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A M E R I C A N C O L L E G E O F



P H Y S I C I A N S[®]

Mechanical Ventilation in ARDS*

A State-of-the-Art Review

Timothy D. Girard, MD; and Gordon R. Bernard, MD, FCCP

Mechanical ventilation is an essential component of the care of patients with ARDS, and a large number of randomized controlled clinical trials have now been conducted evaluating the efficacy and safety of various methods of mechanical ventilation for the treatment of ARDS. Low tidal volume ventilation (≤ 6 mL/kg predicted body weight) should be utilized in all patients with ARDS as it is the only method of mechanical ventilation that, to date, has been shown to improve survival. High positive end-expiratory pressure, alveolar recruitment maneuvers, and prone positioning may each be useful as rescue therapy in a patient with severe hypoxemia, but these methods of ventilation do not improve survival for the wide population of patients with ARDS. Although not specific to the treatment of ARDS, protocol-driven weaning that utilizes a daily spontaneous breathing trial and ventilation in the semirecumbent position have proven benefits and should be used in the management of ARDS patients. (CHEST 2007; 131:921–929)

Key words: acute lung injury; ARDS; mechanical ventilation; positive end-expiratory pressure; prone position; tidal volumes

Abbreviations: ALI = acute lung injury; ALVEOLI = Assessment of Low Tidal Volume and Elevated End-Expiratory Pressure To Obviate Lung Injury; APACHE = acute physiology and chronic health evaluation; APRV = airway pressure release ventilation; ARMA = Respiratory Management in Acute Lung Injury/Acute Respiratory Distress Syndrome; CI = confidence interval; FI_{O_2} = fraction of inspired oxygen; IL = interleukin; IRV = inverse ratio ventilation; PEEP = positive end-expiratory pressure; Pflex = lower inflection point on the pressure-volume curve of the respiratory system

Prior to the development and widespread use of positive-pressure ventilators, acute lung injury (ALI) and ARDS, often termed *double pneumonia*, were nearly universally fatal forms of respiratory failure. However, in 1967 when Ashbaugh and colleagues¹ described the clinical entity that they called “acute respiratory distress in adults,” positive-pressure mechanical ventilation was an important com-

ponent of the care of patients with acute respiratory failure, and it was clear that this therapy was vital to the survival of patients with ARDS. Over the next 3 decades, general improvements in critical care contributed to some decline in the mortality associated with ARDS, but these benefits reached a plateau by the 1990s.²

Later that decade, the first randomized trials were conducted showing that an experimental method of mechanical ventilation (low tidal volume ventilation) could reduce mortality compared with traditional methods of ventilation. This article will review these and other clinical trials and make recommendations regarding the use of mechanical ventilation in the treatment of ARDS patients.

LOW TIDAL VOLUME VENTILATION

Early interest in low tidal volume ventilation was prompted by animal studies^{3,4} showing that ventilation with large tidal volumes and high inspiratory

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pressures resulted in the development of ALI characterized by hyaline membranes and inflammatory infiltrates. While tidal volumes of 10 to 15 mL/kg had traditionally been used in the majority of patients with respiratory failure,⁵ it was recognized in the mid-1980s that ARDS resulted in a significant reduction in the amount of normally aerated lung tissue. The “baby lung” that is typical of ARDS patients was markedly overdistended by high tidal volumes.⁶

Multiple animal studies of excessive alveolar distension, such as that seen in ARDS, provided investigators with a scientific rationale to hypothesize that low tidal volume ventilation would improve mortality among patients with ARDS. High tidal volume ventilation incites an inflammatory response in the lung that promotes systemic inflammation, often resulting in multiple organ system dysfunction. Tremblay et al⁷ observed that high tidal volume ventilation in rats resulted in increased levels of inflammatory mediators (*ie*, tumor necrosis factor- α , interleukin [IL]-6, and IL-10) in BAL fluid, and von Bethmann et al⁸ confirmed that increased levels of tumor necrosis factor- α and IL-6 are released into the circulation from lungs ventilated with high tidal volumes. Kolobow et al³ evaluated sheep that had been subjected to high or low tidal volume ventilation and found that those ventilated with high tidal volumes died with severe respiratory failure and shock within 48 h. These studies prompted Hickling and colleagues⁹ to use a low tidal volume/low inspiratory pressure strategy of ventilation in patients with severe ARDS, and a retrospective analysis of a series of 50 such patients indicated that mortality was signif-

icantly lower than that predicted by acute physiology and chronic health evaluation (APACHE) II scores (16% vs 39.6%, respectively; $p < 0.001$).

