Severe respiratory failure: Advanced treatment options

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Background: **Severe respiratory failure (including acute lung injury and acute respiratory distress syndrome) continues to be associated with significant mortality and morbidity in patients of all ages.**

Objective: **To review the laboratory and clinical data in support of and future directions for the advanced treatment of severe respiratory failure.**

Data Sources: **MEDLINE/PubMed search of all relevant primary and review articles.**

Data Synthesis: **Our understanding of lung pathophysiology and the role of ventilator-induced lung injury through basic science investigation has led to advances in lung protective strategies for the mechanical ventilation support of patients with severe respiratory failure. Specific modalities reviewed include low-tidal volume ventilation, permissive hypercapnia, the open lung approach, recruitment maneuvers, airway pressure release ventilation, high-frequency oscillatory ventilation, prone positioning, and extracorporeal life support. The pharmacologic strategies (including corticosteroids, surfactant, and nitric oxide) investigated for the treatment of severe respiratory failure are also reviewed.**

Conclusion: **In patients with severe respiratory failure, an incremental approach to the management of severe hypoxemia requires implementation of the strategies reviewed, with knowledge of the evidence base to support these strategies. (Crit Care Med 2006; 34[Suppl.]:S278–S290)**

KEY WORDS: acute lung injury; acute respiratory distress syndrome; respiratory failure; critical care; mechanical ventilation; corticosteroids; surfactant; nitric oxide; extracorporeal support

Severe respiratory failure (including acute lung injury [ALI] and acute respiratory distress syndrome [ARDS]) is characterized by a profound deterioration in systemic oxygenation or ventilation, or both, despite supportive respiratory therapy. ARDS is an acute and progressive respiratory disease of a non-cardiac nature in association with progressively diffuse, bilateral pulmonary infiltrates visible on a chest radiograph, reduced pulmonary compliance, and hypoxemia (1).

The American-European Consensus Conference on ARDS in 1994 defined ALI as "a syndrome of inflammation and increased permeability that is associated with a constellation of clinical, radiologic, and physiologic abnormalities that cannot be explained by, but may coexist with, left atrial or pulmonary capillary hypertension" (2). The clinical criteria for ALI include the following: acute onset of pulmonary failure, hypoxia with a Pao_2/Fio_2 ratio 300 mm Hg, bilateral chest infiltrates visible on a chest radiograph, and a pulmonary artery occlusion pressure 18 mm Hg or no clinical evidence of increased left atrial pressure. ARDS is defined as a more severe form of ALI with the same criteria, except the ratio of Pao_2/Fio_2 is 200 mm Hg, regardless of the positive end-expiratory pressure (PEEP) level used on the mechanical ventilator.

A recent prospective population-based study documented a crude incidence of acute lung injury of 78.9 per 100,000 person-years (considerably higher than previous reports) with an in-hospital mortality rate of 38.5%. Importantly, the mortality rate increased with increasing age (Fig. 1). These data suggest an estimated 190,600 cases of ALI annually in the United States, which are associated with 74,500 deaths and 3.6 million hospital days (3). Interestingly, a recent single-center, 5-yr observational study reported that the rate of ARDS in trauma has decreased significantly (Fig. 2), with a >50% reduction in the incidence of ARDS after injury, despite similar patient demographics and injury severities (4).

ARDS and ALI are associated with pathologically complex changes in the lung, manifested by an early exudative phase and followed by proliferative and fibrotic phases (5). The acute inflammatory state leads to increased capillary permeability and the accumulation of proteinaceous pulmonary edema, leading to hypoxemia. Hypoxia may further aggravate lung injury, and treatment strategies, therefore, focus on improvement of oxygenation and correction of the underlying problem (6). More recently, clinical studies have examined outcome differences in pulmonary (direct) and extrapulmonary (indirect) lung injury to examine potential treatment response differences. Additional prognostic determinants of ARDS in adults may need to be considered in the conduct of future clinical trials in this area (7).

The treatment of ALI and ARDS is supportive care, including optimized mechanical ventilation, nutritional support, manipulation of fluid balance, source control and treatment of sepsis, and prevention of intervening medical complications. Paramount in the support of the patient with severe respiratory failure and ALI/ARDS is the use of mechanical ventilatory support. Mechanical ventilatory support can be injurious and lead to additional lung injury when used at the extremes of pulmonary physiology, a concept that has been termed ventilator-induced lung injury (8). There are a number of mechanisms that can lead to the development of ventilator-induced lung injury, including barotrauma, diffuse alveolar injury resulting from overdis-

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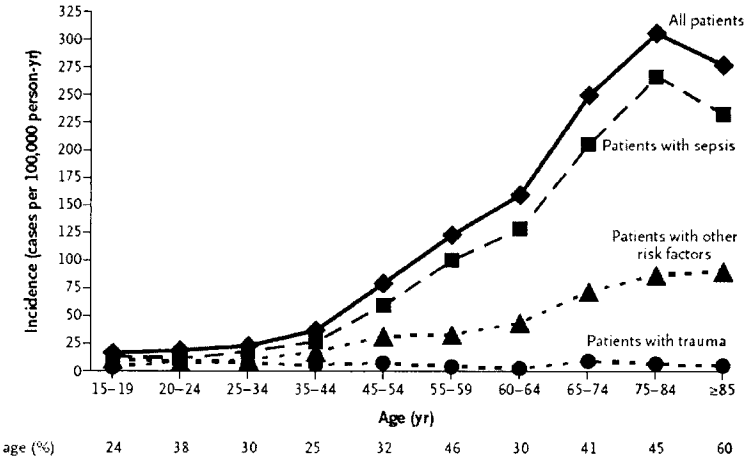

Figure 1. Age- and risk-specific incidence of and age-specific mortality from acute lung injury. Reprinted with permission from Rubenfeld et al (3).

