Severe Hypoxemic Respiratory Failure: Part 1 — Ventilatory Strategies

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The American-European Consensus Conference on ARDS standardized the definition of acute lung injury (ALI) and ARDS on the basis of the following clinical parameters: acute onset of severe respiratory distress; bilateral infiltrates on frontal chest radiograph; absence of left atrial hypertension, a pulmonary capillary wedge pressure $\leq$ 18 mm Hg, or no clinical signs of left heart failure; and severe hypoxemia (ALI, $\text{Pa}_O_2/\text{Fi}_O_2$ ratio $\leq$ 300 mm Hg; ARDS, $\text{Pa}_O_2/\text{Fi}_O_2$ ratio $\leq$ 200 mm Hg). The definition does not take into consideration, however, the etiology (pulmonary or extrapulmonary) or the level of positive end-expiratory pressure (PEEP) required. More than 80% of patients with ARDS require intubation and mechanical ventilation. A lung-protective ventilation strategy should be used with a tidal volume of 4 to 8 mL/kg ideal body weight (IBW), a plateau pressure (Pplat) of $\leq$ 30 cm H$_2$O, and modest levels of PEEP. Such an approach affords a survival benefit and is standard care.

Patients with ARDS who are placed on lung-protective mechanical ventilation may have an improvement in oxygenation and disease severity within 24 h; their mortality is 13% to 23%$^4,5$; and they should be continued on lung-protective ventilator settings. In patients with little improvement in $\text{Pa}_O_2/\text{Fi}_O_2$ ratio in the first 24 h after instituting mechanical ventilation, the observed mortality is significantly higher and varies from 53% to 68%$^4,5$. In one study, setting PEEP at 10 cm H$_2$O allowed better differentiation of ARDS and ALI. After the PEEP trial, about one-third of patients initially classified as having ARDS were reclassified as having ALI, and 9% had a $\text{Pa}_O_2/\text{Fi}_O_2$ ratio of $> 300$ mm Hg. The mortality rates for reclassified categories were 45% for ARDS, 20% for ALI, and 6% for others.$^6$
Another parameter that may identify patients with severe ARDS is a PEEP requirement of ≥ 15 cm H2O to maintain adequate oxygenation. Indirect evidence for this parameter comes from Kallet and Branson,7 who reviewed data for 197 patients from 16 studies. They determined that 84% of patients with ARDS had a lower inflection point of ≤ 15 cm H2O on the pressure-volume curve, suggesting that a PEEP of ≥ 15 cm H2O may identify severe ARDS. In a series of 47 patients with ARDS, refractory hypoxemia was associated with a 16% mortality rate among ARDS deaths.8 In the same vein, Luhr et al5 reported that patients with a PaO2/FIO2 ratio of < 100 mm Hg required more aggressive therapy for oxygenation.

The oxygenation index (OI) incorporates the severity of oxygenation impairment (PaO2/FIO2 ratio) and mean airway pressure into a single variable:

\[
OI = \frac{FIO2 \times mPaw \times 100}{PaO2}
\]

(where mPaw = mean airway pressure). The OI is used more commonly in neonatal and pediatric patients but also has been used in adults with ARDS and may be a better predictor of poor outcome than the PaO2/FIO2 ratio.9-12 A high OI 12 to 24 h after the onset of ARDS and rising values of OI from persistent ARDS have been shown to be independent risk factors for mortality.10-12 An OI of >30 is reported to represent failure of conventional ventilation and may be considered an indication for nonconventional modes of ventilation.9,13-16

For the purpose of this article, we have used the following definition of refractory hypoxemia: PaO2/FIO2 ratio of < 100 mm Hg or inability to maintain Pplat < 30 cm H2O despite a tidal volume of 4 mL/kg IBW or the development of barotrauma. An OI of >30 also categorizes a patient as having refractory hypoxic respiratory failure. We define high ventilator requirement as an FIO2 of ≥ 0.7 mm Hg and a PEEP of > 15 cm H2O or Pplat > 30 cm H2O with a tidal volume of < 6 mL/kg IBW. This requirement should be recognized early in the course of ARDS (< 96 h) when the potential for alveolar recruitment is greatest.17,20 Consideration also should be given to transferring patients with refractory hypoxemia to a center with established expertise in caring for such patients.21-23

What is the physiologic basis for rescue therapies in severe ARDS? In the lungs of patients with ARDS, there are alveoli that are relatively normal, that are collapsed but recruitable, and that are nonrecruitable.24 Rescue methods are used to recruit the collapsed, but potentially recruitable alveoli. Alveolar recruitment reduces the shunt fraction, reduces dead space, and improves compliance. Another important physiologic concept is optimally matching ventilation and perfusion.

