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Authors

Wilson, Jennifer G
Matthay, Michael A

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Mechanical Ventilation in Acute Hypoxemic Respiratory Failure: A Review of New Strategies for the Practicing Hospitalist

Jennifer G. Wilson, MD, MS¹ and Michael A. Matthay, MD^{2,*}

¹Department of Medicine, Division of Critical Care, University of California San Francisco, San Francisco, California

²Cardiovascular Research Institute and Departments of Medicine and Anesthesiology, Division of Pulmonary and Critical Care, University of California San Francisco, San Francisco, California

Abstract

BACKGROUND—The goal of mechanical ventilation in acute hypoxemic respiratory failure is to support adequate gas exchange without harming the lungs. How patients are mechanically ventilated can significantly impact their ultimate outcomes.

METHODS—This review focuses on emerging evidence regarding strategies for mechanical ventilation in patients with acute hypoxemic respiratory failure including: low tidal volume ventilation in the acute respiratory distress syndrome (ARDS), novel ventilator modes as alternatives to low tidal volume ventilation, adjunctive strategies that may enhance recovery in ARDS, the use of lung-protective strategies in patients without ARDS, rescue therapies in refractory hypoxemia, and an evidence-based approach to weaning from mechanical ventilation.

RESULTS—Once a patient is intubated and mechanically ventilated, low tidal volume ventilation remains the best strategy in ARDS. Adjunctive therapies in ARDS include a conservative fluid management strategy, as well as neuromuscular blockade and prone positioning in moderate-to-severe disease. There is also emerging evidence that a lung-protective strategy may benefit non-ARDS patients. For patients with refractory hypoxemia, extracorporeal membrane oxygenation should be considered. Once the patient demonstrates signs of recovery, the best approach to liberation from mechanical ventilation involves daily spontaneous breathing trials and protocolized assessment of readiness for extubation.

CONCLUSIONS—Prompt recognition of ARDS and use of lung-protective ventilation, as well as evidence-based adjunctive therapies, remain the cornerstones of caring for patients with acute hypoxemic respiratory failure. In the absence of contraindications, it is reasonable to consider lung-protective ventilation in non-ARDS patients as well, though the evidence supporting this practice is less conclusive.

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*Address for correspondence and reprint requests: Michael A. Matthay, MD, University of California Cardiovascular Research Institute, Box 0624, 505 Parnassus Avenue, Room M917, San Francisco, CA 94143; Telephone: 415-353-1206; Fax: 415-353-1990; michael.matthay@ucsf.edu.

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The indications for endotracheal intubation and mechanical ventilation in acutely hypoxemic patients depend on the severity of respiratory failure as well as the patient's hemodynamic and neurologic status. Once intubated, however, how a patient is ventilated can have a significant impact on the subsequent hospital course and ultimate outcome. Regardless of whether the hospitalist manages the ventilator directly, comanages patients in the intensive care unit (ICU), or merely transfers a hypoxemic patient into or out of an intensivist-run unit, a basic familiarity with the evidence supporting various mechanical ventilation strategies will enhance the care provided. It is also helpful to understand the goals of mechanical ventilation in acute hypoxemic respiratory failure, such as minimizing the risk of ventilator-induced lung injury, enhancing recovery from the underlying cause of respiratory failure, and limiting the duration of mechanical ventilation.¹⁻³ With these objectives in mind, this review will examine the evidence that supports specific ventilator strategies in common clinical conditions that cause acute hypoxemia.

First, we will discuss the evidence supporting the use of low tidal volume ventilation in patients with the acute respiratory distress syndrome (ARDS), as well as several novel ventilator modes that have been proposed as alternatives to low tidal volume ventilation in ARDS. We will also briefly review adjunctive therapies that may enhance the efficacy of lung-protective ventilation in ARDS. We will then discuss emerging evidence regarding the use of lung-protective ventilation strategies in patients without ARDS, as well as potential contraindications to this approach. Finally, we will cover rescue strategies for refractory hypoxemia, as well as an evidence-based approach to weaning from mechanical ventilation.