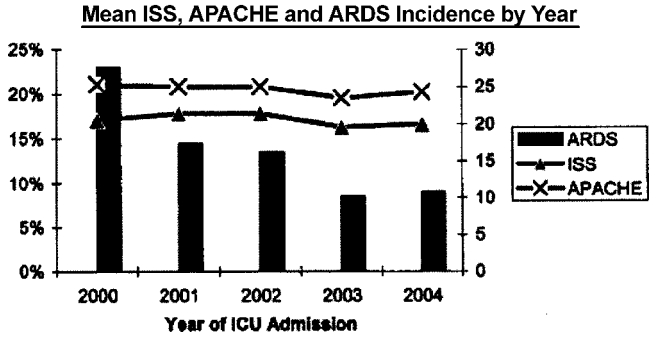

Figure 2. Decreasing incidence of acute respiratory distress syndrome in trauma patients. *ISS*, injury severity score; *APACHE*, Acute Physiology and Chronic Health Evaluation; *ARDS*, acute respiratory distress syndrome. Reprinted with permission from Martin et al (4).

tention (volutrauma), injury caused by repeated cycles of recruitment/derecruitment (atelectrauma), and the most subtle form of injury because of the release of local mediators in the lung (biotrauma) (9).

Clinical studies in which a single variable is manipulated and tested for its effect on outcome in severe respiratory failure have had disappointing results, with a few rare exceptions. It has become apparent that successful advances in the treatment of severe respiratory failure will involve the implementation of algorithms or strategies that take advantage of multiple techniques to provide effective mechanical ventilatory support, while minimizing ventilator-induced lung injury and improving oxygenation/ventilation. This review will focus on recent therapeutic advances in the treatment of severe respiratory failure and strategies for minimizing ventilator-induced lung injury.

Low Tidal Volume Strategy

The use of high tidal volumes and/or high ventilator pressures in an attempt to ventilate the patient with worsening respiratory failure can result in compromise of cardiopulmonary function and the development of ventilator-induced lung injury. There is increasing evidence that alveolar stretch induced by large inspired tidal volumes plays a significant role in the development of ventilator-induced lung injury through the incitement of an exaggerated alveolar inflammatory response, which is associated with systemic inflammation, as well (10).

Significant lung injury caused by barotrauma and alveolar overdistention occurs in patients with ARDS. High plateau and peak inspiratory pressures, for even a brief period of time, have been proven to be detrimental to lung function in animal models (11–13). Barotrauma results when air migrates out of the alveolar space into the extrapulmonary tissues. This can result in the clinical presence of pneumothorax, pneumomediastinum, pneumoperitoneum, subcutaneous emphysema, and air embolism. Barotrauma occurs in 13% of ARDS patients but results in mortality in <2% of patients (14, 15). Only high levels of PEEP have been associated with an increased risk of barotrauma, whereas peak, mean, and plateau airway pressure have not (16).

In ARDS, large proportions of the lung alveoli become consolidated and are not available for gas exchange. The resulting available lung units are small in number and give the patient a functional lung that is analogous to a "baby lung" in size. Attempting to force adult magnitude tidal volume breaths into this baby lung can result in overdistention of the remaining open alveoli and high distending pressures. This alveolar overinflation can exacerbate existing lung injury, leading to microvascular injury and worsening pulmonary edema (17). Experimental studies using body casts to prevent overinflation suggest that this microbarotrauma is primarily the result of lung overinflation rather than high airway pressures (18).

Using a low tidal volume (6 mL/kg) approach to mechanical ventilation in animals with *Pseudomonas aeruginosa*-induced acute lung injury resulted in enhanced oxygenation, increased arterial blood pH, increased blood pressure, and a decrease in extravascular lung water when compared with a high tidal volume group (15 mL/kg) (19). The ARDS Network trial conclusively demonstrated the clinical value of a low tidal volume vs. high tidal volume approach in the mechanical ventilatory support of patients with severe respiratory failure (20). This trial was a multicenter, randomized, controlled study that compared a tidal volume of 6 mL/kg ideal body weight (and plateau pressure <30 cm H_2O) with a tidal volume of 12 mL/kg ideal body weight (and plateau pressure <50 cm H_2O). The trial was stopped after the fourth interim analysis when a total of 861 patients were enrolled and the data analysis showed a significantly lower mortality, 31% vs. 40%; $p = .007$, in the low tidal volume group. The number of ventilator-free days in the first 28 days was significantly higher in the group treated with lower tidal volumes (12 ± 11 vs. 10 ± 11; $p = .007$) as was the number of days without failure of non-pulmonary organs or systems (15 ± 11 vs. 12 ± 11; $p = .006$). The incidence of barotrauma was similar in the two groups, at 10% to 11%. A secondary analysis of a subgroup from this randomized trial confirmed that intrinsic PEEP was significantly higher in patients randomized to the 6 mL/kg protocol group, but the difference of median intrinsic PEEP between the

groups was <1 cm H_2O, and it is unlikely that this was clinically important (21).

In patients with ALI and ARDS, plasma interleukin-6 and -8 are associated with morbidity and mortality. Lower tidal volume ventilation in the ARDS Network prospective, randomized trial was also associated with a more rapid attenuation of the inflammatory response (Fig. 3) (22). There have been some barriers to widespread implementation of the low tidal volume ventilation strategy, particularly with regard to patient discomfort and tachypnea and concerns about hypercapnia, acidosis, and hypoxemia (23). Recent studies document that low tidal volume ventilation does not increase sedation use (24). However, it is important to establish techniques for overcoming these barriers to use, including clinician education, tools to assess patient discomfort, and recommendations for specific ventilator setup.

The recent publication of the "Guidelines for Mechanical Ventilation of the Trauma Patient" (Fig. 4) from the participants of the Inflammation and Host Response to Injury Large-Scale Collaborative Research Program is an important step forward in standardizing clinical management in trauma patients to ensure that a low tidal volume, lung-protective strategy is used for the ventilation of patients who meet criteria for ALI and ARDS. This statement also provides guidelines for the use of PEEP in patients with ALI and guidelines to ensure that discontinuation of mechanical ventilation and extubation occur at the earliest possible time (25).