The primary focus should be on prevention of refractory hypoxemia rather than on reversing it after it develops. If small tidal volumes and adequate levels of PEEP are used and careful attention given to fluid status and patient-ventilator synchrony, the need for rescue therapy may be obviated in many cases.25 Rescue therapies can be categorized arbitrarily as ventilatory and nonventilatory strategies. Nonventilatory interventions, such as neuromuscular blockade, inhaled vasodilator therapy, prone positioning, and extracorporeal life support, are discussed in a companion article forthcoming in the June 2010 issue of CHEST,26 whereas ventilatory approaches are addressed here. Use of rescue therapies is controversial, as, to our knowledge, none to date has been shown to reduce mortality when studied in large heterogeneous populations of patients with ARDS. However, some rescue therapies have been shown to improve oxygenation, which may be important as a short-term goal in the 16% of patients deteriorating with hypoxemic respiratory failure.8 When instituting rescue strategies, an attempt should be made to assess for alveolar recruitment. If alveolar recruitment is demonstrated, higher levels of PEEP should be considered.27-30 Other rescue therapies include airway pressure release ventilation (APRV),31 high-frequency oscillatory ventilation (HFOV),32 and high-frequency percussive ventilation (HFPV).33,34 In patients demonstrating very severe hypoxemic respiratory failure, defined as a PaO2/FIO2 ratio of < 60 mm Hg,37 consideration of extracorporeal life support,35 HFOV, or HFPV may be appropriate.

Because there are no data establishing the superiority of one rescue mode over another,36 the choice of rescue therapy is based on equipment availability and clinician expertise. Some clinicians may choose not to use a rescue therapy, which is legitimate on the basis of the level of available evidence. If a rescue therapy does not result in improved oxygenation or if complications from the therapy occur, that rescue therapy should be abandoned.
Thus, a reasonable evidence-based approach might be one in which lung-protective ventilation is used (volume and pressure limitation with modest PEEP). This approach may require permissive hypercapnia (ie, a higher-than-normal PaCO$_2$) and permissive hypoxemia (ie, a lower-than-normal PaO$_2$). If a clinical decision is made to implement rescue therapy for the patient with ARDS and refractory hypoxemia, one or more of the strategies described in this article can be used.

In this narrative review, we discuss ventilatory techniques that have been used in the setting of refractory hypoxemia in patients with ARDS. A PubMed search was conducted, with each strategy used as a key term. We narrowed the search to articles published in English and those that studied human subjects. We broadened the search to include additional articles, as appropriate, from the reference lists of those identified from our primary search.

**Positive End-Expiratory Pressure**

Increasing the level of PEEP often is the first consideration when the clinician is faced with a patient with refractory hypoxemia. If PEEP results in alveolar recruitment, the shunt is reduced, and PaO$_2$ increases. Three randomized controlled trials (RCTs) have evaluated modest vs high levels of PEEP in patients with ALI and ARDS (Table 1). Although none of these studies reported a survival advantage for use of higher PEEP, each reported a higher PaO$_2$/FiO$_2$ ratio in the higher PEEP group. Moreover, two of the studies reported lower rates of refractory hypoxemia, death with refractory hypoxemia, and use of rescue therapies.

The National Heart, Lung, and Blood Institute ARDS Clinical Trials Network set individualized PEEP using a table of FiO$_2$-PEEP combinations based on oxygenation. Mercat et al set individualized PEEP to a level set to reach a plateau pressure of 28 to 30 cm H$_2$O. Post hoc analysis of data from their study suggested that compared with ARDS, mild lung injury may be associated with less benefit and more adverse effects from higher levels of PEEP. Thus, a strategy of a higher PEEP and lower tidal volume with a plateau pressure target of 28 to 30 cm H$_2$O should not be used in patients with ALI. Moreover, critics have argued that the low PEEP (5-9 cm H$_2$O) used in the control group in Mercat et al may have been excessively conservative and a suboptimal control.

The benefit of PEEP in patients with refractory hypoxemia might depend on the potential for alveolar recruitment. If the recruitment potential is low, then an increase in PEEP will have a marginal effect on shunt and PaO$_2$, and it may contribute to overdistension of already-open alveoli, which could lead to increased risk for ventilator-induced lung injury and increased dead space and might potentially result in redistribution of pulmonary blood flow to nonventilated regions of the lungs. If an increase in PEEP results in alveolar recruitment, then the strain (distribution of pressure) in the lungs is reduced. On the other hand, if an increase in PEEP increases transpulmonary pressure, then the stress (change in size of the lungs during inflation) on the lungs is increased. PEEP may adversely affect PaO$_2$ in the presence of unilateral lung disease.

The potential for recruitment can be identified in an individual patient by use of a short (30-min) trial of increased PEEP. If an increase in PEEP results in minimal improvement (or worsening) of PaO$_2$, an increase in dead space (increased PaCO$_2$) with stable minute ventilation, and worsening compliance, then alveolar recruitment is minimal. Conversely, if an increase in PEEP results in a large increase in PaO$_2$, a decrease in PaCO$_2$, and improved compliance, it suggests significant recruitment. Some have suggested a decremental rather than an incremental PEEP trial. With this approach, PEEP is set to ≥ 20 cm H$_2$O and then decreased to identify the level that produces the best PaO$_2$ and compliance.