LUNG-PROTECTIVE VENTILATION IN ARDS

Low Tidal Volume Ventilation

Over a decade following the original ARDS Clinical Network trial of lower versus traditional tidal volume ventilation, it is broadly accepted that ventilation with tidal volumes 6 mL/kg predicted body weight, targeting a plateau pressure 30 cm H₂O, reduces mortality and increases ventilator-free days in patients with ARDS.⁴⁻⁶ Moreover, lung-protective ventilation appears to reduce mortality in all patients with ARDS, regardless of the associated clinical disorder.⁷ The substantial decline in mortality in ARDS observed over the past decade (Figure 1) is due in part to the broader use of lung-protective ventilation.^{8,9}

Despite the strong evidence supporting the value of lung-protective ventilation for decreasing mortality in ARDS, adherence to low tidal volume strategies in ARDS patients remains variable.^{10,11} This may be due to several reasons, including (1) mistakenly using actual instead of predicted body weight to determine appropriate tidal volume, (2) lack of awareness of the changes made by the most recent consensus-based definition of ARDS (Table 1),¹² (3) under-recognition of the heterogeneity of chest radiograph findings in ARDS (Figure 2), and (4) underdiagnosis of ARDS by providers.¹³ Thus, prompt recognition of ARDS and the immediate initiation of lung-protective ventilation strategies should be a high priority in caring for all patients with ARDS. Table 2 summarizes how to implement the ARDS network lung-protective strategy, including how to determine the correct tidal volume based on predicted body weight, calculated from the patient's sex and

height. Although a full discussion of the relative merits of pressure control versus volume control ventilation is outside the scope of this review, it is worth noting that either mode can be used to achieve low tidal volumes, and which mode is selected is often determined by individual patient factors and institutional or provider preference.

Positive End-Expiratory Pressure and Recruitment Maneuvers

The application of positive end-expiratory pressure (PEEP) can prevent alveolar derecruitment and atelectrauma; too much PEEP, however, can cause alveolar overdistension or hemodynamic compromise due to high intrathoracic pressures and decreased venous return. Likewise, recruitment maneuvers, in which a high PEEP is applied for a brief interval, may improve oxygenation by opening up atelectatic alveoli, but can also cause barotrauma or hemodynamic compromise. Thus, in addition to research into the effects of low tidal volume ventilation, 3 additional trials have tested the potential value of higher versus lower PEEP in ARDS.^{14–16} Although none of these trials showed a significant reduction in mortality with a higher PEEP strategy, a recent meta-analysis of the data from all 3 trials reported a statistically significant mortality benefit for ARDS patients with a higher-PEEP strategy versus a lower-PEEP strategy (adjusted relative risk [RR], 0.90; 95% confidence interval [CI], 0.81–1.00; $P = 0.049$).¹⁷ Because of differences in trial design and patient selection, however, a change of practice cannot be reasonably based on this meta-analysis alone. Current research is focused on whether there is a subset of ARDS patients who may benefit from a higher PEEP strategy, and how best to determine optimal PEEP more generally.^{18,19} In addition to these ongoing questions about PEEP, the value of recruitment maneuvers remains uncertain.^{1,20}

High-Frequency Oscillating Ventilation

High-frequency oscillating ventilation (HFOV) is a technique in which very small tidal volumes are delivered at high frequency (3–15 breaths per second) at high mean airway pressures. Until recently, trials of HFOV in ARDS have been inconclusive due to small size or inappropriate control arms that did not utilize low tidal volume ventilation.²¹ However, 2 recent large, multicenter, randomized trials comparing HFOV to low tidal volume ventilation in ARDS have shown that there is no benefit (and perhaps even harm) associated with HFOV. The Oscillation in ARDS (OSCAR) trial reported no change in mortality, whereas the Oscillation for Acute Respiratory Distress Syndrome Treated Early (OSCILLATE) trial found that HFOV was associated with increased risk of death.^{22,23} As such, HFOV is no longer recommended in ARDS.

