Clinical review: Acute respiratory distress syndrome – clinical ventilator management and adjunct therapy

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Abstract

Acute respiratory distress syndrome (ARDS) is a potentially devastating form of acute inflammatory lung injury with a high short-term mortality rate and significant long-term consequences among survivors. Supportive care, principally with mechanical ventilation, remains the cornerstone of therapy – although the goals of this support have changed in recent years – from maintaining normal physiological parameters to avoiding ventilator-induced lung injury while providing adequate gas exchange. In this article we discuss the current evidence base for ventilatory support and adjunctive therapies in patients with ARDS. Key components of such a strategy include avoiding lung overdistension by limiting tidal volumes and airway pressures, and the use of positive end-expiratory pressure with or without lung recruitment manoeuvres in patients with severe ARDS. Adjunctive therapies discussed include pharmacologic techniques (for example, vasodilators, diuretics, neuromuscular blockade) and nonpharmacologic techniques (for example, prone position, alternative modes of ventilation).

Introduction

Acute respiratory distress syndrome (ARDS) was first described in 1967 [1], and represents a common clinical problem in ICU patients. The syndrome is associated with a short-term mortality of approximately 45% [2] as well as significant long-term morbidity [3]. Despite being both a major clinical problem and a focus of research for the critical care community, ARDS remains difficult to define and a source of considerable controversy [4-7].

Using the 1994 American–European consensus criteria, ARDS was defined by widespread pulmonary infiltrates on chest radiograph, hypoxaemia, and the absence of elevated pulmonary capillary wedge pressure or other evidence of left atrial hypertension [8]. The new Berlin Definition of ARDS categorises ARDS as mild, moderate or severe, and was designed to address a number of issues that had become apparent with the previous definition (Table 1) [9].

ARDS represents a complex response to local and systemic inflammatory factors. Regardless of the underlying insult, the pathophysiological correlate of ARDS – diffuse alveolar damage – involves neutrophil activation and endothelial injury, leading to noncardiogenic pulmonary oedema and atelectasis [10]. Studies using computed tomography have demonstrated that, in contrast to chest radiograph appearances, the distribution of disease is heterogeneous with atelectatic-dependent regions and relatively well-aerated ‘baby lungs’ in nondependent areas [11,12]. Recognition of the heterogeneity of disease distribution has led to the concept of recruitable lung regions and the need to deliver lower than historical tidal volumes to avoid overdistension of the baby lung.

The main differential diagnoses for ARDS are cardiogenic pulmonary oedema, atypical infections, and diseases such as cryptogenic organising pneumonia, acute eosinophilic pneumonia, and acute interstitial pneumonitis. While mimicking conditions such as cryptogenic organising pneumonia may produce an indistinguishable clinical picture, they are much less common than ARDS. [9] An important point to recognise is that ARDS is a clinical syndrome with heterogeneous underlying pathological processes rather than a discrete diagnostic entity. Conditions associated with the onset of ARDS are diverse and are often classified as extrapulmonary (examples include sepsis, trauma, burns and pancreatitis) or pulmonary, such as pneumonia, pulmonary contusion or aspiration of gastric contents. Addressing the underlying condition in a timely fashion is essential – for example, with
antibiotics and source control for sepsis – in addition to the provision of supportive care. The majority of patients with ARDS will require invasive mechanical ventilation, although the successful use of non-invasive ventilation has also been described [13]. ARDS may resolve with supportive treatment, heal with interstitial fibrosis, or contribute to systemic inflammation and death. We review current evidence-based practices for invasive ventilation and discuss adjunctive therapies for ARDS.

Clinical ventilator management

Goals of mechanical ventilation

The goals of mechanical ventilation for ARDS are to minimise iatrogenic lung injury while providing acceptable oxygenation and carbon dioxide clearance.

While the contribution of ventilator-induced lung injury (VILI) to ARDS has not been fully elucidated, it is clear from animal models that mechanical ventilation can cause pathologic changes consistent with ARDS in the absence of other insults [14]. Mechanisms of VILI include alveolar overdistension (volutrauma), repetitive alveolar opening and closure (atelectrauma), oxygen toxicity, and biotrauma, the pulmonary and systemic response to alveolar overdistension that may exacerbate lung inflammation and contribute to multiple organ dysfunction [15,16]. Efforts to minimise VILI are focused on the use of low tidal volume ventilation to prevent volutrauma, the use of positive end-expiratory pressure (PEEP) to reduce alveolar collapse, and minimisation of exposure to potentially harmful oxygen concentrations. Specific therapies targeted at the immune response remain experimental to date.