In the late 1990s, four randomized controlled trials^{10–13} were conducted to evaluate the benefit of low tidal volume ventilation in ARDS patients compared with traditional tidal volume ventilation (Table 1). Only one of these trials, conducted by Amato and colleagues,¹⁰ showed a significant reduction in mortality in the experimental treatment group. Patients randomized to tidal volumes of ≤ 6 mL/kg actual body weight and driving pressures of < 20 cm H₂O were significantly less likely to die during the 28-day study period than were patients randomized to the traditional 12 mL/kg actual body weight tidal volumes and unlimited driving pressures (38% vs 71%, respectively; $p = 0.001$). A similar mortality benefit was not shown in the three other randomized trials,^{11–13} and the high mortality in the control group studied by Amato et al¹⁰ made the results of this trial subject to criticism. All four studies had limited statistical power due to small sample sizes, and the differences in tidal volume between treatment groups achieved in the three negative trials were notably smaller than that in the one positive trial, as follows: tidal volumes were 7.0 vs 10.7 mL/kg ideal body weight in the trial by Stewart et al¹¹; 7.1 vs 10.3 mL/kg dry body weight in the trial by Brochard et al¹²; and 7.3 vs 10.2 mL/kg predicted body weight in the trial by Brower et al.¹³

In light of the limitations and conflicting results of the aforementioned randomized trials, a large, well-conducted trial was needed to definitively determine

Table 1—Randomized Controlled Trials Evaluating Strategies of Mechanical Ventilation for the Treatment of ARDS*

Study	Patients, No.	Intervention	Mortality Rates†	p Value
Amato et al ¹⁰	53	≤ 6 mL/kg ABW; VT; < 20 cm H ₂ O Pdriving	38% vs 71%‡	0.001
Stewart et al ¹¹	120	≤ 8 mL/kg IBW; VT; ≤ 30 cm H ₂ O Pplat	50% vs 47%	0.72
Brochard et al ¹²	116	6–10 mL/kg IBW; VT; 25–30 cm H ₂ O Pplat	47% vs 38%§	0.38
Brower et al ¹³	52	≤ 8 mL/kg PBW; VT; ≤ 30 cm H ₂ O Pplat	50% vs 46%	0.61
ARMA ¹⁴	861	≤ 6 mL/kg PBW; VT; ≤ 30 cm H ₂ O Pplat	31% vs 40%	0.007
Derdak et al ³²	148	HFOV	37% vs 52%	0.10
Bollen et al ³³	61	HFOV	43% vs 33%	0.59
ALVEOLI ³⁵	549	High-PEEP protocol	28% vs 25%	0.48
Villar et al ³⁶	103	5–8 mL/kg PBW; VT; PEEP of Pflex + 2 cm H ₂ O	34% vs 56%	0.04
Gattinoni et al ⁴⁹	304	Prone position 6 h/d for 10 d	63% vs 59%¶	0.65
Guerin et al ⁵⁰	791	Prone position 8 h/d	32% vs 32%‡	0.77
Mancebo et al ⁵¹	136	Prone position 20 h/d	50% vs 62%	0.22

*ABW = actual body weight; VT = tidal volume; Pdriving = driving pressure; IBW = ideal body weight; Pplat = plateau pressure; PBW = predicted body weight; HFOV = high-frequency oscillatory ventilation.

†Values are given as the in-hospital mortality rates of intervention vs control group, unless otherwise noted.

‡28-day mortality rate.

§60-day mortality rate.

||30-day mortality rate.

¶180-day mortality rate.

the effect of low tidal volume ventilation in ARDS patients. In response to this need, from 1996 to 1999 the National Heart, Lung, and Blood Institute (NHLBI) ARDS Network enrolled 861 patients at 10 institutions in a randomized controlled trial known as the Respiratory Management in Acute Lung Injury/ARDS (ARMA) trial (originally a factorial trial known as KARMA, the Ketoconazole and Respiratory Management in Acute lung injury/ARDS). ARMA¹⁴ compared a ventilatory protocol using tidal volumes of ≤ 6 mL/kg predicted body weight and maintaining plateau pressures of ≤ 30 cm H₂O with conventional mechanical ventilation using higher tidal volumes. The lower tidal volume protocol in ARMA achieved more pronounced differences between the intervention and control groups in tidal volume (6.2 vs 11.8 mL/kg predicted body weight, respectively) and plateau pressure (25 vs 33 cm H₂O, respectively) than those achieved in previous studies. The hospital mortality rate was significantly reduced in the low tidal volume group compared with the control group (31% vs 39.8%, respectively; $p = 0.007$) [Fig 1]. Additionally, patients treated with low tidal volume ventilation had a greater mean (\pm SD) number of days free of mechanical ventilation (12 ± 11 vs 10 ± 11 days, respectively; $p = 0.007$) and a greater number of days free of nonpulmonary organ failure (15 ± 11 vs 12 ± 11 days, respectively; $p = 0.006$).¹⁴