Airway Pressure Release Ventilation

Airway pressure release ventilation (APRV) is a mode of ventilation, in which a relatively high level of continuous positive airway pressure (P high) is applied for a large portion of the respiratory cycle. During the time spent at P high (T high), the patient can take small spontaneous breaths, with or without the assistance of additional pressure support. At the end of T high, the applied pressure “releases” to a lower level (P low) for a brief time (T low) to allow CO₂ clearance (Figure 3).

Theoretically, the long inflation time in APRV allows for more uniform recruitment of alveoli and raises mean airway pressure without increasing barotrauma. APRV also allows for spontaneous breathing even at high levels of support. Despite preclinical and observational data suggesting that APRV may reduce the development or progression of lung injury,^{24–27} prospective clinical trials comparing APRV to low tidal volume ventilation have yet to support any clear benefit, and 1 trial has demonstrated a trend toward more days of mechanical ventilation.^{28,29} Multiple clinical trials are ongoing (NCT01901354, NCT01339533), but in the interim, the use of APRV instead of conventional low tidal volume ventilation is not supported by high-level evidence.

ADJUNCTIVE THERAPIES IN ARDS

Although a full discussion of the numerous nonventilatory therapies that have been tested for ARDS is beyond the scope of this focused review, several of these strategies have been shown to improve outcomes and deserve mention here.

Fluid Management

The first such therapy is the implementation of a fluid conservative strategy. This approach is based on the ARDS network Fluid and Catheter Treatment Trial (FACTT), which demonstrated that in the absence of shock or oliguria, a fluid-conservative strategy improves lung function and decreases the duration of mechanical ventilation in ARDS patients.³⁰ Indeed, multiple studies have found that a positive fluid balance is associated with worsened multiorgan dysfunction and poor outcomes in patients with ARDS.³¹ In terms of translating this evidence into practice, the ARDS Network has published a simplified algorithm for conservative fluid management based on the results of FACTT.³²

Prone Positioning

Although prone positioning during mechanical ventilation improves oxygenation by improving lung recruitment and ventilation-perfusion matching, several early trials of prone positioning did not demonstrate a mortality benefit. Although a 2010 meta-analysis of 10 previous trials did find a mortality benefit in the most hypoxemic patients, there was also an increased risk of pressure ulcers and endotracheal tube obstruction.³³ Thus, the indications for prone positioning in ARDS remained uncertain until 2013, when Guerin et al. reported the results of a large, multicenter, randomized trial that demonstrated a major reduction in mortality in ARDS patients treated with prone positioning.³⁴ The trial included 466 patients with early ARDS, in whom the ratio of partial pressure of arterial oxygen to fraction of inspired oxygen ($\text{PaO}_2/\text{FiO}_2$) was < 150 mm Hg on an FiO_2 of at least 0.6 and PEEP of at least 5 cm H_2O . Of note, all the sites involved in the trial (26 centers in France, 1 in Spain) had extensive experience with prone positioning prior to the trial. The rate of death at 28 days was 33% in the supine group and 16% in the prone group (hazard ratio 0.39 [95% CI, 0.25–0.63]; $P < 0.001$); this mortality reduction persisted at 90 days, and after adjustment for Sequential Organ Failure Assessment (SOFA) score, use of vasopressors, and use of neuromuscular blockade. Finally, there was no difference in adverse events (such as unplanned extubation) between groups. Implementation of prone-positioning protocols in less experienced centers with higher rates of obesity will be challenging, and additional

confirmatory trials would be ideal. Nevertheless, this trial will prompt broader application of prone positioning in patients with moderate to severe ARDS.