Acceptable parameters for the partial pressure of arterial oxygen (PaO₂) and the partial pressure of arterial carbon dioxide are difficult to define. Although PaO₂ of 55 to 80 mmHg is considered the target range in many studies, more profound hypoxaemia may be well tolerated, as evidenced by the relatively rare occurrence of death due to refractory hypoxaemia in ARDS [17], the occurrence of well-tolerated profound hypoxaemia (average of 24.6 mmHg or 3.28 kPa) in climbers on Everest [18], and the reported survival of patients with ARDS and PaO₂ <30 mmHg (4 kPa) [19]. However, caution should be exercised in view of the reported correlation between cognitive defects in survivors of ARDS and duration of arterial oxygen saturation <90% [20].

Inhalation of high concentrations of oxygen (fraction of inspired oxygen (FiO₂ ≥0.8) is associated with progressive alveolar damage and death in animal studies [21]. In healthy human volunteers exposed to high concentrations of oxygen, tracheobronchitis develops after several hours [22] and prolonged exposure is associated with decreased vital capacity [23], increased dead space, increased production of reactive oxygen species, and biochemical markers of alveolar-capillary leak [24]. In a small series of patients with ARDS, ventilation with 100% oxygen was associated with increased intrapulmonary shunt, attributed to nitrogen reabsorption and atelectasis [25]. Compared with other aspects of VILI, however, relatively little work has been done on oxygen toxicity in adults with ARDS, and the threshold for toxicity, particularly in the setting of an open lung strategy and low tidal volume ventilation, is unknown. Based on the limited available data, our practice is to aim for FiO₂ ≤0.6 and to consider adjunctive therapies where this cannot be achieved by recruitment manoeuvres and higher PEEP alone.

Since low tidal volumes are protective despite resulting in higher partial pressure of arterial carbon dioxide levels [26], there has been increasing acceptance of hypercapnia as being harmless or even potentially beneficial by virtue of rightward shift of the oxyhaemoglobin dissociation curve, systemic and microcirculatory vasodilatation, and inhibitory effects on neutrophils and other inflammatory cells [27]. The optimal partial pressure of arterial carbon dioxide level for patients with ARDS is not clear, but mean levels of 66.5 mmHg (8.87 kPa) and pH 7.23 appear safe [28,29] in the absence of a clear contraindication to hypercapnia, such as raised intracranial pressure.

### Table 1. Berlin Definition of acute respiratory distress syndrome

| Timing | Within 1 week of a known clinical insult or new/worsening respiratory symptoms |
|---|---|
| Chest imaging | Bilateral opacities – not fully explained by effusions, lobar/lung collapse, or nodules |
| Origin of oedema | Respiratory failure not fully explained by cardiac failure or fluid overload; need objective assessment (for example, echocardiography) to exclude hydrostatic oedema if no risk factor present |

#### Oxygenation

| Severity | PaO₂/FiO₂ | PEEP |
|---|---|---|
| Mild | 200 < PaO₂/FiO₂ ≤300, with PEEP or CPAP ≥5 cmH₂O | |
| Moderate | 100 < PaO₂/FiO₂ ≤200, with PEEP ≥5 cmH₂O | |
| Severe | PaO₂/FiO₂ ≤100, with PEEP ≥5 cmH₂O | |

CPAP, continuous positive airway pressure; FiO₂, fraction of inspired oxygen; PaO₂, partial pressure of arterial oxygen; PEEP, positive end-expiratory pressure. *Chest X-ray or computed tomography scan. **At altitude higher >1,000 m, correction factor should be made as follows: PaO₂/FiO₂ x (barometric pressure / 760). This may be delivered non-invasively in the mild acute respiratory distress syndrome group. Adapted with permission from [9].
Ventilation

Following numerous animal and observational human studies, the landmark ARDS Network study provided clear evidence of large mortality benefit when patients with ARDS were ventilated with a lung-protective strategy aimed at avoidance of alveolar overdistension using tidal volumes of 6 ml/kg predicted body weight (Box 1) with plateau pressures ≤30 cmH₂O [26]. Adjustment of the ventilator rate was used to target a normal pH, with a mean respiratory rate of 30 breaths/minute in the low tidal volume arm. Tidal volumes in patients with ARDS should therefore be in the order of 6 ml/kg predicted body weight with plateau pressures ≤30 cmH₂O, accepting pH as low as 7.15 to achieve these targets.