Permissive Hypercapnia

Mechanical ventilatory strategies to reduce tidal volumes and, thereby, reduce volutrauma can result in inadequate lung ventilation. Permissive hypercapnia is a consequence of a ventilator strategy that accepts deliberate hypoventilation in an effort to reduce pulmonary overdistention and high transalveolar pressures within the compliant non-collapsed lung in patients with ARDS. This technique induces the side effect of hypercarbia and respiratory acidosis, which are managed medically. The tidal volume is gradually reduced to allow a progressive rise in the $Paco_2$, not to exceed 10 mm Hg/hr, to a maximum of 80–100 mm Hg. This is done to keep the static peak airway pressure <40 cm H_2O and maintain the arterial oxygenation saturation (Sao_2) >90%, while tolerating a pH as low as 7.15 before initiating administration of intravenous buffering agents (26). Buffering agents such as $NaHCO_3$ (50 mEq/L) or THAM (36 g/L, tromethamine) can be administered as a continuous intravenous infusion if the arterial pH falls less than 7.15 in asthma patients or 7.28 in patients at risk for simultaneous metabolic acidosis (27).

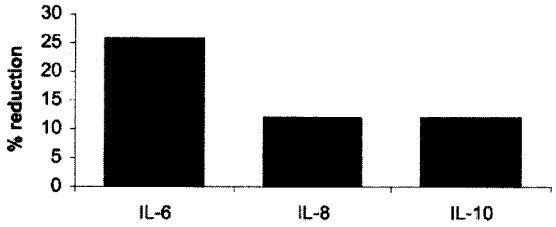

Figure 3. Percent reduction in 6 mL/dg group vs. 12 mL/kg group during the first three study days. The 95% confidence intervals are 12% to 37% for interleukin (*IL*)-6, 1% to 23% for IL-8, and -4% to 25% for IL-10. Reprinted with permission from Parsons et al (22).

Higher levels of sedation may be required to offset the respiratory drive induced by hypercapnia and to avoid patient discomfort. A recent study documented that higher doses of propofol, but not midazolam, were required to sedate patients managed with permissive hypercapnia (28). The effects of hypercapnia may worsen intracranial pressure, and this technique should potentially be avoided in trauma patients with evidence of brain injury. The negative inotropic effect of respiratory acidosis can usually be overcome by producing a compensatory metabolic alkalosis but must be managed medically with intravenous buffering agents when it occurs. Mortality in adult patients with ARDS was reduced to 26%, compared with the expected mortality of 53% based on Acute Physiology and Chronic Health Evaluation II scores when low tidal volume, pressure-limited ventilation with permissive hypercapnia was prospectively applied to 64 patients with ARDS (29)(29).

In burned children, a ventilator strategy was followed using a peak inspiratory pressure of 40 cm H_2O and accepting an elevated $Paco_2$ as long as the arterial pH was >7.20 (30). An overall mortality rate of 3.7% occurred with no respiratory deaths. In 11 of these children, a high degree of inhalation injury was present. The average maximum $Paco_2$ was 62 mm Hg, with a range of 50–111 mm Hg and a simultaneous average pH of 7.27. A strategy of high-frequency pressure-controlled ventilation with low tidal volumes and high PEEP (7–30 cm H_2O) was performed in 53 children with severe ARDS (31). The peak inspiratory pressure was minimized, and mild hypercapnia was tolerated with $Paco_2$ levels ranging from 45 to 60 mm Hg. The hospital survival rate in these patients was 89% and compared favorably with the 28% to 60% survival rates of six previous studies using higher peak inspiratory pressure, higher maximum Fio_2, and lower PEEP settings.

Most recently, a secondary analysis of the ARDS Network low tidal volume multicenter trial (n = 861) documented that hypercapneic acidosis was associated with a reduced 28-day mortality (adjusted odds ratio, 0.14; 95% CI, 0.03–0.70; $p = .016$) in the 12 mL/kg predicted body weight tidal volume group after controlling for comorbidities and severity of lung injury, but no difference was identified in the 6 mL/kg tidal volume group (32). These results are consistent with a protective effect of hypercapneic acidosis against ventilator-induced lung injury that was not found when the further ongoing injury was reduced by 6 mL/kg predicted body weight tidal volumes.

Open Lung Strategy

Depletion of surfactant and low levels of PEEP can lead to cyclic atelectasis with repeated collapse and opening of those few functional alveoli that remain in severe ARDS. This cycling of alveoli opening and closing can lead to activation of neutrophils, promote additional lung injury, and lead to loss of functional residual lung capacity (FRC). One of the more common means of recruiting collapsed alveoli and increasing FRC is to use increased levels of PEEP. By not allowing all the pressure in the lung to escape during exhalation, alveoli that are unstable and prone to collapse cannot do so. This technique can be thought of as holding the lung partially open so that the next breath is not starting from total collapse in a noncompliant lung.

The optimal level of PEEP to use is difficult to determine, but emerging evidence suggests that maximum recruitment and maintenance of lung volume occurs when the PEEP is set at a level just above the lower inflection point (P_{flex}) on the pressure-volume curve in a patient with ARDS (33, 34). A single breath compliance curve with tidal volume plotted against static airway pressure will demonstrate two inflection points (Fig. 5). The lower one represents the theoretical critical opening pressure of most alveoli available for recruitment, and the upper point represents the loss of elastic properties on the lung secondary to overdistention. Setting the PEEP slightly higher than the P_{flex} will result in maintenance of alveolar distention throughout the ventilatory cycle. The anticipated end result is an increase in the recruitment of functional residual capacity, decreased intrapulmonary shunting, and improved arterial blood oxygenation.

Combining the use of low-volume tidal volume strategies, with the application of PEEP at levels above the lower inflection point, and permissive hypercapnia has been termed the "open-lung approach." Amato et al. (35) describe a technique in which PEEP is maintained above the lower inflection point of the pressure-volume curve, tidal volume is kept at <6 mL/kg, static peak pressure is <40 cm H_2O, permissive hypercapnia is allowed, and the stepwise use of pressure-limited modes of ventilation are used. Using this technique in a prospective study vs. conventional mechanical ventilation in ARDS yielded improved survival at 28 days (62% vs. 29%; $p < .001$), a higher rate of weaning from mechanical ventilation, and a lower rate of barotrauma in the open-lung or protective strategy group. There was no difference in the overall hospital mortality between groups, and the high 28-day mortality in the conventional mechanical ventilatory group raises concern about the overall impact of this strategy.

In a similar trial, which used pressure and volume-limited ventilation, with peak inspiratory pressure maintained at <30 cm H_2O and the tidal volume at <8 mL/kg vs. conventional ventilation, Stewart et al. (36) demonstrated no difference in mortality between the "limited ventilation" group (50%) and the patients undergoing conventional mechanical ventilation (47%). The limited ventilation group did have a significantly lower baseline Pa_{O_2}/F_{IO_2} ratio when compared with the control group that underwent conventional ventilation.