Neuromuscular Blockade

In addition to conservative fluid management, early consideration of neuromuscular blockade (NMB) in patients with moderate-to-severe ARDS likely improves outcomes. NMB may enhance the protective effects of low tidal volume ventilation in the most hypoxemic ARDS patients, because it removes the resistance of the chest wall and the diaphragm, and more importantly, reduces dyssynchrony between the patient and the ventilator. Although previous studies of NMB in ARDS yielded conflicting results, a more recent well-done randomized clinical trial showed a mortality benefit. In this trial, 340 patients with a PaO₂/FiO₂ ratio of <150 mm Hg were randomized to receive a 48-hour infusion of cisatracurium (a non-depolarizing neuromuscular blocking agent) or placebo within 48 hours of ARDS onset.³⁵ Both groups were deeply sedated and ventilated with low tidal volumes, but mortality was lower in patients treated with NMB compared to patients who did not receive NMB. Although there are understandable concerns that NMB will mask the ability to detect important changes in the patient's clinical exam and increase risk of ICU-acquired weakness, the results of this trial suggest that clinicians should strongly consider early, short-term NMB with cisatracurium in patients with moderate-to-severe ARDS.

Other Pharmacotherapies

Although several other pharmacologic interventions for ARDS have been studied (eg, glucocorticoids, exogenous surfactant, activated protein C, inhaled β -agonists), none has demonstrated a mortality benefit.⁹

BEYOND ARDS: LUNG-PROTECTIVE VENTILATION FOR ALL?

Low Tidal Volume Ventilation Strategies in Patients Without ARDS

Given concerns about ventilator-induced lung injury and the known benefits of lung-protective ventilation in patients with ARDS, there is growing interest in determining whether low tidal volume ventilation may be beneficial to mechanically ventilated patients who do not have ARDS. In 2010, Serpa Neto et al. published a meta-analysis of 20 studies (mixed population of >2800 ICU and operating room patients) comparing lower versus higher tidal volume ventilation in patients without ARDS.³⁶ They found that low tidal volume ventilation (mean tidal volume of 6.5 mL/kg) was associated with significantly decreased mortality and risk of lung injury compared to ventilation with higher tidal volumes (mean tidal volume 10.6 mL/kg). This investigation has been followed by a randomized, double-blind trial of intraoperative low tidal volume ventilation in 400 patients at intermediate or high risk for pulmonary complications after major abdominal surgery.³⁷ Remarkably, lower tidal volume ventilation was associated with a decreased risk of both pulmonary and extrapulmonary complications in the first week following surgery. These studies are in line with preclinical animal studies that show an association between higher tidal volume ventilation and development of lung injury.³⁸ Although this evidence does not warrant indiscriminate low tidal volume ventilation in all critically ill patients, it certainly

suggests that clinicians should strongly consider lung protective ventilation in patients at high risk for ARDS (eg, patients with pneumonia, aspiration, sepsis, or massive transfusion), and points to an urgent need for more randomized clinical trials of low tidal volume and lung-protective ventilation in various groups of patients who do not have ARDS.

Potential Contraindications to Lower Tidal Volume, Higher PEEP Ventilation

Despite speculation that a lower tidal volume ventilation strategy may be superior to conventional ventilation in most mechanically ventilated patients, there are some clinical scenarios in which typical lung-protective ventilation protocols are not appropriate. First, there are some patients (eg, patients with neurologic injury or pulmonary hypertension) in whom the lower oxygenation and permissive hypercapnia targeted by lung-protective ventilation protocols may be harmful. Second, higher PEEP protocols may be dangerous for patients with pneumothorax or who are at risk for bronchopleural fistula. Third, patients with airway obstruction often require lower respiratory rates to permit maximization of expiratory time; if tidal volume is lowered aggressively as part of a lung-protective ventilation protocol, higher respiratory rates may be required to achieve PaCO₂/arterial pH goals, leading to decreased expiratory time and worsening air trapping. Finally, because mandatory low tidal volumes may be poorly tolerated in some patients, allowing low-risk patients to transition directly to a spontaneous breathing mode may have benefits that outweigh those of lung-protective ventilation protocols, including decreased need for sedating medications, less muscle atrophy, shorter duration of intubation and mechanical ventilation, and a lower incidence of delirium.³⁹

RESCUE THERAPIES FOR REFRACTORY HYPOXEMIA

Despite treatment with lung-protective ventilation and the best adjunctive strategies, some patients may progress to develop life-threatening, refractory hypoxemia. Beyond the therapies already discussed (ie, prone positioning or neuromuscular blockade), there are additional interventions that should be considered in such cases.