Many ventilation modes have been employed in ARDS. To add to the confusion, manufacturers often use different names for similar modes. One must choose between spontaneous breathing modes with partial ventilatory support, or controlled modes; either a pressure-controlled mode in which tidal volume is the dependent variable, or a volume-controlled mode in which peak pressure may vary.

Spontaneous breathing with partial ventilatory support has been postulated to allow for better patient–ventilator synchrony, lower sedation requirements, and better preservation of diaphragmatic function with earlier liberation from mechanical ventilation. Data supporting this hypothesis, however, are currently very limited. A recent systematic review [30] identified only two small randomised controlled trials (RCTs) addressing this question, both of which used airway pressure release ventilation as the spontaneous breathing mode. One of these trials suggested improved oxygenation and increased number of ventilator-free days [31], but concerns exist that these may have been driven largely by decrements in the control group; meanwhile, the other trial showed no effect on clinical outcomes [32]. The main disadvantage of spontaneous breathing is the potential for the patient to generate high transpulmonary pressures and tidal volumes; suppression of this often requires the use of high doses of sedation with or without muscle relaxants. Balancing the risks between increasing sedation in order to provide lung protection and allowing spontaneous ventilation in a more awake patient is often a difficult clinical problem with limited applicable evidence. Our practice is to aim for spontaneous breathing with partial ventilatory support, frequently using pressure support ventilation, in patients with mild to moderate ARDS, while in moderate to severe ARDS patients we use sedation and muscle relaxants as necessary to achieve lung-protective ventilation.

Proponents of pressure-controlled ventilation argue that this allows for better patient–ventilator synchrony, that the decelerating flow pattern allows better distribution of inspired gases, and that high transpulmonary pressures are more easily avoided [33]. Conversely, volume-controlled ventilation allows safe tidal volumes to be delivered in a consistent pattern, thus avoiding alveolar overdistension [34]. Pressure-regulated volume control ventilation aims to combine the advantages of both approaches, but may be problematic when patients are making variable or intermittent inspiratory efforts. There is no evidence of benefit for any one mode, the important point being to ensure both safe tidal volumes (6 ml/kg predicted body weight) and plateau pressures (≤30 cmH₂O) regardless of the mode used.

Various less conventional modes (for example, proportional assist ventilation, neurally adjusted ventilatory assist, and so forth) have so far not been demonstrated to offer significant benefits over conventional modes of ventilation in ARDS.

Alveolar recruitment and positive end-expiratory pressure

Higher levels of PEEP with or without recruitment manoeuvres are often used to improve oxygenation. Using a transient increase in transpulmonary pressure, recruitment manoeuvres attempt to open previously atelectatic alveoli. This increase in the size of the ARDS baby lung [12] allows distribution of inspired gas among greater numbers of lung units, leading to less overdistension of individual alveoli and potentially less VILI [35]. Several methods have been described, the most commonly used of which is a sustained inflation breath; for example, 40 cmH₂O for 40 seconds [35]. Another manoeuvre that appears to be gaining popularity is a step-wise increase in PEEP accompanied by low levels of pressure control ventilation [36,37]. Common complications of any recruitment manoeuvre include transient hypotension and desaturation, while pneumothorax and other manifestations of barotrauma have been reported and transient alveolar overdistension during the manoeuvre may paradoxically worsen VILI [35]. Recruitment manoeuvres are associated with an immediate improvement in oxygenation with variable sustainability, but have not been shown to improve clinically important outcomes [38,39]. They may be most useful as a rescue therapy in refractory hypoxaemia or following deterioration in oxygenation attributable to worsening atelectasis.