Mechanical Ventilation Protocol – Inflammation and the Host Reponse to Injury

In patients with ALI or established ARDS ($PaO_2/FiO_2 \leq 300$ or $PaO_2/FiO_2 \leq 200$, respectively, with bilateral pulmonary infiltrates) aim for the following within 24 hrs of meeting criteria:

- Initial tidal volumes may be set at 8 mL/kg predicted body weight (PBW); tidal volumes should be reduced by 1 mL/kg at intervals of < 2 hours until the tidal volume = 6 mL/kg.
- Tidal volume calculations are based on predicted body weight as follows:
- For males: PBW (kg) = 50 + 2.3 [height (inches) – 60]
- For females: PBW (kg) = 45 + 2.3 [height (inches) – 60]
- PaO_2 55-80 mm Hg or S_pO_2, 88% - 95%. FiO_2/PEEP ratio should be ≤ 5 and PEEP must be ≤ 35 cm H_2O
- Arterial pH 7.25-7.45 with RR < 35 and $PaCO_2 \geq 25$. HCO3 infusion may be given if necessary. If pH < 7.15 then Vt may be increased by 1 mL/kg to pH ≥ 7.15 and target plateau pressures (see below) may be exceeded.
- Plateau pressures (PP) ≤ 30 cm H_2O. Reduce Vt to no less than 4 mL/kg. If Vt < 6 mL/kg and PP < 25 then increase Vt until PP = 25-30 or Vt = 6 mL/kg

Patients not meeting ALI/ARDS criteria can be ventilated using the mode, rate and tidal volume chosen at the treating physician's discretion.

Patients should undergo a daily assessment of their readiness for a spontaneous breathing trial (SBT):

(a) resolution or stabilization of the underlying disease process
(b) no residual effects of neuromuscular blockade
(c) exhibiting respiratory efforts
(d) hemodynamically stable
(e) $FiO_2 \leq 0.5$ and PEEP ≤ 8 cm H_2O
(f) $PaO_2 > 70$ mm Hg
(g) Ve < 15 L/min
(h) Arterial pH between 7.30-7.50
(i) ICP < 20 cm H_2O

If not ready for an SBT, then return to a comfortable, non-fatiguing mode of ventilator support and reassess daily. If ready, then the patient should receive **a trial of spontaneous breathing (SBT) on CPAP for 30-90 minutes.**

Criteria for failure of a SBT:

(a) RR > 35 for ≥ 5 minutes
(b) SpO_2 < 90% for ≥ 30 seconds
(c) HR > 140 or increase or decrease of 20% from baseline;
(d) SBP > 180 mm Hg or < 90 mm Hg
(e) Sustained evidence of respiratory distress
(f) Cardiac instability or dysrhythmias
(g) Arterial pH ≤ 7.32
(h) ICP ≥ 20 cm H_2O

If any criteria are met, the CPAP trial is terminated and patient returned to a non-fatiguing mode of support and rested overnight. Repeat CPAP trial in the morning.

If patient completes CPAP trial, the following criteria should be assessed to determine **readiness for extubation** and patient extubated if possible:

(a) does not require suctioning more than Q 4 hours
(b) good spontaneous cough
(c) endotracheal tube cuff leak
(d) no recent upper airway obstruction or stridor
(e) no recent reintubation for bronchial hygiene

Figure 4. Summary of mechanical ventilation protocol for trauma. *ALI*, acute lung injury; *ARDS*, acute respiratory distress syndrome; *PEEP*, positive end-expiratory pressure; *RR*, relative risk; *Vt*, tidal volume; *Ve*, minute volume or expired volume per min; *ICP*, intracranial pressure; *CPAP*, continuous positive airway pressure; *Q*, every. Reprinted with permission from Nathens et al (25).

The ARDS Network study comparing high PEEP with the previously reported ARDS Network low-PEEP strategy was terminated early for futility (37). In this study, the patients in the high-PEEP group received an average of 13.2 ± 3.5 cm H_2O PEEP compared with 8.3 ± 3.2 cm H_2O of PEEP in the low-PEEP group. Neither of these PEEP levels is particularly high, and the mean PEEP value for the high-PEEP group was lower than the level used by Amato et al. (35) in their open-lung trial, which was at least 16 cm H_2O.

Most recently, a prospective, randomized study (ARIES, Acute Respiratory Insufficiency: Espana Study) comparing a mechanical ventilation strategy with a PEEP level set on day 1 above P_{flex} (P_{flex} + 2 cm H_2O PEEP) and a low tidal volume (5–8 mL/kg of predicted body weight; "P_{flex}/LTV") compared with a control strategy with a higher tidal volume (9–11 mL/kg predicted body weight) and relatively low PEEP (5 cm H_2O) was stopped early because of increased efficacy in the P_{flex}/LTV group. Intensive care unit (ICU) mortality (53.3 vs. 32%; $p = .04$), hospital mortality (55.5 vs. 34%; $p = .04$), and ventilator-free days ($p = .008$) favored the P_{flex}/LTV group (38).

Based on the ARDS Network trials and others detailing the open-lung approach, most clinicians today avoid high-peak in-

spiratory pressures, use low tidal volumes, and apply appropriate levels of PEEP to encourage lung recruitment and avoid cyclic atelectasis. This approach is the current "gold standard" for mechanical ventilatory support and avoiding additional ventilator-induced lung injury in patients with severe ARDS.

However, the extent to which tidal volumes and inspiratory airway pressures should be reduced to optimize clinical outcomes is a controversial topic. A recent study examined all patients with plateau pressures (P_{plat}) in the ARDS network lower tidal volume trial (39). Fig. 6 demonstrates the relationship of mortality vs. P_{plat} for all patients and shows decreasing mortality as day 1 P_{plat} declines from high to low levels. It does not reveal a safe P_{plat} threshold within the range of day 1 P_{plat} levels measured in patients with ALI/ARDS. Bivariate analysis also demonstrated that lower P_{plat} quartiles were associated with reduced mortality when compared with higher P_{plat} quartiles ($p = .039$) (Fig. 7). The ARDS Network volume- and pressure-limited strategy used a tidal volume goal of 6 mL/kg predicted body weight, and with this approach, mean P_{plat} was approximately 25 cm H_2O. This additional analysis does not substantiate the widespread belief that tidal volume reduction is without benefit when P_{plat} is already <30–35 cm H_2O.