Inhaled Vasodilator

Inhaled vasodilators may improve ventilation-perfusion matching and improve pulmonary hypertension by selectively causing local vasodilation in well-ventilated areas of the lung. Although there are several inhaled vasodilators available, including inhaled nitric oxide (iNO), inhaled prostacyclin, and inhaled prostaglandin E1, the best studied in ARDS is iNO. Although multiple studies have found transient improvement in oxygenation with iNO therapy in ARDS, a mortality benefit has never been demonstrated.⁴⁰ In addition, concerns about high cost, sophisticated equipment requirements, the risk of methemoglobinemia, and the potential increased risk of renal failure found in a 2007 meta-analysis have limited the use of iNO in ARDS.⁴¹ Thus, inhaled vasodilators should be considered only for patients with preexisting pulmonary hypertension or as a true rescue therapy in refractory hypoxemia cases, where the transient oxygenation could act as a bridge to other therapies.⁴⁰

Extracorporeal Membrane Oxygenation

The use of extracorporeal membrane oxygenation (ECMO) in refractory acute hypoxemic respiratory failure in adults is an evolving therapy for which evidence is still emerging. During ECMO, blood is removed from the body, circulated by a mechanical pump through a membrane oxygenator, and then returned to the body. Observational studies have shown improved survival with ECMO compared to historic survival rates, and a study of 75 matched pairs of patients with severe influenza A (H1N1)-related ARDS comparing mortality between patients transferred to an ECMO center and those who continued to receive conventional care, found improved survival in transferred patients compared to matched, nonreferred patients.⁴² The Conventional Ventilation or ECMO for Severe Adult Respiratory Failure (CESAR) trial was a multicenter trial in which 180 patients with severe but potentially reversible respiratory failure were randomized to receive either conventional management or referral for consideration of ECMO to a major referral center in the United Kingdom.⁴³ Of the 90 patients referred for ECMO consideration, 76% actually received ECMO. Death or severe disability at 6 months occurred in 37% of the ECMO-referred patients versus 53% of the conventional therapy patients (RR, 0.69; 95% CI, 0.05–0.97; $P = 0.03$). Whether the benefit observed in the CESAR trial was due to ECMO itself or due to coin-terventions and expert management at the referral ECMO center remains unclear. The exact indications, timing, titration, optimal cointerventions, and end points of ECMO therapy are likewise unsettled, and further trials are ongoing in Europe (NCT01470703). Nonetheless, based on the findings of the CESAR trial, consideration of transfer to an experienced ECMO center is recommended for patients with refractory hypoxemia who fail aggressive conventional therapy, and have potentially reversible disease or are possible candidates for lung transplant.⁴⁴

LIBERATION FROM MECHANICAL VENTILATION

Once the underlying cause of respiratory failure is resolved and the patient demonstrates improvement, clinicians' attention must turn to decreasing the duration of mechanical ventilation. Some argue that the phrase "weaning from mechanical ventilation" is not always appropriate, as it implies a protracted, gradual process that is often not required; "liberation from mechanical ventilation" has been offered as a better description of the task of transitioning a patient back to normal breathing after they demonstrate readiness for spontaneous breathing and extubation.³ Regardless of the terminology, the same principle applies: once ready, patients should be extubated as expeditiously as possible.