The sustainability of improvements in oxygenation with recruitment manoeuvres may depend on the use of PEEP as a means of maintaining recruitment. In selecting a
PEEP level, one must consider both the target level (low, moderate, high) and the method for determining the actual numeric value of PEEP. In terms of target level, there is at least observational evidence to suggest that very low levels of PEEP (<5 cmH₂O) are associated with worse mortality [40]. The debate regarding targets of moderate versus higher levels of PEEP is informed by three recent large RCTs that maintained low tidal volumes in all patients [41-43]. While none of these trials individually showed a significant mortality benefit, when combined in an individual-patient meta-analysis the patients with moderate–severe ARDS (PaO₂/FiO₂ ≤200) had lower mortality and more ventilator-free days with higher levels of PEEP (approximately 15 cmH₂O on day 1) [44]. In contrast, patients with mild ARDS (PaO₂/FiO₂ = 201 to 300) showed a nonsignificant trend towards worse outcomes with higher PEEP; no benefit was seen in the overall population (see Figure 1) [44].

In terms of determining the exact level of PEEP for an individual patient within a targeted approach, several methods have been described. These methods most commonly consist of using a PEEP/FiO₂ table in which PEEP is titrated to provide acceptable oxygenation [26,41,42], titrating PEEP to a maximal acceptable plateau pressure while maintaining a safe tidal volume [43], or a decremental PEEP approach where a recruitment manoeuvre is followed by titration of PEEP to the minimum required to prevent de-recruitment and atelectrauma [45]. This decremental approach is most easily achieved by a sustained inflation breath or pressure control recruitment manoeuvre, followed by a decremental reduction in PEEP until a deterioration in compliance or oxygenation occurs, followed by a further recruitment manoeuvre and setting the PEEP 2 cmH₂O above this point [35]. This method of identifying a point of de-recruitment correlates well with that found on serial computed tomography imaging [46]. Similar results may be obtained regardless of the specific target used as a marker of lung opening [47].

An intriguing recent report describes setting PEEP guided by oesophageal pressures as a surrogate for pleural pressure [48]. Transpulmonary pressure is then calculated and the PEEP set to achieve a positive end-expiratory transpulmonary pressure, with higher pressures used for higher FiO₂ requirements. In a small single-centre RCT this approach led to improvements in oxygenation and even a suggestion of improved mortality [48]. Given the complexities involved in measuring and standardising oesophageal pressure measurements, and the preliminary nature of these findings, we believe that confirmation in the form of a larger multicentre RCT is required before this approach is used in the majority of ARDS patients. Other experimental methods of setting PEEP include titration to the minimum dead space fraction [49], optimal cardiac output, or transcutaneous oxygen tension [50], although none of these methods appears widely used in current clinical practice.

Our pragmatic approach is to use the lower ARDS Network PEEP/FiO₂ tables as a guide in most mechanically ventilated patients [26], with adjustment according to clinical response and our impression of chest wall compliance (obesity, oedema, or intra-abdominal hypertension may imply the need for higher PEEP to prevent gravitational alveolar collapse). In patients with moderate ARDS (PaO₂/FiO₂ = 101 to 200) we typically switch to a higher PEEP/FiO₂ table [41,42], and if oxygenation remains problematic in severe ARDS (PaO₂/FiO₂ <100) we often use recruitment manoeuvres followed by a decremental PEEP trial.

The inspiratory:expiratory ratio is generally set at a ratio of 1:2 as a default, but may be increased to 1:1 as needed in order to increase the mean alveolar pressure, to allow more time for filling of lung units with long time constants, and to increase alveolar recruitment. The main risk from this ratio increase is gas trapping, and therefore monitoring of the flow–time curve to ensure near-cessation of flow prior to inhalation is essential. Inverse ratio ventilation, with inspiratory:expiratory ratio >1:1, results in higher mean airway pressures and can improve oxygenation but appears less useful than increasing PEEP – and the associated intrinsic PEEP may worsen gas exchange, volutrauma, and haemodynamics [51,52].

**Pharmacological adjuncts**

**Pulmonary vasodilators**

Inhaled nitric oxide is a potent but extremely short-acting pulmonary vasodilator that selectively improves perfusion to well-ventilated alveoli, reducing intrapulmonary shunt and improving oxygenation. Despite improvements in oxygenation, the use of inhaled nitric oxide is not associated with any mortality benefit, is expensive, and requires a specialist delivery system [53,54]. A recent systematic review found a suggestion of increased renal failure in association with its use, although biologically plausible explanations for this remain speculative [53]. Our practice is to use inhaled nitric oxide in ARDS as rescue therapy for reversible, life-threatening hypoxaemia, usually as a starting dose of 5 ppm and titrating to a maximum of 20 ppm, with discontinuation if no significant improvement in oxygenation is apparent after a short trial.