Airway Pressure Release Ventilation

Airway pressure release ventilation (APRV) is a pressure-limited, time-cycled mode of mechanical ventilation that allows a patient unrestricted spontaneous breathing during the application of continuous positive airway pressure. It is an alternative approach to open-lung ventilation. Although recruitment maneuvers may be effective in improving gas exchange and compliance, these effects may not be sustained and may require repeated maneuvers. APRV may be viewed as a nearly continuous recruitment maneuver, with high-pressure providing 80% to 95% of the cycle time, creating a stabilized open lung while facilitating spontaneous breathing. The ventilator maintains a high-pressure setting for the bulk of the respiratory cycle, which is followed by a periodic release to a low-pressure setting analogous to PEEP (Fig. 8) (40). Patients who are not receiving neuromuscular blockade can spontaneously breathe on top of this form of continuous positive airway pressure, which is periodically lowered to allow ventilation and CO_2 clearance. The spontaneous breathing allowed during APRV can decrease intrathoracic pressure, as inspiration by the patient results in periodic cycles of negative pressure from the diaphragm and chest wall excursion. APRV is no different from pressure-controlled inverse ratio mechanical ventilation in patients receiving neuromuscular blockade. To date, an adequately designed and powered study to demonstrate a reduction in mortality or ventilator days with APRV compared with optimal lung protective conventional ventilation has not yet been performed.

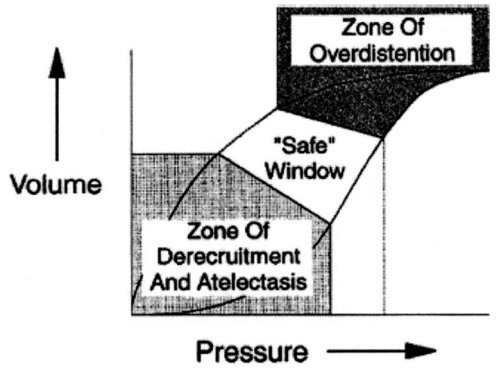

Figure 5. Pressure-volume curve of a moderately diseased lung, such as one with adult acute respiratory distress syndrome. Two hazard zones exist: overdistention and derecruitment and atelectasis. High end-expiratory pressures and small tidal volumes are needed to stay in the "Safe" window. High-frequency oscillatory ventilation may have a larger margin of safety in keeping the lung open within the desired target range of alveolar overdistention. Reprinted with permission from Imai and Slutsky (46).

High-Frequency Oscillatory Ventilation

High-frequency oscillatory ventilation (HFOV) involves the use of a piston pump-driven diaphragm to deliver small tidal volumes at frequencies between 3 and 15 Hz. HFOV is unique in that expiration is active in addition to inspiration, with this component created by the backward movement of the diaphragm, which generates negative pressure.

Oxygenation is manipulated by adjusting mean airway pressure, which controls lung inflation in a manner similar to the use of PEEP in conventional mechanical ventilation (CMV). Changing the tidal volume, also known as the amplitude or power, controls ventilation and carbon dioxide elimination. Besides the F_{IO_2}, there are only a total of four variables to manipulate when using HFOV. First, mean airway pressure is initiated at 1–2 cm H_2O higher than for CMV in premature newborns, 2–4 cm H_2O higher than CMV in full-term newborns and children, and 5 cm H_2O higher than CMV in adults. Second, frequency (Hz) is set at 12 Hz in premature infants and 5–10 Hz in all others. Lowering the frequency will result in an increase in the tidal volume and a decrease in the $Paco_2$. Third, inspiratory time is usually set at 33%, but it may be lengthened to increase the tidal volume. Fourth, amplitude or power is set to achieve appropriate chest wall movement and adequate CO_2 elimination.

HFOV was initially used as a rescue strategy when other modes of mechanical ventilation had failed (41, 42). The MOAT (Multicenter Oscillatory Ventilation for Acute Respiratory Distress Syndrome Trial) compared HFOV with a pressure-controlled ventilation strategy (n = 148). HFOV was associated with early (<16 hrs) improvement in Pa_{O_2}/F_{IO_2} compared with the conventional ventilation group ($p = .008$); however, this difference did not persist beyond 24 hrs. The oxygenation index decreased similarly during the first 72 hrs in both groups. Thirty-day mortality was 37% in the HFOV group and was 52% in the conventional ventilation group ($p = .1$). No differences were identified in the percentage of patients alive without mechanical ventilation at day 30 (36% HFOV vs. 31% conventional; $p = .7$). There were no significant differences in hemodynamic variables, oxygenation or ventilation failure, barotrauma, or mucus plugging between treatment groups. The authors concluded that HFOV is a safe and effective mode of

ventilation for the treatment of ARDS in adults (43).

A similar multicenter randomized trial (n = 61) comparing HFOV with conventional ventilation in adult ARDS was conducted in Europe but was stopped prematurely because of a low inclusion rate and the completion of the Derdak trial (22), and no significant differences were identified in this small trial (44).

A review of the clinical experience with HFOV in Toronto (n = 156) in severe ARDS patients (mean $Pa_{O_2}/F_{I_{O_2}}$ ratio, 91 ± 48 mm Hg) concluded that HFOV had beneficial effects on oxygenation and may be an effective rescue therapy for adults with severe hypoxemia and that the early institution of HFOV may be advantageous (45).

HFOV is, in theory, the ideal "lung-protective" method, and may have a larger margin of safety in keeping the lung open within the desired target range of alveolar overdistention in heterogeneously injured ARDS lungs, but outcome benefits have not yet been proven in a large prospective, randomized trial (46). Because it has been suggested that the early initiation of HFOV in patients with severe ARDS may be important to successful outcomes, the active identification of patients with ARDS who may be potential candidates for HFOV is important. Although the exact severity threshold at which to initiate a trial of HFOV remains unclear, an emerging approach includes the following severity criteria: (47)

- $F_{I_{O_2}}$ >0.60 and Sp_{O_2} <88% on CMV with PEEP >15 cm H_2O, or
- Plateau pressures >30 cm H_2O, or
- Mean airway pressure 24 cm H_2O, or
- Airway pressure release ventilation high pressure 35 cm H_2O.