In addition to evidence-based management strategies aimed at limiting the time a patient requires mechanical ventilation (such as lung-protective ventilation, a fluid conservative strategy, and ventilator-associated pneumonia prevention bundles), there is also the question of how to best assess whether a patient is ready for transition back to normal breathing, and how to operationalize that transition. This process may account for more than half of the total duration of mechanical ventilation in some cases.³ Based on evidence from trials assessing various weaning protocols published in the 1990s, daily spontaneous breathing trials (in which the ventilator provides zero or minimal support during patient triggered breaths) are favored over slow weaning of pressure support or intermittent mandatory

ventilation.⁴⁵ Although several novel ventilator modes aimed at improving patient-ventilator interaction (eg, adaptive support ventilation, proportional assist ventilation, and neurally adjusted ventilatory assistance) have been proposed as optimal weaning modes, their benefit is theoretical, and data demonstrating improved outcomes are lacking.²⁸

In addition to evidence supporting daily spontaneous breathing trials (SBTs), a Cochrane Database systematic review and meta-analysis published in 2011 found that protocolized weaning was associated with shorter duration of mechanical ventilation than usual care.² Although the specifics of what constitutes the optimal weaning protocol remain unclear, there is general agreement that a standardized approach involving prespecified criteria and daily assessment for readiness for spontaneous breathing and potential extubation improves patient outcomes.³ If the SBT is well tolerated hemodynamically, respiratory mechanics and gas exchange remain adequate, and airway factors and mental status permit, the patient should be extubated.

As emphasized in an excellent recent review by McConville and Kress, patients who fail 3 or more SBTs, or remain mechanically ventilated for 7 or more days following their first failed SBT, as well as patients who require reintubation after failed extubation, are at increased risk of in-hospital mortality and prolonged hospital stay.^{3,46} For patients who fall into these categories without a clearly reversible cause, clinicians should consider initiating discussions about tracheostomy and goals of care. It should be noted, however, that multiple trials have failed to demonstrate the benefit of early tracheostomy, and the optimal timing of this intervention remains uncertain.⁴⁷

CONCLUSIONS

When hypoxemic respiratory failure requires endotracheal intubation and mechanical ventilation, the clinician's management of the ventilator can have a profound impact on patient outcomes. Prompt recognition of ARDS and use of a lung-protective ventilation strategy, as well as evidence-based adjunctive therapies, remain the cornerstones of caring for patients with ARDS. Based on 2 recent large trials, HFOV is no longer recommended in ARDS. APRV in ARDS is also not supported by current evidence, though clinical trials are ongoing. In contrast, certain adjunctive therapies in ARDS, such as a conservative fluid strategy, early neuromuscular blockade, and prone positioning for moderate-to-severe cases, improve outcomes. There is also preliminary evidence to support the use of a lung-protective strategy in selected non-ARDS patients, especially in patients at high risk for developing ARDS. In cases of refractory hypoxemia and potentially survivable disease, extracorporeal membrane oxygenation should be considered. Finally, once the patient demonstrates signs of recovery, the best approach to liberation from mechanical ventilation involves daily protocolized, spontaneous breathing trials and assessment of readiness for extubation.

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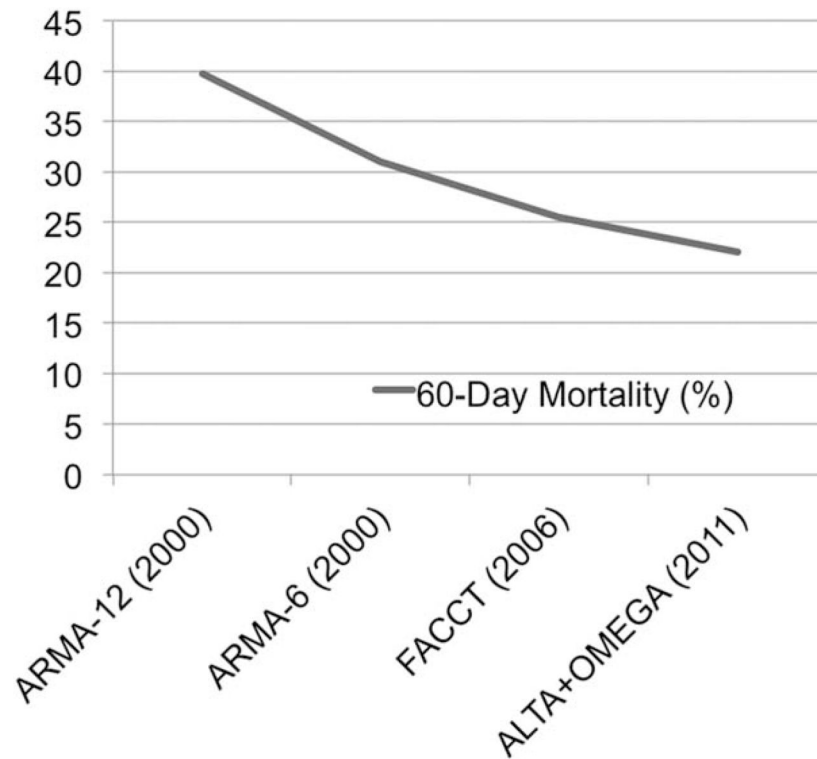