Inhaled prostacyclin has similar theoretical benefits to nitric oxide in terms of selective pulmonary vasodilatation, but has been less extensively studied in the context of ARDS [55]. Small physiological studies suggest an equivalent effect on pulmonary artery pressures and oxygenation to inhaled nitric oxide, although none have been powered to compare clinically important endpoints
Evidence for prostacyclin use is confined to these small studies and case reports. The clinical relevance of theoretical side effects such as systemic vasodilatation and platelet dysfunction is unknown. Prostacyclin is considerably less expensive and does not require the same commercial delivery system as nitric oxide, but the nebuliser requires continual observation during prostacyclin delivery, and the technique remains an unproven rescue therapy for life-threatening hypoxaemia.

**Fluid balance**

The three factors involved in oedema formation are hydrostatic pressure, colloid osmotic pressure, and the capillary filtration coefficient. In the absence of effective methods to reduce pulmonary capillary leak (that is, the filtration coefficient), efforts to reduce extravascular lung water in ARDS are centred on minimising hydrostatic pressure by avoiding fluid overload, and potentially the use of albumin solutions to increase colloid osmotic pressure.

An association between positive fluid balance and worse outcome in patients with ARDS has been demonstrated in a number of studies [57,58]. Data from the ARDS Network Fluids and Catheter Therapy Trial support the use of a conservative fluid management strategy in ARDS, with the use of diuretics in haemodynamically stable patients to achieve an even fluid balance associated with improved oxygenation and faster liberation from mechanical ventilation [59]. While a dry approach to patients with sepsis and particularly ARDS has traditionally been assumed to benefit lungs at the expense of renal and other organ perfusion, a growing body of evidence exists to the contrary. In ARDS patients enrolled in the Fluids and Catheter Therapy Trial, for instance, conservative fluid management was associated with lower rates of acute kidney injury in ARDS patients once correction for changes in the volume of distribution of creatinine was used [60]. These findings of acute improvements from the Fluids and Catheter Therapy Trial need to be interpreted in light of a recent report showing potential for worse long-term cognitive function in a subset of the trial survivors [61].

In general, unnecessary fluid administration should be minimised using small-volume fluid boluses titrated to resolution of hypoperfusion states. Diuretics or ultrafiltration should be employed to restore euvolaemia in haemodynamically stable patients who have received fluid loading in the resuscitation phase of their illness. However, in some patients, particularly those with severe ARDS requiring high mean airway pressures for oxygenation, hypovolaemia may exacerbate hypoxaemia by virtue of increased intrapulmonary shunt, and clinical benefit may result from the careful administration of fluid boluses.

**Neuromuscular blockade**

Neuromuscular blockers are used in ARDS to improve patient–ventilator synchrony, to facilitate lung-protective ventilation, and to improve chest wall compliance. These blockers also reduce oxygen consumption by respiratory (and other skeletal) muscles, leading to an improved mixed venous saturation and in turn to an improved partial pressure of arterial oxygen, all other things being equal in most ARDS patients. In a recent large RCT, cisatracurium infusion for a 48-hour period early in the course of moderate–severe ARDS' (PaO₂/FiO₂ ratio...
ing in ARDS. Unfortunately, several large trials have demonstrated that although oxygenation generally improves with prone positioning, this does not appear to result in a survival benefit when all patients with ARDS are considered [79-83]. Two recent meta-analyses did, however, demonstrate an improvement in ICU mortality in patients with severe ARDS [84]. The benefit appears to be greater when the prone position is maintained for longer (that is, 17 or 18 hours), and although significant complications can develop (skin necrosis, dislodgement of catheters and tubes) these are not significantly more frequent when prone positioning is used. Prone positioning should be considered as an option to improve oxygenation for patients in whom conventional measures have failed and for patients with severe ARDS (PaO₂/FiO₂ <100).

The injurious effects and limitations of conventional ventilation have led to the development of a number of alternative modes of ventilation. Airway pressure release ventilation is a spontaneous breathing mode in which a high baseline pressure is released to a low level intermittently (6 to 12 times/minute) to allow ventilation, with spontaneous breaths permitted throughout the cycle. This technique may result in improvements in lung recruitment, oxygenation, and patient–ventilator synchrony, although with the potential cost of alveolar overdistension. Although some early studies have been promising, no definite outcome benefit has been demonstrated to date for this mode of ventilation [31,32,85].