Recruitment Strategies

Alveolar recruitment is one of the primary goals of respiratory therapy for ALI and ARDS. It is aimed at improving pulmonary gas exchange, preventing ventilator-induced lung injury, atelectasis, and "atelectrauma" (48). PEEP may decrease ventilator-induced lung injury by keeping lung regions open that otherwise would be collapsed. Recruitment maneuvers can be used to increase alveolar FRC (49).

A recent study documented that the percentage of potentially recruitable lung (mean ± SD, 13 ± 11) varied widely in patients with ALI or ARDS and that, on average, 24% of the lung could not be recruited. Furthermore, patients with a higher percentage of potentially recruitable lung (which was strongly associated with a favorable response to PEEP) had poorer oxygenation and higher rates of death than patients with a lower percentage of potentially recruitable lung (50).

Effective recruitment maneuvers and sustained levels of PEEP to avoid derecruitment may obviate the need for the prone position in ARDS for alveolar recruitment (51). A large amount of experimental data suggests that alveolar recruitment is beneficial in ALI and ARDS. However, there is no single clinical study that clearly proves the effectiveness of alveolar recruitment for lung protection and survival.

The combination of recruitment maneuvers (initial cycle of up to three sustained inflation recruitment maneuvers of 40 cm H_2O for 40 secs) and HFOV in a prospective, multicenter clinical trial (Treatment with Oscillation and an Open Lung Strategy, TOOLS Trial) resulted in a rapid and durable improvement in oxygenation and was well-tolerated, feasible, and physiologically sound (52).

Prone Positioning

Changes in patient positioning can have a sometimes dramatic effect on ox-

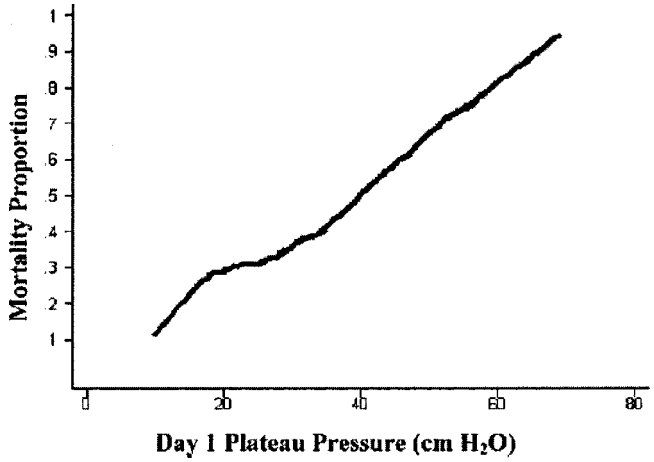

Figure 6. Relationship between mortality and day 1 plateau pressures. Reprinted with permission from Hager et al (39).

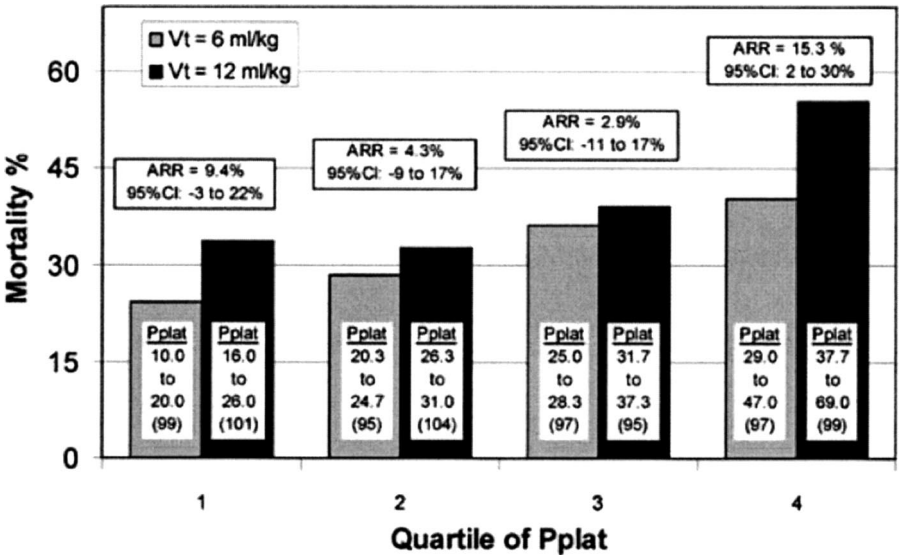

Figure 7. Mortality differences based on day 1 plateau airway pressures. *Vt*, tidal volume; *ARR*, absolute risk reduction; *CI*, confidence interval; *Pplat*, plateau pressure. Reprinted with permission from Hager et al (39).