FIG. 1.

Sixty-day mortality in the Acute Respiratory Distress Syndrome (ARDS) Network trials: change over time. Sixty-day mortality reported over the last 11 years in randomized clinical trials from the ARDS Network. ARMA-12 refers to the mortality rate in the higher-tidal volume arm of the original ARDS Network trial of lower tidal volumes (And Respiratory Management of Acute Lung Injury/ARDS), whereas ARMA-6 refers to patients in the lower-tidal volume arm.⁶ FACCT fluid conservative refers to the mortality of patients enrolled into the fluid-conservative arm of the Fluid and Catheter Treatment Trial.³⁰ ALTA and OMEGA refer to the combined mortalities of 2 more recent trials: Albuterol for the Treatment of ALI,⁴⁸ and Omega-3 Fatty Acid, Gamma-Linolenic Acid, and Antioxidant Supplementation in the Management of ALI or ARDS.⁴⁹ Figure adapted from Matthay et al.⁹

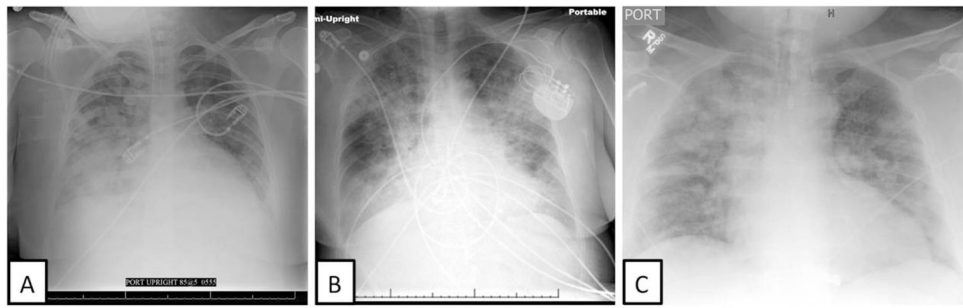
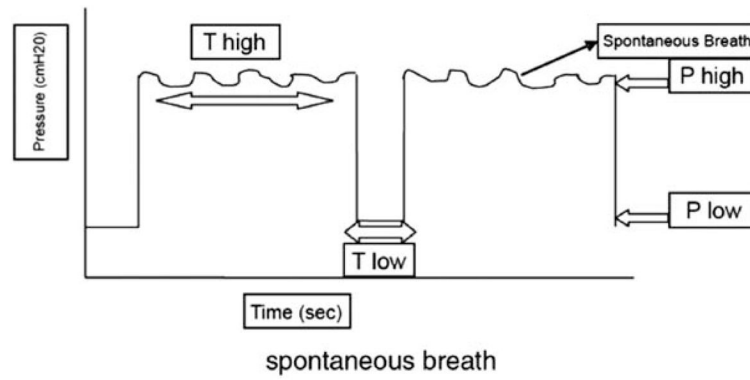


FIG. 2. Chest radiograph findings in acute respiratory distress syndrome (ARDS). (A) Anterior-posterior portable chest radiograph of a previously healthy 28-year-old woman with severe ARDS due to aspiration. (B) Anterior-posterior chest radiograph of a 62-year-old woman with moderate ARDS due to bacterial pneumonia. (C) Anterior-posterior chest radiograph of a 52-year-old man with moderate ARDS due to influenza-related pneumonia.