Compared with the previous studies of low tidal volume ventilation, ARMA had considerable power to detect a difference in clinical outcomes due to the

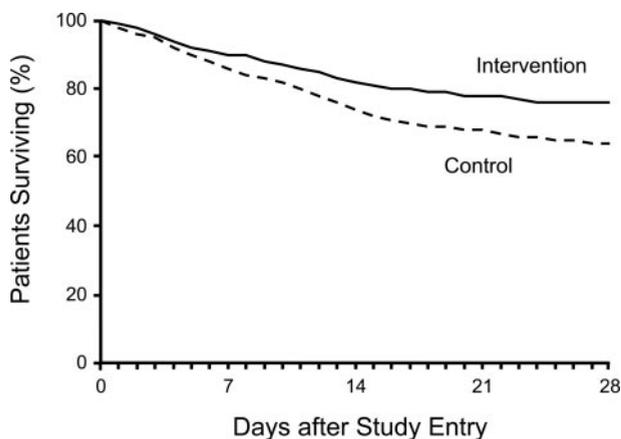


FIGURE 1. Kaplan-Meier analysis of survival during the first 28 days after randomization in patients with ALI and ARDS. The in-hospital mortality rate was 31.0% in the group treated with lower tidal volumes compared with 39.8% in the group treated with traditional tidal volumes ($p = 0.007$; 95% CI for the difference between groups, 2.4 to 15.3%). A Kaplan-Meier analysis of survival during the first 180 days after study entry is presented in the publication by the Acute Respiratory Distress Syndrome Network.¹⁴

large number of patients enrolled (Table 1). And, as described above, the difference in tidal volumes used in the two study groups in ARMA was larger than that obtained in other studies.¹⁵ In fact, it has been proposed that the mortality benefit demonstrated in ARMA was attributable to a high mortality rate in the control group resulting from tidal volumes that were higher than the standard of care. However, in an international survey of physicians' practices in 1992,¹⁵ a broad range of tidal volumes used in ARDS patients was reported, indicating that no uniform standard of care existed, and more than half of the respondents reported using tidal volumes that were as high as or higher than those used in the ARMA control group.

The only method of mechanical ventilation that has been shown in randomized controlled trials to improve survival in patients with ARDS is low tidal volume ventilation (Table 1, Fig 2). In ARMA, ventilation with low tidal volumes and plateau pressures resulted in a nearly 9% absolute reduction in the risk of death.¹⁴ Therefore, high tidal volumes and high plateau pressures should be avoided in patients with ARDS, and critical care clinicians should utilize low tidal volumes as part of a ventilatory protocol that also limits plateau pressure. Specifically, it is recommended that practitioners utilize the ventilatory protocol outlined by the ARDS Network investigators in an ARMA publication from 2000,¹⁴ as this protocol involved more than the use of low tidal volumes, as follows: tidal volume size should be based on predicted body weight (calculated from sex and height) rather than actual body weight; tidal volumes should be systematically adjusted (from 4 to 6 mL/kg predicted body weight) to maintain a plateau pressure of ≤ 30 cm H₂O; the respiratory rate should be titrated as needed (from 6 to 35 breaths/min) to maintain a pH of 7.3 to 7.45; and an appropriate combination of fraction of inspired oxygen (FIO₂) and positive end-expiratory pressure (PEEP) should be used to achieve adequate oxygenation (PaO₂, 55 to 80 mm Hg; or pulse oximetric saturation, 88 to 95%).

