, leading to increased local stress, edema formation, and fracture of liquid bridges in airspaces.<sup>136–138</sup> The use of high  $mP_{aw}$  (and therefore high PEEP) during HFOV is thought to

**Table 2** Characteristics of the landmark clinical trials of HFOV in adult patients with ARDS

Study	Patients (N)	HFOV			Conventional mechanical ventilation		
		Frequency titration strategy	$mP_{aw}$ titration strategy	P titration strategy	Mode	Tidal volume	PEEP titration strategy
Ferguson et al <sup>113</sup>	548	3–12 Hz, maximal to keep pH > 7.25	$mP_{aw}$ – $FiO_2$ table	90	PCV	6 mL/kg PBW (6.1 mL/kg)	LOVS PEEP– $FiO_2$ table
Young et al <sup>114</sup>	795	Initially 10 Hz, titrated to keep pH > 7.25, minimum 5 Hz	5 cm H <sub>2</sub> O above CMV	Cycle volume titrated to keep pH > 7.25—some maximum for each frequency	PCV	6–8 mL/kg PBW (8.3 mL/kg)	ARDSNet lower PEEP– $FiO_2$ table

Abbreviations: ARDS, acute respiratory distress syndrome; ARDSNet, ARDSnet RCT of lower tidal volume ventilation; CMV, conventional mechanical ventilation;  $FiO_2$ , fraction of inspired oxygen; HFOV, high-frequency oscillatory ventilation; LOVS, Lung Open Ventilation Study;  $mP_{aw}$ , mean airway pressure; PBW, predicted body weight; PCV, pressure controlled ventilation; PEEP, positive end-expiratory pressure;



prevent atelectasis; however, it is possible that such elevated pressures may necessarily result in volutrauma.<sup>139</sup> Finally, there is emerging evidence that HFOV can place the lung above its natural resonance frequency where ventilation heterogeneity can significantly increase, potentially worsening ventilation-perfusion mismatch, exacerbating hypoxemia<sup>140</sup> and amplifying (to injurious levels) delivered  $V_T$ .<sup>141</sup>

HFOV must be carefully applied to avoid hemodynamic impairment. Through elevated  $mP_{aw}$ , HFOV can have a profound impact on the right ventricle (RV) by increasing afterload and reducing preload.<sup>142,143</sup> Direct measurement of intracardiac pressures in animal studies<sup>144</sup> and echocardiography studies in humans (demonstrating progressive RV dysfunction with increasing  $mP_{aw}$ ) corroborate these findings.<sup>143</sup> RV dysfunction, suggested by the significant increase in vasopressor use and fluid balance with HFOV in the OSCILLATE trial, may explain the increased mortality rate with HFOV observed in that study.<sup>113</sup>

Despite consistently improving oxygenation, HFOV is associated with worse outcomes in unselected ARDS patients and currently recommended as rescue therapy only. Cardiopulmonary effects likely limit the effectiveness of this technique.

## Summary

This review suggests that much progress remains to be made in optimizing mechanical ventilation. The astute clinician will carefully consider the patient's clinical features, physiological status, and response to ventilatory support to determine how to optimally ventilate the patient. The overarching goals of optimal ventilator management are to provide appropriate gas exchange while aiming to minimize dynamic stress and strain on the injured lung. This can be accomplished by minimizing tidal volume to the extent clinically permitted, increasing PEEP if improved mechanics and gas exchange suggest benefit, and implementing evidence-based strategies including neuromuscular blockade (discussed in the article by Syed et al on pp. 101–113) and prone positioning (discussed in the article by Gattinoni et al on pp. 94–100). The judicious use of NIV in appropriately selected candidates with mild/moderate ARDS may also be appropriate. HFOV and APRV may be considered as options for rescue therapy in deteriorating patients, although extracorporeal therapies (discussed in the article by Fan et al on pp. 114–128) may take on more importance in this context.

### Conflict of Interest

Dr. Beitler reports grants from National Heart, Lung, and Blood Institute, during the conduct of the study. Dr. Piraino reports personal fees from Dräger, Philips, and Fisher & Paykel, outside the submitted work.

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