The stress index was recently proposed to assess the level of PEEP to avoid overdistension. This approach uses the shape of the pressure-time curve during tidal volume delivery. Worsening compliance as the lungs are inflated (upward concavity; stress index, > 1) suggests overdistension, and the recommendation is to decrease PEEP (Fig 1). Improving compliance as the lungs are inflated (downward concavity; stress index, < 1) suggests tidal recruitment and potential for additional recruitment, thus a recommendation to increase PEEP.

The use of an esophageal balloon to assess intrapleural pressure has been advocated to allow more precise setting of PEEP. If pleural pressure is high relative to alveolar pressure (ie, PEEP), there may be potential for alveolar derecruitment, which is most likely seen with a decrease in chest wall compliance, such as occurs with abdominal compartment syndrome, pleural effusion, or obesity. In this case, it is desirable to keep PEEP greater than pleural pressure. Unfortunately, artifacts in esophageal pressure, especially in supine patients who are critically ill, make it very difficult to measure absolute pleural pressure accurately. Although it is important to consider pleural pressure when setting PEEP, the use of an esophageal balloon may not be required. In patients with abdominal compartment syndrome, bladder pressure may be useful to assess intrabdominal pressure, the potential collapsing effect on the lungs, and...
the amount of PEEP necessary to counterbalance this effect.48

The available evidence does not clearly indicate the best method to select PEEP in patients with ARDS. Various options are listed in Table 2. A PEEP setting of 0 cm H2O generally is accepted to be harmful in the patient with ARDS. A PEEP setting of 8 to 15 cm H2O is appropriate in most patients with ARDS. Higher levels of PEEP should be used in patients for whom a greater potential for recruitment can be demonstrated. Care must be taken to avoid overdistension when PEEP is set. Higher PEEP settings may be required in patients with refractory hypoxemia; however, a PEEP of > 24 cm H2O seldom is required. In the decision-making for each patient, the potential benefit of high levels of PEEP should be balanced against the risk of harm (ventilator-induced lung injury, barotrauma, hypotension).

LUNG RECRUITMENT MANEUVERS

A recruitment maneuver is a transient increase in transpulmonary pressure intended to promote reopening of collapsed alveoli52-54 and has been shown to open collapsed alveoli, thereby improving gas exchange.17,18,55-58 However, to our knowledge, there have been no RCTs demonstrating a mortality benefit from this improvement in gas exchange.

A variety of techniques have been described as recruitment maneuvers (Table 3).52,54 One approach involves a sustained high-pressure inflation using pressures of 30 to 50 cm H2O for 20 to 40 s.51,56 A sustained inflation usually is achieved by changing to a continuous positive airway pressure (CPAP) mode and setting the pressure to the desired level. Pressure-controlled ventilation can be applied in addition to the sustained high pressure.18,57 Another approach is to use intermittent sighs, using three consecutive sighs set at a pressure of 45 cm H2O.59 An extended sigh also has been used in which there is a stepwise increase in PEEP and a decrease in tidal volume over 2 min to a CPAP level of 30 cm H2O for 30 s.60 Another method applies an intermittent increase in PEEP for 2 breaths/min.55 Pressure-controlled ventilation (PCV) of 10 to 15 cm H2O with PEEP of 25 to 30 cm H2O to reach a peak inspiratory pressure of 40 to 45 cm H2O for 2 min also has been used as a recruitment maneuver.57 Prone positioning61 and HFOV62 also have been used to improve alveolar recruitment.

Just as it is unclear which, if any, recruitment maneuver is superior to another, the optimal pressure, duration, and frequency of recruitment maneuvers has not been established. Many patients require increased sedation, paralysis, or both during the application of a recruitment maneuver. Studies using a decremental PEEP trial after a recruitment maneuver have reported significant oxygenation benefits for at least 4 to 6 h.18,44 However, it is unclear whether this finding was due to the recruitment maneuver, the PEEP titration strategy, or both. An improvement in oxygenation with a recruitment maneuver may indicate that the level of PEEP is too low. A recruitment maneuver may be of limited benefit when higher levels of PEEP are used.53

A recent systematic review reported the acute physiologic effects of a recruitment maneuver in approximately 1,200 patients.52 Oxygenation was significantly increased after a recruitment maneuver (Fig 2). Hypotension (12%) and desaturation (8%) were the most common complications of recruitment maneuvers. Serious adverse events, such as barotrauma (1%) and arrhythmia (1%), were infrequent. The overall mortality was similar to observational studies of patients with ALI (38%). The finding of improved oxygenation was more common in the following subgroups: difference between pre- and post-recruitment maneuver PEEP (≤ 5 cm H2O vs > 5 cm H2O), baseline PaO2/FIO2 ratio (< 150 mm Hg vs ≥ 150 mm Hg), and baseline respiratory system compliance (< 30 mL/cm H2O vs ≥ 30 mL/cm H2O).