Since the publication of ARMA, low tidal volume ventilation has remained underutilized in the treatment of patients with ARDS.^{16–18} Common barriers to the initiation of low tidal volume ventilation include unwillingness to relinquish control of the ventilator, failure to recognize patients as having ALI/ARDS, and perceived contraindications to low tidal volume ventilation.¹⁹ Significant barriers to the continuation of low tidal volume ventilation include concerns regarding patient discomfort and tachypnea or hypercapnia and acidosis.¹⁹

While barriers to the initiation of low tidal volume ventilation remain a significant challenge, more re-

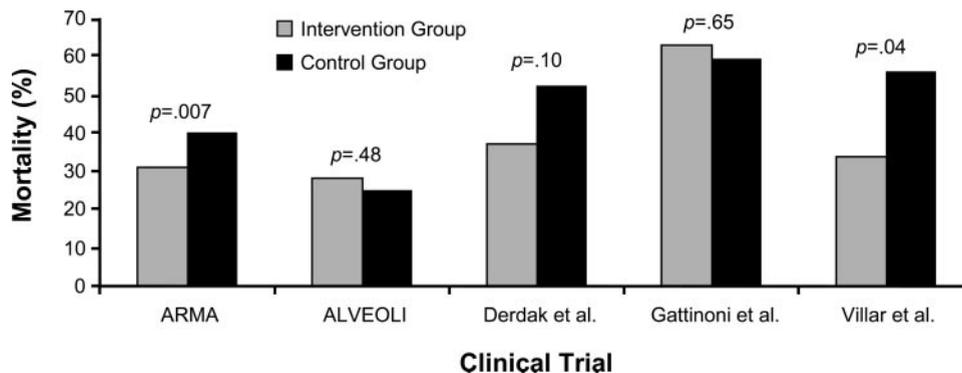


FIGURE 2. Mortality according to treatment group in representative randomized controlled trials evaluating strategies of mechanical ventilation in patients with ALI/ARDS. ARMA compared lower tidal volume ventilation with higher tidal volume ventilation and measured the in-hospital mortality rate.¹⁴ ALVEOLI compared a high-PEEP protocol with lower PEEP and measured the in-hospital mortality rate.³⁵ Derdak et al³² compared high-frequency oscillatory ventilation with conventional ventilation and measured the 30-day mortality rate. Gattinoni et al⁴⁹ compared prone positioning with conventional ventilation and measured the 180-day mortality rate. Villar et al³⁶ compared a protocol of lower tidal volumes with PEEP above the Pflex with higher tidal volumes and lower PEEP, and measured the in-hospital mortality rate.

cent studies have addressed concerns regarding both hypercapnia and patient discomfort. While an acutely elevated PaCO_2 may result in physiologic abnormalities such as vasodilation, tachycardia, and hypotension, multiple studies^{20–22} have demonstrated that modest, permissive hypercapnia occurring as a result of lowering tidal volumes and minute ventilation is safe. While permissive hypercapnia is tolerated in the majority of ARDS patients, those with preexisting metabolic acidosis may require treatment to prevent worsening acidosis. In fact, ARMA¹⁴ allowed the use of both increased respiratory rates (up to 35 breaths/min) and bicarbonate infusions in such patients.

No evidence exists supporting the notion that low tidal volume ventilation results in additional patient discomfort or the need for increased sedation compared with ventilation using larger tidal volumes. In fact, in ARMA the percentage of days during which sedation was used among patients ventilated with low tidal volumes was no different than that among patients ventilated with traditional tidal volumes (*ie*, $65\% \pm 26\%$ vs $65\% \pm 24\%$ in patients discharged home and breathing without assistance; $73\% \pm 24\%$ vs $71\% \pm 28\%$ in patients who died).¹⁴ Additionally, a recent secondary analysis²³ of patients who were enrolled at one center during ARMA demonstrated that low tidal volume ventilation was associated neither with increased dose nor with increased duration of sedatives in patients with ARDS. Therefore, patients with ARDS who are being ventilated with low tidal volumes should be managed with the sedation strategies recommended for all critically ill, mechanically ventilated patients. Specifically, seda-

tion protocols using standardized sedation scales^{24,25} and sedation goals²⁶ have been proven to reduce the duration of mechanical ventilation, and preference should be given to the daily interruption of sedation²⁷ and the use of intermittent boluses rather than continuous infusions,²⁸ when tolerated.