Neurally adjusted ventilatory assist utilises an oesophageal electrode to measure diaphragmatic electrical activity, delivering positive pressure proportionately. While potentially useful in patients who are difficult to manage with conventional ventilation due to asynchrony [86,87], no prospective outcome studies have been carried out in ARDS patients.

High-frequency oscillatory ventilation utilises rapidly cycling positive and negative pressure oscillations around a high mean airway pressure to deliver very small tidal volumes at high frequencies (5 to 15 Hz or 300 to 900 per minute). The mechanisms of gas flow and ventilation involved are complex, but high-frequency oscillatory ventilation appears to result in maintenance of lung recruitment as well as improvements in oxygenation and ventilation in ARDS patients refractory to conventional ventilation and is potentially less injurious to the lung [88]. At the current time, high-frequency oscillatory ventilation appears safe and appropriate as rescue therapy for patients with refractory hypoxemia [89]. Results are expected in the near future from at least two large clinical trials comparing high-frequency oscillatory ventilation with conventional ventilation in moderate–severe ARDS patients.

The role of extracorporeal lung support in ARDS is controversial and availability is currently limited to
specialist centres. The most extensively studied form used in ARDS patients is venovenous extracorporeal membrane oxygenation (ECMO). A recent RCT of transfer to an ECMO centre found a mortality benefit when compared with conventional therapy [90]. However, this study has been criticised for conflating ECMO treatment and regionalisation effects, and for a lack of well-documented protective ventilation in the control group. Even more recently the H1N1 influenza epidemic has highlighted the potential benefits of extracorporeal lung support [91,92]. Potential drawbacks of extracorporeal lung support include lack of widespread availability and the need for systemic anticoagulation. Transfer to an ECMO centre should be considered in patients with reversible disease in whom lung-protective ventilation cannot provide acceptable gas exchange when other rescue measures have failed, and should be utilised early in the course of disease, before irreversible lung injury has occurred.

Future directions
There remain a large number of unanswered questions in the management of ARDS. The role of nonconventional ventilatory techniques is currently under study, as are the utility of extracorporeal carbon dioxide removal in conjunction with ultra-low tidal volume ventilation and the utility of ECMO for severe ARDS. Dependence on conventional positive-pressure ventilation may decline if these new technologies find a place.

Conclusion
Understanding mechanical ventilation as a potentially harmful yet life-saving intervention has led to the development of an approach that aims to minimise harm while providing acceptable gas exchange. Ventilation in ARDS should include the use of low tidal volumes, the avoidance of high plateau pressures, titration of PEEP to provide acceptable oxygenation, and avoidance of high inspired oxygen concentrations. Individualised targets for oxygenation and carbon dioxide clearance should be set, recognising the lack of harm associated with hypercapnia and the risk of harm associated with high inspired oxygen concentrations.

Useful rescue strategies when lung-protective ventilation fails to provide acceptable gas exchange include recruitment manoeuvres and optimisation of PEEP, neuromuscular blockade, and prone positioning. Fluid overload must be avoided, and diuretics or ultrafiltration should be used to achieve a negative fluid balance in stable patients. Failure of these measures should lead to consideration of nonconventional modes of ventilation or the use of extracorporeal therapies in selected patients with reversible disease. In spite of all these measures, however, ARDS remains a difficult clinical problem and carries a high mortality – we still have work to do [2].

Abbreviations
ARDS, acute respiratory distress syndrome; ECMO, extracorporeal membrane oxygenation; FiO2, fraction of inspired oxygen; PaO2, partial pressure of arterial oxygen; PEEP, positive end-expiratory pressure; RCT, randomised controlled trial; VILI, ventilator-induced lung injury.

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Competing interests
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In-hospital time to death

Patients with ARDS

HR, 0.85 (95% CI, 0.73-0.99); P = .03

Patients without ARDS

HR, 1.32 (95% CI, 0.87-2.00); P = .20

No. at risk

|                | Higher PEEP | Lower PEEP |
|----------------|-------------|------------|
| 949            | 760         | 693        |
| 760            | 693         | 666        |
| 693            | 666         | 183        |
| 666            | 183         | 158        |
| 183            | 158         | 148        |
| 158            | 148         | 144        |

Days After Randomization