Many of the studies of recruitment maneuvers reported a rapid decline in oxygenation gains, some within 15 to 20 min of the maneuver.52 The application of higher levels of PEEP after a recruitment maneuver may affect the sustainability of the effect. Whether improvements in oxygenation associated with recruitment maneuvers result in reduced lung injury.

![Figure 1](https://example.com/figure1.png)
and improved outcomes remains to be determined. Some studies have shown a survival advantage with a lung-protective ventilation strategy incorporating recruitment maneuvers, whereas others have not. The potential for lung recruitment likely varies considerably among patients, which likely affects the response to a recruitment maneuver.

The routine use of recruitment maneuvers is not recommended at this time. Given that they pose little risk of harm if the patient is carefully monitored during their application and that some patients may have a dramatic improvement in oxygenation with their application, recruitment maneuvers may play a role in patients who develop life-threatening refractory hypoxemia. It is prudent to avoid the use of recruitment maneuvers in patients with hemodynamic compromise and those at risk for barotrauma. If the application of a recruitment maneuver results in an important improvement in oxygenation, higher levels of PEEP should be used to maintain recruitment. However, caution must be exercised to avoid overdistension with excessive levels of PEEP.

**Pressure-Controlled Ventilation**

In patients with severe ARDS, some clinicians choose PCV as an alternative to volume-controlled ventilation (VCV) based on several lines of reasoning. First, the peak inspiratory pressure is lower on PCV, but this is related to the flow pattern during pressure control and, for the same tidal volume delivery, there is no difference in plateau pressure for PCV and VCV. Second, patient-ventilator synchrony is believed to be better with PCV, and improved outcomes remain to be determined. However, caution must be exercised to avoid overdistension with excessive levels of PEEP.

### Pressure-Controlled Ventilation

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**Table 1—Summary of Results of Three Randomized Controlled Trials of Lower vs Higher Levels of PEEP**

<table>
<thead>
<tr>
<th>Study</th>
<th>Control Group</th>
<th>Experimental Group</th>
<th>Major Findings</th>
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<tr>
<td>ALVEOLI</td>
<td>Volume assist-control, Vt = 6 mL/kg IBW; Pplat ≤ 30 cm H₂O. Combinations of PEEP and FIO₂ to maintain PaO₂ (55-80 mm Hg) or SpO₂ (88%-90%). PEEP on days 1-4 was 5.3 ± 3.2 cm H₂O. n = 273</td>
<td>Volume assist-control, Vt = 6 mL/kg IBW; Pplat ≤ 30 cm H₂O. Combinations of PEEP and FIO₂ to maintain PaO₂ (55-80 mm Hg) or SpO₂ (88%-95%). PEEP on days 1-4 was 13.2 ± 3.5 cm H₂O. In the first 80 patients, recruitment maneuvers may play a role in patients who develop life-threatening refractory hypoxemia.</td>
<td>Higher PaO₂/FIO₂ ratio in high PEEP group (220 ± 89 vs 168 ± 66) on day 1. Higher compliance in the higher-PEEP group (39 ± 34 vs 31 ± 15 mL/cm H₂O) on day 1. Mortality before hospital discharge (low PEEP, 24.9%; high PEEP, 27.5%; P = .48). Ventilator-free days (low PEEP, 14.5 ± 10.4 d; high PEEP, 13.8 ± 10.6 d; P = .50). Incidence of barotrauma (low PEEP, 10%; high PEEP, 11%; P = .51).</td>
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<tr>
<td>LOV</td>
<td>Volume assist-control, Vt = 6 mL/kg IBW; Pplat ≤ 30 cm H₂O. Combinations of PEEP and FIO₂ to maintain PaO₂ (55-80 mm Hg) or SpO₂ (88%-90%). PEEP on days 1-3 was 9.8 ± 2.7 cm H₂O. n = 508</td>
<td>Pressure control, Vt = 6 mL/kg IBW; Pplat ≤ 40 cm H₂O. Combinations of PEEP and FIO₂ to maintain PaO₂ (55-80 mm Hg) or SpO₂ (88%-95%). PEEP on days 1-4 was 14.6 ± 3.4 cm H₂O. Recruitment maneuvers after each disconnect from the ventilator of 40 cm H₂O for 30 s. n = 475</td>
<td>Higher PaO₂/FIO₂ ratio in higher-PEEP group (187 ± 69 vs 149 ± 61) on day 1. Higher Pplat in the high-PEEP group (30.2 ± 6.3 vs 24.9 ± 5.1). The higher-PEEP group had lower rates of refractory hypoxemia (4.6% vs 10.2%; P = .01), death with refractory hypoxemia (4.2% vs 8.9%; P = .03), and previously defined eligible use of rescue therapies (5.1% vs 9.3%; P = .045). Twenty-eight day mortality (high PEEP, 28.4%; low PEEP, 32.3%; P = .2). Incidence of barotrauma (high PEEP, 11.2%; low PEEP, 9.1%; P = .33).</td>
</tr>
<tr>
<td>EXPRESS</td>
<td>Volume assist-control. Vt = 6 mL/kg IBW. Moderate PEEP (5-9 cm H₂O). n = 382</td>
<td>Volume assist-control. Vt = 6 mL/kg IBW. PEEP set to reach Pplat of 28-30 cm H₂O (14.6 ± 3.2 cm H₂O) on day 1. n = 385</td>
<td>Higher PaO₂/FIO₂ ratio in higher-PEEP group (218 ± 97 vs 150 ± 69) on day 1. Higher compliance in the high-PEEP group (37.2 ± 22.7 mL/cm H₂O vs 33.7 ± 14.3 mL/cm H₂O) on day 1. The increased PEEP group had higher median number of ventilator-free days (7 d vs 3 d; P = .04), organ-failure-free days (6 d vs 2 d; P = .04), and use of adjunctive therapies. Incidence of barotrauma (high PEEP, 6.8%; low PEEP, 5.8%; P = .57).</td>
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ALVEOLI = Assessment of Low Tidal Volume and Elevated End-Expiratory Pressure to Obviate Lung Injury Trial; EXPRESS = Expiratory Pressure Trial; IBW = ideal body weight; LOV = Lung Open Ventilation Trial; PEEP = positive end-expiratory pressure; Pplat = plateau pressure; SpO₂ = oxygenation by pulse oximetry; Vt = tidal volume.
been violated in many patients. 66 Third, some clinicians expect an improvement in gas exchange with PCV. With PCV, the pressure waveform approximates a rectangle, and flow decreases during the inspiratory phase. The resulting increased mean airway pressure and lower end-inspiratory flow theoretically should improve gas exchange. However, on many current-generation ventilators, a descending ramp of flow can be used with VCV, and this may result in similar findings with PCV and VCV with a descending ramp waveform. 67–70 With careful attention to tidal volume, plateau pressure, PEEP, and inspiratory time, the differences between PCV and VCV are minor, and neither is clearly superior to the other. It is also worth pointing out that the ARDSNet trial was conducted with VCV. 3