Some have proposed that high-frequency oscillatory ventilation is an ideal mode of ventilation for ARDS patients as it is the natural culmination of low tidal volume ventilation. This mode of ventilation rapidly delivers small tidal volumes that are typically 1 to 5 mL/kg.²⁹ Animal studies³⁰ as well as observational human studies³¹ have suggested that high-frequency oscillatory ventilation improves gas exchange and reduces ventilator-induced lung injury. However, both randomized controlled trials^{32,33} that have been conducted to date to evaluate the efficacy of high-frequency oscillatory ventilation in the treatment of ARDS have failed to demonstrate an improvement in mortality (Table 1). The larger of the two trials, conducted by Derdak and colleagues,³² enrolled 148 ARDS patients and noted that patients who were randomized to high-frequency oscillatory ventilation experienced an early improvement in oxygenation that was not seen in patients who were randomized to conventional ventilation ($p = 0.0008$). The 30-day mortality rate was lower in the high-frequency oscillatory ventilation group compared with that in the control group, but this difference was not statistically significant (37% vs 52%, respectively; $p = 0.10$). Additionally, subjects in the control group were ventilated with higher tidal volumes (mean tidal volume at 72 h, 8 ± 2 mL/kg actual body weight). Therefore, an adequately

powered randomized trial is needed to determine the efficacy of high-frequency oscillatory ventilation compared with low tidal volume ventilation before its use can be widely recommended.

HIGH PEEP AND ALVEOLAR RECRUITMENT

PEEP is an essential component of mechanical ventilation for patients with ARDS that should be utilized to increase the proportion of nonaerated lung, resulting in improved oxygenation. Traditionally, PEEP values of 5 to 12 cm H₂O have been used in the ventilation of patients with ARDS.³⁴ However, it currently remains unclear whether these values are ideal since randomized trials^{14,35,36} have not shown that higher levels of PEEP lead to a reduction in mortality rate.

Early observations that PEEP greatly improves oxygenation in patients with ARDS led to its widespread use in such patients, but the level of PEEP needed to achieve maximum benefit with minimum complications was never established. Additionally, animal models³⁷ have suggested that repetitive opening and closing of the alveoli during the respiratory cycle can promote lung injury. Therefore, several randomized trials evaluated the efficacy of high levels of PEEP in the treatment of ARDS. In the study of a protective-ventilation strategy, by Amato and colleagues,¹⁰ PEEP was significantly higher in the intervention group compared with the control group (mean PEEP on days 2 to 7, 13.2 ± 0.4 vs 9.3 ± 0.5 cm H₂O; *p* < 0.01). Villar et al³⁶ evaluated a similar strategy in a randomized controlled trial that enrolled patients with persistent ARDS (the PaO₂/FIO₂ ratio remained ≤ 200 for at least 24 h while standard ventilator settings were used). Patients in the intervention group were ventilated with tidal volumes of 5 to 8 mL/kg predicted body weight, and PEEP was set on day 1 at 2 cm H₂O above P_{flex}, defined as the lower inflection point on the pressure-volume curve of the respiratory system. The control group was ventilated with tidal volumes of 9 to 11 mL/kg predicted body weight and a PEEP of ≥ 5 cm H₂O. This difference resulted in a significantly higher PEEP among intervention patients compared with control patients (mean PEEP on day 1, 14.1 ± 2.8 vs 9.0 ± 2.7 cm H₂O, respectively; *p* < 0.001) as well as a significantly lower ICU mortality rate among intervention patients (32% vs 53.3%, respectively; *p* = 0.04). Ranieri et al³⁸ determined that a similar ventilatory strategy (mean PEEP at 2 to 3 h, 14.8 ± 2.7 vs 6.5 ± 1.7 cm H₂O, respectively; mean tidal volume at 2 to 3 h, 7.6 ± 1.1 vs 11.1 ± 1.9 mL/kg, respectively) resulted in an attenuation of the cytokine response observed in

patients who were ventilated with higher tidal volumes and lower PEEP. But neither these findings nor the significantly lower mortality rates observed in the intervention groups in the trials of both Villar et al³⁶ and Amato et al¹⁰ could be solely attributed to higher levels of PEEP since the intervention strategies in these trials employed both low tidal volumes and high levels of PEEP. The isolated benefit to survival of low tidal volume ventilation was demonstrated in ARMA,¹⁴ as discussed previously, since patients in the intervention group were treated with levels of PEEP that were no different than those utilized in the control group. But another trial was needed to evaluate the efficacy of high PEEP in which all patients received low tidal volume ventilation.