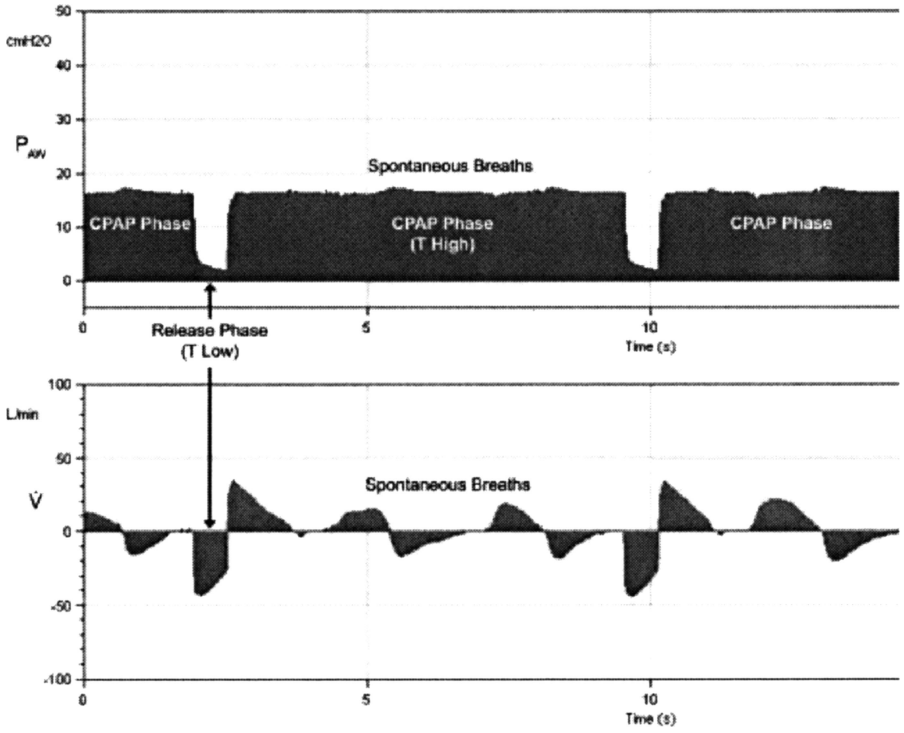

Figure 8. Airway pressure release ventilation is a form of continuous positive airway pressure (*CPAP*). The P_{high} is equivalent to a CPAP level; T_{high} is the duration of P_{high}. The CPAP phase (P_{high}) is intermittently released to a P_{low} for a brief duration (T_{low}) reestablishing the CPAP level on the subsequent breath. Spontaneous breathing may be superimposed at both pressure levels and is independent of time cycling. Reprinted with permission from Habashi (40).

ygenation and ventilation in severe ARDS. Changing the patient position to prone or a steep lateral decubitus position can improve the distribution of perfusion to ventilated lung regions, decreasing intrapulmonary shunt and improving oxygenation (53).

The use of intermittent prone positioning can significantly improve oxygenation in 60% to 70% of patients (54, 55). A multicenter randomized trial of conventional treatment vs. placing patients in a prone position for 6 or more hrs daily for 10 days was conducted on patients 16 yrs of age with ALI or ARDS (56). No differences in mortality or complications were identified for the prone vs. conventional positioning group at any time point during the study, with up to 6 months follow-up. The mean increase in the Pao_2/Fio_2 ratio was greater in the prone than supine group (63 ± 67 vs. 45 ± 68; $p = .02$). Of note is that the mean Pao_2 of 85–88 mm Hg and mean Pao_2/Fio_2 ratio of 125–129 are still high for patients with severe ARDS, and therefore, these patients may not have been likely to benefit considerably by the prone intervention with regard to mortality. A retrospective analysis of patients in the pronation arm of this study revealed that ALI/ARDS patients who responded to prone positioning with a reduction in their $Paco_2$ 1 mm Hg showed an increase in survival at 28 days with a decrease in the mortality rate from 52% to 35% (57).

A recent multicenter, randomized, controlled clinical trial of supine vs. prone positioning in 102 pediatric patients failed to demonstrate a significant difference in the main outcome measure, which was ventilator-free days to day 28. There were also no differences in the secondary endpoints study conducted including proportion alive and ventilator-free on day 28, mortality, the time to recovery from lung injury, organ failure-free days, and functional health (58).

A prospective, randomized study (n = 136), with guidelines established for ventilator settings and weaning, examined the efficacy of the prolonged prone position (continuous prone position for 20 hrs daily) in severe ARDS patients with 48 hrs of tracheal intubation. Multivariate analysis documented that randomization to the supine position was an independent risk factor for mortality (odds ratio, 2.53; $p = .03$). These authors concluded that prone ventilation is feasible and safe and may reduce mortality in patients with severe ARDS when it is initiated early and applied for most of the day (59).

Prone positioning is labor intensive with associated risks, including inadvertent extubation and pressure sores, and requires the use of appropriate cushioning of the dependent portions of the body to avoid pressure ulcerations. However, the technique can be performed safely by a trained and dedicated nursing staff that are aware of its potential benefits in critically ill patients with severe pulmonary failure in conjunction with judicious use by ICU physicians. In our experience, prone positioning is a useful tool for treatment of hypoxemia, can prevent the need for extracorporeal life support (ECLS), and is used for lung recruitment in patients undergoing ECLS. We do not, however, use prone positioning until the Pao_2/Fio_2 ratio is significantly <100. One technique involves alternating prone with supine positioning every 6 hrs. Patients will often experience an initial worsening in their respiratory status with each change in position, but this passes quickly in the first 15–30 mins to eventual improvement in oxygenation and ventilation, with 70% of the overall improvement occurring in the first hour of pronation. Prone positioning, although not associated with a significant survival advantage, may serve a role as rescue therapy for patients with ARDS and refractory life-threatening hypoxemia.

Extracorporeal Life Support

In patients who have acute and severe respiratory failure who are failing all advanced modes of mechanical ventilation, the use of extracorporeal life support (ECLS) is an option. ECLS is a proven modality for the treatment of severe respiratory failure in the neonate (60, 61). Its use in adults remains controversial, but ongoing clinical trials and research have indicated a possible benefit for its use to salvage those patients failing aggressive conventional therapy. For infant, pediatric, and adult patients with severe ARDS, ECLS therapy has produced respective survival rates of 85%, 74%, and 52% in these patients (62). The indications for ECLS are listed in Table 1 for infants and Table 2 for adults. Referral to an ECLS center should occur early if there is a suspected need for this technology. This will allow safe transport of the patient and avoidance of the "crash on" with all of its inherent complications.

Table 1. Neonate extracorporeal life support criteria

Indications	Contraindications
Duration of ventilation	Prolonged conventional mechanical ventilation
≤10–14 days	Intracranial hemorrhage (> grade I)
Reversible lung pathology	Incurable disease
Oxygenation	Age <30 wks
A-a$\dot{D}o_2$ >605–620 for not >4–12 hrs	Weight <1 kg
Oxygenation index >25	Unresolved surgical issues

Recommend cranial ultrasound and echocardiogram before cannulation.