Pressure-Controlled Inverse-Ratio Ventilation

Following reports 71–75 of improved oxygenation with pressure-controlled inverse-ratio ventilation (PCIRV) published 20 years ago, considerable enthusiasm for this method was generated. The approach to PCIRV is to use an inspiratory time greater than the expiratory time to increase mean airway pressure and, thus, improve arterial oxygenation. PCIRV most often is used with PCV, although VCV with inverse ratio also has been described. 76 Following the initial enthusiasm for this ventilatory approach, a number of subsequent controlled studies reported no benefit or marginal benefit of PCIRV over more conventional approaches to ventilatory support in patients with ARDS. 68,77–80 The elevated mean airway pressure and auto-PEEP that occur with PCIRV also may adversely affect hemodynamics. Because this approach can be very uncomfortable for the patient, sedation and paralysis often are required. On the basis of the available evidence, there is no clear benefit for PCIRV in the management of patients with ARDS. The likelihood of an improvement in oxygenation with PCIRV is small, and the risk of auto-PEEP and hemodynamic compromise is great. 81–83

Airway Pressure Release Ventilation

APRV is a mode of ventilation designed to allow patients to breathe spontaneously while receiving high airway pressure with an intermittent pressure release (Fig 3). The high airway pressure maintains adequate alveolar recruitment. Oxygenation is determined by high airway pressure and FiO2. The timing and duration of the pressure release (low airway pressure) as well as the patient’s spontaneous breathing determine alveolar ventilation (PaCO2). The ventilator-determined tidal volume depends on lung compliance, airway resistance, and the duration and timing of the pressure-release maneuver.

Table 2—Methods for Selecting PEEP

<table>
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<tr>
<th>Method</th>
<th>Description</th>
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<tbody>
<tr>
<td>Incremental PEEP</td>
<td>This approach uses combinations of PEEP and FiO2 to achieve the desired level of oxygenation or the highest compliance.</td>
</tr>
<tr>
<td>Decremental PEEP</td>
<td>This approach begins with a high level of PEEP (eg, 20 cm H2O), after which PEEP is decreased in a stepwise fashion until derecruitment occurs, typically with a decrease in PaO2 and decrease in compliance.</td>
</tr>
<tr>
<td>Stress index measure</td>
<td>The pressure-time curve is observed during constant-flow inhalation for signs of tidal recruitment and overdistension.</td>
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<tr>
<td>Esophageal pressure measurement</td>
<td>This method estimates the intrapleural pressure by using an esophageal balloon to measure the esophageal pressure and subsequently determine the optimal level of PEEP required.</td>
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APRV is a mode of ventilation designed to allow patients to breathe spontaneously while receiving high airway pressure with an intermittent pressure release (Fig 3). The high airway pressure maintains adequate alveolar recruitment. Oxygenation is determined by high airway pressure and FiO2. The timing and duration of the pressure release (low airway pressure) as well as the patient’s spontaneous breathing determine alveolar ventilation (PaCO2). The ventilator-determined tidal volume depends on lung compliance, airway resistance, and the duration and timing of the pressure-release maneuver.