In order to determine the isolated benefit of high levels of PEEP in patients with ARDS, the National Heart, Lung, and Blood Institute ARDS Network conducted another large randomized controlled trial known as the ALVEOLI trial (Assessment of Low tidal Volume and Elevated End-Expiratory Pressure To Obviate Lung Injury).³⁵ Patients were randomized to a ventilatory protocol utilizing high levels of PEEP (12 to 24 cm H₂O) or low levels of PEEP (5 to 24 cm H₂O); all patients were ventilated with low tidal volumes (6 mL/kg predicted body weight). PEEP was significantly higher among intervention patients compared with control patients throughout the study period (mean PEEP on day 1, 14.7 ± 3.5 vs 8.9 ± 3.5 cm H₂O, respectively; mean PEEP on day 3, 12.9 ± 4.5 vs 8.5 ± 3.7 cm H₂O, respectively; mean PEEP on day 7, 12.9 ± 4.0 vs 8.4 ± 4.3 cm H₂O, respectively). Although the patients treated with higher PEEP clearly experienced increases in oxygenation, as measured by the PaO₂/FIO₂ ratio, compared with patients treated with lower PEEP, the in-hospital mortality rate was similar in the two treatment groups (*p* = 0.48) [Table 1]. The duration of mechanical ventilation and the duration of non-pulmonary organ failure were similar in the two groups as well.

The ALVEOLI trial also evaluated the safety and efficacy of recruitment maneuvers in the first 80 patients randomized to the high-PEEP group. These maneuvers, like high levels of PEEP, are intended to promote alveolar recruitment and to attenuate the injurious effects of the repetitive opening and closing of the alveoli. Continuous positive airway pressure of 35 to 40 cm H₂O was applied for 30 s, and the results were compared to those of a sham recruitment maneuver. Because the interventions resulted in only small and transient increases in oxygenation, they were discontinued. Such maneuvers have been associated with transient but significant hypotension and hypoxemia,³⁹ and their long-term benefit re-

mains unproven; therefore, their routine use is not recommended in patients with ARDS.

PRONE POSITIONING

Mechanical ventilation in the prone position was first proposed in 1974 by Bryan,⁴⁰ who suggested that the procedure would result in better expansion of the dorsal lung regions, thus improving oxygenation. Shortly thereafter, two nonrandomized studies^{41,42} reported the successful use of prone positioning as an adjunct to mechanical ventilation for the treatment of ARDS, with patients experiencing improved oxygenation. In the 3 decades following these initial reports, interest in prone positioning has remained strong, although the physiologic mechanisms leading to improved oxygenation during prone positioning are not yet fully understood.⁴³ The existing evidence suggests that mechanical ventilation in the prone position improves oxygenation and respiratory mechanics via multiple mechanisms, including alveolar recruitment,⁴⁴ redistribution of ventilation toward dorsal areas resulting in improved ventilation/perfusion matching,^{45,46} and the elimination of compression of the lungs by the heart.⁴⁷ Additionally, prone ventilation may lower the incidence of ventilator-induced lung injury by reducing parenchymal lung stress and lung strain.⁴⁸

Three randomized controlled trials^{49–51} of prone positioning during mechanical ventilation in ARDS patients have shown consistent findings. While the majority of patients experience improved oxygenation in response to prone positioning, this method of mechanical ventilation does not lead to a reduction in mortality (Table 1).^{49–51} In the largest of these trials, Guerin and colleagues⁵⁰ enrolled 791 patients with acute respiratory failure (413 had ALI/ARDS), randomizing each to prone position placement for at least 8 h daily or to standard therapy in the supine position. $\text{PaO}_2/\text{FIO}_2$ ratio was significantly higher throughout the 28-day study period in the prone position group ($p < 0.001$), but this physiologic change did not decrease the mortality rate at 28 days (prone position, 32.4%; supine position, 31.5%; $p = 0.77$) or at 90 days (prone position, 43.3%; supine position, 42.2%; $p = 0.74$). Prone positioning did result in a significantly higher incidence of several complications compared with ventilation in the supine position, including selective intubation ($p = 0.01$), endotracheal tube obstruction ($p = 0.002$), and pressure sores ($p = 0.005$). Gattinoni et al⁴⁹ enrolled ALI/ARDS patients exclusively and reported similar findings. A *post hoc* analysis of patients with the lowest $\text{PaO}_2/\text{FIO}_2$ ratio (≤ 88) found that the 10-day mortality rate was significantly

lower in the prone position group compared with the supine position group (23.1% vs 47.2%, respectively; relative risk, 0.49; 95% confidence interval [CI], 0.25 to 0.95). Prone positioning was similarly beneficial for patients with high severity-of-illness scores or high tidal volumes, but the benefits noted in the *post hoc* analyses did not persist beyond ICU discharge.