**FIG. 3.**

Airway pressure release ventilation: pressure versus time. Pressure versus time curve in airway pressure release ventilation. Spontaneous breathing appears during P high. Abbreviations: P high, the high positive end-expiratory pressure (PEEP); P low, the low PEEP; T high, the duration of P high; T low, the duration of P low. From Daoud EG. *Ann Thorac Med.* 2007;2:176–179. Reused pursuant to Creative Commons Attribution License.

TABLE 1

The Berlin Definition of Acute Respiratory Distress Syndrome¹⁰

Timing	Within 7 days of known clinical insult or new/worsening respiratory symptoms.
Chest imaging	Chest radiograph or CT: bilateral opacities consistent with pulmonary edema and not fully explained by effusions, atelectasis, or nodules.
Cause of edema	Respiratory failure not fully explained by cardiac failure or fluid overload. Objective assessment (eg, echocardiography) required to exclude hydrostatic edema if no ARDS risk factor present.
Oxygenation deficit	Mild: $\text{PaO}_2/\text{FiO}_2 < 300$ but > 200 mm Hg, on 5 cm H_2O PEEP/CPAP* Moderate: $\text{PaO}_2/\text{FiO}_2$ 200 but > 100 mm Hg, on 5 cm H_2O PEEP/CPAP Severe: $\text{PaO}_2/\text{FiO}_2$ 100 mm Hg on 5 cm H_2O PEEP/CPAP

NOTE: **Abbreviations:** ARDS, acute respiratory distress syndrome; CPAP, continuous positive airway pressure; CT, computed tomography; FiO_2 , fraction of inspired oxygen; PaO_2 , partial pressure of arterial oxygen; PEEP, positive end-expiratory pressure.

* This PEEP/CPAP may be delivered noninvasively in the mild group.

TABLE 2
Acute Respiratory Distress Syndrome Network Ventilatory Management Protocol⁶

To calculate predicted body weight:													
Male PBW: 50 + 2.3 (height in inches – 60) or 50 + 0.91 (height in centimeters – 152.4)													
Female PBW: 45.5 + 2.3 (height in inches – 60) or 45.5 + 0.91 (height in centimeters – 152.4)													
Select assist control mode													
Set initial V _T at 8 mL/kg PBW													
Reduce V _T by 1 mL/kg at intervals < 2 hours until V _T = 6 mL/kg PBW													
Set initial RR to approximate baseline minute ventilation (maximum RR = 35/minute)													
Adjust V _T and RR further to achieve P _{plat} and pH goals													
If P _{plat} > 30 cm H ₂ O: decrease V _T by 1 mL/kg PBW (minimum = 4 mL/kg PBW)													
If pH < 7.30, increase RR (maximum = 35)													
If pH < 7.15, increase RR to 35; consider sodium bicarbonate administration or increase V _T													
FIO ₂ /PEEP combinations													
FIO ₂													
0.3	0.4	0.4	0.5	0.5	0.6	0.7	0.7	0.7	0.8	0.9	0.9	1.0	
PEEP (cm H ₂ O)													
5	5	8	8	10	10	10	10	12	14	14	16	18	18, 22, 24

NOTE: See the ARDSNet website (<http://www.ardsnet.org>) for further details about the protocol, including the approach for setting positive end-expiratory pressure and fraction of inspired oxygen.

Abbreviations: FIO₂, fraction of inspired oxygen; PBW, predicted body weight; PEEP, positive end-expiratory pressure; P_{plat}, plateau pressure (airway pressure at the end of delivery of a tidal volume breath during a condition of no airflow); RR, respiratory rate; V_T, tidal volume.