Table 3—Different Lung Recruitment Maneuvers

<table>
<thead>
<tr>
<th>Recruitment Maneuver</th>
<th>Method</th>
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<tbody>
<tr>
<td>Sustained high-pressure inflation</td>
<td>Sustained inflation delivered by increasing PEEP to 30–50 cm H2O for 20–40 s</td>
</tr>
<tr>
<td>Intermittent sigh</td>
<td>Three consecutive sighs/min with the tidal volume reaching a Pplat of 45 cm H2O</td>
</tr>
<tr>
<td>Extended sigh</td>
<td>Stepwise increase in PEEP by 5 cm H2O above baseline with a simultaneous stepwise decrease in tidal volume over 2 min leading to implementing a CPAP level of 30 cm H2O for 30 s</td>
</tr>
<tr>
<td>Intermittent PEEP increase</td>
<td>Intermittent increase in PEEP from baseline to set level for 2 consecutive breaths/min</td>
</tr>
<tr>
<td>Pressure control + PEEP</td>
<td>Pressure control ventilation of 10–15 cm H2O with PEEP of 25–30 cm H2O to reach a peak inspiratory pressure of 40–45 cm H2O for 2 min</td>
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</table>

CPAP = continuous positive air pressure. See Table 1 legend for expansion of other abbreviation.
An active exhalation valve allows the patient to breathe spontaneously throughout the ventilator-imposed pressures, although spontaneous breathing typically occurs only during high airway pressure due to the short time at low airway pressure. Diaphragmatic contraction associated with spontaneous breaths during APRV may recruit dependent (dorsal) juxtadiaphragmatic alveoli, thus reducing shunt and improving oxygenation. Because high airway pressure usually is much longer than low airway pressure, APRV is functionally the same as PCIRV in the absence of spontaneous breathing. Because the patient’s ability to breathe spontaneously is preserved, APRV allows for a prolonged inspiratory phase without the need for heavy sedation and paralysis.

Various time ratios for high-to-low airway pressure have been used with APRV, ranging from 1:1 to 9:1 in different studies.\textsuperscript{84,88} In order to sustain optimal recruitment, the greater part of the total time cycle (80%-95%) occurs at high airway pressure. In order to minimize derecruitment, the time spent at low airway pressure is brief (0.2-0.8 s in adults).\textsuperscript{89} Neumann et al\textsuperscript{88} demonstrated that spontaneous inspiratory and expiratory time intervals are independent of the time at high to low airway pressure cycle because patients who are breathing spontaneously can maintain their innate respiratory drive during high and low airway pressure; thus, the release phase does not reflect the only expiratory time. If the time at low airway pressure is too short, expiration may be incomplete, and intrinsic PEEP may result.\textsuperscript{88} However, creating intrinsic PEEP is, by design, required with some approaches to APRV in which low airway pressure is set to 0 cm H$_2$O.\textsuperscript{89} With this approach, the time at low airway pressure is set such that the expiratory flow reaches 50% to 75% of the peak expiratory flow.

Crossover studies have reported improvements in physiologic end points with APRV.\textsuperscript{31,85,86,90-92} These studies reported that APRV required lower inflation pressure and less sedation and often produced better oxygenation than other forms of mechanical ventilation. Putensen et al\textsuperscript{87} randomized 30 trauma patients to APRV or PCV. With APRV, the inotropic support was lower, and the duration of ventilatory support and length of ICU stay were shorter. However, these findings are debatable because patients randomized to the conventional ventilation group were paralyzed for the initial 72 h of support. The largest RCT of APRV\textsuperscript{84} was terminated early for futility after recruiting 58 out of a targeted 80 subjects. At 28 days, there were no statistical differences in the number of ventilator-free days. In addition, mortality at 28 days and at 1 year was similar. However, the authors used prone positioning in both arms, which is known to improve the oxygenation in 60% to 70% of patients; thus, prone position may have eclipsed any oxygenation differences between the two groups. Additionally, the ventilator used to provide APRV in the test group is not designed to provide APRV and required modification to the expiratory limb.