Despite consistently leading to short-term improvements in oxygenation, prone positioning during mechanical ventilation has failed to improve mortality rates in multiple randomized controlled trials (Table 1) and cannot be recommended for the broad population of patients requiring mechanical ventilation due to ARDS. However, for those patients requiring potentially injurious levels of FIO_2 (*ie*, $> 60\%$) or plateau pressure (*ie*, > 30 cm H_2O) due to persistent, severe hypoxemia, whose conditions are being managed in an experienced institution, prone positioning may be considered as a short-term rescue therapy. In such circumstances, the potential for life-threatening complications of prone positioning, including accidental dislodgment of the endotracheal tube or central venous catheters and endotracheal tube obstruction, should be weighed against the short-term benefit of improved oxygenation.

ALTERNATIVE MODES/METHODS OF MECHANICAL VENTILATION

Both large trials conducted by the ARDS Network utilized the volume assist/control mode of ventilation. In fact, this was the only mode of ventilation used in each of the three randomized controlled trials of ARDS in which the intervention significantly reduced mortality.^{10,14,35} Although the efficacy of low tidal volume ventilation is not necessarily contingent on the use of the volume assist/control mode of ventilation, it continues to be the recommended mode in the general population of patients with ARDS.

However, other modes of mechanical ventilation are available and may provide critical care and respiratory care practitioners with alternative treatments for ARDS patients with refractory hypoxemia. In addition to the previously described high-frequency oscillatory ventilation, inverse ratio ventilation (IRV) and airway pressure release ventilation (APRV) may be considered in difficult-to-manage ARDS patients. IRV, during which the ratio of inspiratory time to expiratory time exceeds 1, can be achieved using either volume or pressure modes of ventilation. Prolongation of the inspiratory time results in increased mean airway pressures, often improving oxygenation. APRV uses high continuous airway pressure to promote alveolar recruitment and

to maintain adequate lung volume, and a time-cycled release phase to a lower pressure in supplementing spontaneous minute ventilation.⁵² By allowing unrestricted spontaneous breathing throughout the ventilator cycle, APRV allows for better ventilation of dependent lung regions; spontaneous breathing reduced atelectasis and improved end-expiratory lung volume in oleic acid-induced lung injury.⁵³ This can lead to improved ventilation-perfusion matching and better oxygenation, changes that have been demonstrated in patients with ARDS who have received ventilation with APRV with spontaneous breathing.⁵⁴ While both IRV and APRV may provide short-term physiologic benefits to patients with severe ARDS, their widespread use is not recommended due to the lack of randomized controlled trials demonstrating their efficacy against clinically relevant end points in ARDS, such as mortality and duration of mechanical ventilation.

Partial liquid ventilation using perfluorocarbons for the treatment of ARDS has been evaluated in two randomized controlled trials. Hirschl et al⁵⁵ randomized 90 patients with ARDS to perflubron or conventional ventilation and found no difference in mortality or duration of mechanical ventilation, while Kacmarek et al⁵⁶ randomized 311 ARDS patients to receive high-dose perflubron, low-dose perflubron, or conventional ventilation and found no improvement in outcome. Therefore, partial liquid ventilation is not recommended for the treatment of ARDS.

Noninvasive positive-pressure ventilation (*ie*, mechanical ventilation administered without the use of an invasive endotracheal airway) has been used successfully for the treatment of acute respiratory failure in a number of clinical trials, and it has been suggested⁵⁷ that noninvasive positive-pressure ventilation may be useful for the treatment of ARDS. However, randomized trials evaluating the efficacy and safety of noninvasive positive-pressure ventilation in patients with hypoxemic respiratory failure have failed to show a benefit in subgroups of patients with ARDS.⁵⁸ Therefore, while noninvasive positive-pressure ventilation may have value in some ARDS patients who are carefully selected by experienced practitioners, its routine use in this population of patients is not recommended.⁵⁹

LIBERATION FROM MECHANICAL VENTILATION

As the majority of patients who are mechanically ventilated for acute respiratory failure spend approximately two thirds of their time on the ventilator in the “weaning” period,³⁴ a systematic, evidence-based approach to liberating ARDS patients from mechanical ventilation is an essential component of their

care. This approach should be protocol-directed, and a daily spontaneous breathing trial should be the central component of that protocol.

Several randomized controlled trials^{60–62} have demonstrated that the duration of mechanical ventilation is significantly reduced in patients who have been assessed once daily with a spontaneous breathing trial, consisting of a period of 30 to 120 min of unassisted breathing. Esteban et al⁶⁰ enrolled 546 patients with respiratory failure (319 patients had ALI/ARDS) and randomized those who failed an initial 2-h spontaneous breathing trial to one of four weaning methods. Patients managed with a once-daily spontaneous breathing trial were extubated more quickly than those managed with intermittent mandatory ventilation ($p < 0.006$) and those managed with pressure-support ventilation ($p < 0.04$). Ely et al⁶¹ randomized 300 patients (42 patients had ARDS) to a weaning protocol utilizing a daily spontaneous breathing trial or to usual care and determined that patients managed with the weaning protocol were extubated more quickly than those managed with usual care ($p < 0.001$) [Fig 3]. A T-piece, continuous positive airway pressure, or pressure support ventilation of ≤ 7 cm H₂O may be utilized,⁶³ and the spontaneous breathing trial should be performed only in patients meeting the following standardized safety criteria: (1) some reversal of the

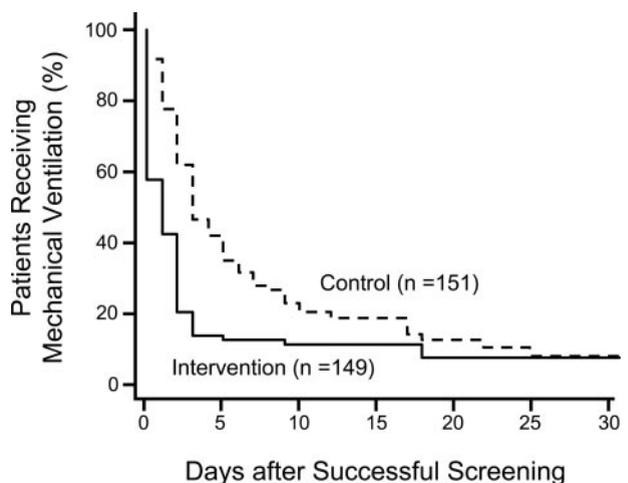


FIGURE 3. Kaplan-Meier analysis of the duration of mechanical ventilation in medical ICU patients with acute respiratory failure. After adjustment for the severity of illness at baseline (as measured by APACHE II score), age, sex, race, location of the ICU, and duration of intubation before enrollment, a Cox proportional hazards analysis showed that mechanical ventilation was discontinued more rapidly in the intervention group than in the control group (relative risk of successful extubation, 2.13; 95% CI, 1.55 to 2.92; $p < 0.001$). The intervention consisted of a weaning protocol mandating the daily screening of respiratory function followed by 2-h spontaneous breathing trials in those who met the screening criteria. Copyright 1996 Massachusetts Medical Society. All rights reserved.⁶¹

underlying cause for respiratory failure; (2) PEEP of ≤ 8 cm H₂O and FIO₂ of $\leq 50\%$; (3) hemodynamic stability; and (4) ability to initiate inspiratory efforts.⁶⁴ When possible, all mechanically ventilated patients should be placed in a semirecumbent position in order to reduce the incidence of ventilator-associated pneumonia.⁶⁵

CONCLUSION

In the management of patients with ARDS, low tidal volume ventilation (*ie*, ≤ 6 mL/kg predicted body weight) with the maintenance of plateau pressures of < 30 cm H₂O, when possible, remains the standard of care as it is the only method of mechanical ventilation that has been proven to reduce the mortality rate. While modifications of these parameters could result in even better outcomes than those observed in the ARMA and ALVEOLI trials (Fig 2), randomized controlled trials should be performed to determine the efficacy and safety of such alterations. Other methods, such as high-PEEP ventilation, alveolar recruitment maneuvers, and prone positioning, may be useful as rescue therapy in carefully defined situations of severe hypoxemia, but their use is not widely recommended as these methods do not improve mortality in the broad population of ARDS patients. Ongoing trials are currently evaluating the efficacy of newer modes and methods of mechanical ventilation, such as high-frequency oscillatory ventilation. The results of these studies will guide the management of ARDS patients in the future.

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