Spontaneous breathing during high airway pressure has the potential to generate negative pleural pressures that may add to the stretch applied from the ventilator. This situation must be considered when evaluating the maximal stretch to which the lungs are exposed. Neumann et al\textsuperscript{88} reported tidal volumes of approximately 1 L and large pleural pressure swings with APRV. There is concern that these relatively large tidal volumes and transpulmonary pressures could contribute to the risk of ventilator-induced lung injury. The potential benefits of improved oxygenation and reduced need for sedation may make APRV an attractive ventilator mode.\textsuperscript{89} However, without RCTs demonstrating improved patient outcomes, routine use of this mode cannot be recommended. If APRV is used, auto-PEEP and tidal volume must be closely monitored.

**High-Frequency Oscillatory Ventilation**

High-frequency ventilation is any application of mechanical ventilation with a respiratory rate of >100 breaths/min. This can be achieved with a small tidal volume and rapid respiratory rate with conventional mechanical ventilation, various forms of external chest wall oscillation, HFPV, high-frequency jet ventilation, or HFOV, which currently is the form of high-frequency ventilation most widely used in adult critical care.\textsuperscript{62,93-95} It delivers a small tidal volume by...
HFOV oscillates the gas delivered to pressures above and below the mean airway pressure (mPaw). The mPaw and FIO\textsubscript{2} are the primary determinants of oxygenation, whereas the pressure amplitude of oscillation (\(\Delta P\)) and the respiratory frequency are the determinants of CO\textsubscript{2} elimination. The tidal volume varies directly with \(\Delta P\) and inversely with frequency.\textsuperscript{95} The mPaw is initially set to a level approximately 5 cm H\textsubscript{2}O above that with conventional ventilation, and \(\Delta P\) is set to induce “wiggle,” which is visible to the patient’s mid-thigh.\textsuperscript{96,97} Much of the pressure applied to the airway is attenuated by proximal airways and does not reach the alveoli, resulting in a small tidal volume that may be less than dead space.\textsuperscript{98,99} The delivery of a small tidal volume and a high mPaw may result in improved alveolar recruitment with less risk of overdistension, thus providing improved gas exchange and lung protection. HFOV also has been combined with other strategies, such as recruitment maneuvers,\textsuperscript{100} inhaled nitric oxide,\textsuperscript{101} and prone positioning.\textsuperscript{102}

Most of the evidence for HFOV has been from small observational studies,\textsuperscript{9,99,103,104} often in the setting of refractory hypoxemia. These studies have shown that HFOV is safe and effective, resulting in improvements in oxygenation and providing ample ventilation in adult patients with severe ARDS. There have been only two RCTs of HFOV in adult patients with ARDS.\textsuperscript{32,105} Derdak et al\textsuperscript{112} randomized 148 patients to receive either HFOV or conventional ventilation. The HFOV group showed an early improvement in the Pa\textsubscript{O\textsubscript{2}}/FIO\textsubscript{2} ratio, but this was not sustained beyond 24 h. There was a nonsignificant trend toward a lower 30-day mortality in the HFOV group (37% vs 52%; \(P = .102\)). A criticism of this trial is that patients in the conventional ventilation

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**Figure 3.** Display of airway pressure and flow vs time during airway pressure-release ventilation. Spontaneous breaths occur at a high pressure level, leading to a pressure release to a lower pressure level, as seen in this figure. During this mode, ventilation occurs by intermittent switching between the two pressure levels while allowing spontaneous breathing to occur in either phase of the ventilator cycle. Because time at low airway pressure is brief, in practice, spontaneous breathing occurs primarily during the time of high airway pressure. Maintaining an adequate level of time during a high airway pressure enhances alveolar recruitment, whereas keeping time short prevents alveolar collapse during the release to low airway pressure. CPAP = continuous positive air pressure; P\textsubscript{aw} = airway pressure; T High = time at high airway pressure; T Low = time at low airway pressure; V = flow.\textsuperscript{99} (Reprinted with permission from the Intensive Care On-line Network.)
group were ventilated with relatively large tidal volumes, which may have contributed to the high mortality in the control group. Bollen et al reported no significant difference in mortality between patients randomized to HFOV and those to conventional ventilation. A post hoc analysis, however, suggested that HFOV might improve mortality in patients with a higher oxygenation index. Complications reported with HFOV are relatively infrequent and include barotrauma, hemodynamic compromise, mucus inspissations resulting in endotracheal tube occlusion or refractory hypercapnia, and increased use of sedation or neuromuscular blocking agents. In the two RCTs comparing HFOV with conventional ventilation, Derdak et al reported no significant effect of HFOV on hemodynamics, barotrauma, or mucus plugging, and Bollen et al did not report any increased risk of complications with HFOV.

The use of HFOV may improve oxygenation in patients with refractory hypoxemia. However, there is not sufficient evidence to conclude that HFOV reduces mortality or long-term morbidity in patients with ALI or ARDS.

**High-Frequency Percussive Ventilation**

HFPV was introduced in the early 1980s as the Volumetric Diffusive Respirator (Percussionaire Corporation; Sandpoint, ID). Compared with HFOV, only a few studies have investigated the use of HFPV in adult patients with ARDS. HFPV is a flow-regulated, pressure-limited, and time-cycled ventilator that delivers a series of high-frequency (200-900 cycles/min) small volumes in a successive stepwise stacking pattern, resulting in the formation of low-frequency (upper limit, 40-60 cycles/min) convective pressure-limited breathing cycles (Fig 4).
An interplay of the Volume Diffusive Respirator control variables, either singly or in combination, contribute to the determination of mean airway pressure and gas exchange. At high percussion frequencies (300-600 cycles/min), oxygenation is enhanced, whereas at low percussion frequencies (180-240 cycles/min), CO₂ elimination is enhanced.

**Figure 5.** Ventilatory strategies for the management of refractory hypoxemic respiratory failure, showing the alternative ventilator strategies that can be used in patients with acute lung injury or ARDS with refractory hypoxemia following evaluation of the recruitment potential of the lungs. In patients with recruitable lungs, higher levels of positive end-expiratory pressure (PEEP) or other methods of setting appropriate levels of PEEP may be used initially. However, failure of the aforementioned techniques can result in the use of the alternative ventilatory strategies in centers familiar with their use. * = other methods of setting appropriate levels of PEEP include setting PEEP to reach a plateau pressure of 28 to 30 cm H₂O using esophageal pressure monitoring or the stress index. ALI = acute lung injury; APRV = airway pressure-release ventilation; ECLS = extracorporeal life support; ETCO₂ = end-tidal carbon dioxide; HFOV = high-frequency oscillatory ventilation; HFPV = high-frequency percussive ventilation. See Table 1 legend for expansion of other abbreviations.
HFPV has been reported to improve oxygenation and ventilation in patients with ARDS refractory to conventional ventilation, although these studies are small in size, few in number, and nonrandomized. In a prospective trial of seven patients with ARDS requiring increased ventilator support on conventional ventilation, Gallagher et al. found that when the patients were switched to HFPV at the same level of airway pressure and FIO₂, the patients had a significant increase in PaO₂, a slight reduction in PaCO₂, and no change in cardiac output. In another prospective study comparing HFPV and conventional ventilation in 100 adult patients with acute respiratory failure, there was no difference between the two groups in the time to reach the study end points of PaO₂/FIO₂ ratio > 225 or shunt < 20%. In the subgroup of patients with ARDS, HFPV provided equal oxygenation and ventilation at significantly lower airway pressures, although there was no difference in the incidence of barotrauma, ICU days, hospital days, or mortality. In a retrospective series of 32 adult medical and surgical patients with ARDS unresponsive to at least 48 h of conventional ventilation, Velmahos et al. demonstrated improved oxygenation within 1 h of being switched to HFPV. Peak inspiratory pressure decreased with HFPV, but mPaw increased. Although the peak inspiratory pressure decreased, peak alveolar pressure was not reported. In 12 patients with ARDS following blunt trauma who were switched to HFPV after failure of conventional ventilation, there was an improvement in oxygenation within 12 to 24 h. However, these improvements were not due to a rise in mPaw because there was no significant change following the switch to HFPV. The mechanisms that contribute to gas exchange in HFPV and other high-frequency ventilatory techniques have been described in a review by Krishnan and Brower.

An additional reported benefit of HFPV is the enhanced mobilization and drainage of secretions from the lung periphery to the larger airways, potentially decreasing pulmonary infections. Nonetheless, HFPV has not demonstrated improved outcomes. Unlike other ventilatory strategies that might be applied in the patient with refractory hypoxemia, both HFOV and HFPV require a ventilator that is not available in all hospitals as well as respiratory therapists and physicians skilled in its use.

**Summary**

Figure 5 summarizes a proposed algorithmic approach to ventilator management of refractory hypoxemia. We recommend that lung-protective ventilation (volume and pressure limitation with moderate levels of PEEP) be instituted in patients with ALI and ARDS requiring mechanical ventilation. Rescue therapies may be considered in patients who develop refractory hypoxemia, with the use of these therapies based on a variety of factors, such as the severity of hypoxemia, likelihood of alveolar recruitment, response to the intervention, and patient characteristics. Rescue strategies are aimed at improving alveolar recruitment (high PEEP, recruitment maneuvers, APRV, HFOV) and, thereby, oxygenation; however, none of these modalities have been consistently shown to improve outcome in a critically ill patient population. Before a trial of rescue therapy is initiated, the target outcome should be established. If the rescue strategy does not achieve this end point, it should be abandoned. Nonventilatory rescue strategies, such as inhaled vasodilators, prone positioning, and extracorporeal life support, may be considered in conjunction with the ventilatory strategies outlined in this article. They are discussed in detail in part 2 of this series, which will appear in the June 2010 issue of CHEST. Further research is needed to elucidate how these rescue strategies may be better used to provide an outcome benefit.

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