Table 2. Adult extracorporeal life support criteria

Indications	Contraindications
Duration of ventilation	Prolonged conventional mechanical ventilation
≤5–7 days, 7–10 days only if ventilated with high pressures for <7 days	Poor neurologic status
	Incurable disease
Compliance	Age >70 yrs
≤0.5 mL/cm H_2O/kg	Pulmonary artery pressures >2/3 systemic blood pressure
Oxygenation	Unresolved surgical issues
Pao_2/Fio_2 <100	
Shunt >30%	

The technique of ECLS for patients with severe respiratory failure involves a venovenous or venoarterial life support circuit with a membrane oxygenator to temporarily take over the function of the lung. While on ECLS, mechanical ventilator settings are adjusted to minimize ventilator-induced lung injury and to maximize the recruitment of FRC. The treatment program for adults involves an algorithm that aims to normalize body physiology, aggressively recruit FRC, and minimize barotrauma. This algorithm used in 141 patients with respiratory failure referred for consideration of ECLS yielded a survival rate of 62% in patients with severe ARDS (median initial Pao_2/Fio_2 ratio of 66) (63).

The primary indication for the use of ECLS in patients with severe respiratory failure is when the risk of dying from ARDS is considered >80% after optimal ventilator and medical management. This translates to an alveoli-arterial oxygen gradient >600 mm Hg or a Pao_2/Fio_2 ratio of <70 on 100% oxygen. Patients should also have a transpulmonary shunt fraction >30%, despite maximal conventional therapy. Adult patients are typically cannulated percutaneously with large 21- to 23-Fr catheters for drainage and infusion of blood. Anticoagulation is necessary and is titrated by measurement of whole blood-activated clotting time. ECLS allows for a decreasing of mechanical ventilator settings to non-damaging "rest" levels while maintaining FRC recruitment measures. Once the patient's native lung function has improved, the patient is weaned off of ECLS at moderate ventilator settings that allow for potential increases in therapy (e.g., Fio_2 0.5–0.6). If the weaning of ECLS is successful, the cannulas are removed and recovery continues.

In a series of 255 adult patients who were placed on ECLS for severe ARDS refractory to all other treatment, 67% were weaned off ECLS and 52% survived to hospital discharge (64). Multivariate analysis identified the following pre-ECLS variables as significant independent predictors of survival: 1) age; 2) gender; 3) arterial blood pH 7.10; 4) Pao_2/Fio_2 ratio; 5) days of mechanical ventilation. None of the patients who survived required permanent mechanical ventilation or supplemental oxygen therapy. Patients who can be successfully decannulated from ECLS have a 77% chance of being discharged from the hospital alive and a complete recovery.

The CESAR (Conventional Ventilation or ECMO for Severe Adult Respiratory Failure) trial is a prospective, randomized trial underway in the United Kingdom in adults with severe acute respiratory failure. Complete information regarding the inclusion and exclusion criteria, trial design, number of patients recruited, and information for patients and families is available at their website (http://www.lshtm.ac.uk/msu/trials/cesar/). The primary hypothesis for this trial is that "for patients with severe, but potentially reversible, respiratory failure, ECMO will increase the rate of survival without severe disability by 6 months post-randomization."

The findings from this important pivotal trial will provide critical information regarding the efficacy of ECLS in adult patients with ARDS but will need to be interpreted carefully, because all patients allocated to the ECLS arm of the trial will be transported (by an experienced ECMO transport team) to a single center (Glenfield Hospital in Leicester), which is one of the most experienced ECMO centers in the world. The conventional mechanical ventilation arm of the trial will be managed as follows. "Conventional ventilatory support can include any treatment modality thought appropriate by the patient's intensivist (excluding ECMO). Intensivists will have full discretion to treat patients as they think appropriate. It will be recommended that intensivists adopt the low volume ventilation strategy. Adherence to this strategy is defined for the purposes of CESAR as a plateau pressure <30 cm H_2O (or if plateau pressure is not measured the peak inspiratory pressure). This will usually mean a tidal volume of 4–8 mL/kg body weight as defined in the low tidal volume ventilation strategy according to the ARDS Network group."

Most recently, case reports of the use of a pumpless extracorporeal lung assist device (arterial cannula inserted into the femoral artery, membrane oxygenator with venous cannula return to the femoral vein [driving the force is the patient's blood pressure]) in the treatment of severe ARDS review its efficacy, limitations, and associated adverse events (65–68). Prospective, randomized trials are warranted to examine the efficacy of this new technology.

Pharmacologic Strategies

Multiple pharmacologic interventions (including prostaglandins, prostacyclin, lisofylline, ketoconazole, *N*-acetylcysteine, corticosteroids, and nitric oxide) have been investigated in the treatment of ALI and ARDS, but none as yet has demonstrated improved survival (69). Two pharmacologic strategies (ketoconazole and lisofylline) were investigated by the ARDS Clinical Trials Network, and both studies were stopped by the Data

Table 3. Results of multicenter clinical studies of the use of inhaled nitric oxide in patients with acute respiratory failure

Study	Year	Duration of Intervention (Days)	Patients[a]	Intervention		Primary Outcome	Secondary Outcomes
				Control	Inhaled Nitric Oxide		
Dellinger et al. (91)	1998	28	Patients with ARDS enrolled within 72 hrs after diagnosis[b]; patients with severe sepsis, nonpulmonary organ failure, or both, were excluded	Nitrogen in 57 patients	1.25 ppm in 22 patients 5 ppm in 34 patients 20 ppm in 29 patients 40 ppm in 27 patients 80 ppm in 8 patients[c]	Duration of mechanical ventilation	Oxygenation[d]; pulmonary arterial pressure[d]; response; 28-day survival
Lundin et al. (92)	1999	30	Patients with acute lung injury with a Pao_2:FIO_2 <165 mm Hg who had been receiving mechanical ventilation 18–96 hrs[e]	Conventional therapy with no placebo in 93 patients	2, 10, or 40 ppm (lowest effective dose; mean ± SD, 9 ± 8 ppm for 9 ± 6 days) in 87 patients	Reversal of acute lung injury	30- and 90-day survival; dependency on intensive care; duration of hospitalization and acute lung injury; organ failure[f]
Taylor et al. (93)	2004	28	ARDS and a Pao_2: FIO_2 <250 mm Hg[b]; patients with severe sepsis, nonpulmonary organ failure, or both, were excluded	Nitrogen in 193 patients	5 ppm in 192 patients	Survival without need for mechanical ventilation during the first 28 days	Oxygenation and positive end-expiratory pressure[d]; 28-day survival; survival after successful 2-hr trial of unassisted ventilation; survival after oxygenation criteria was met for extubation

ARDS, acute respiratory distress syndrome; ppm, parts per million.

[a]Pao_2:FIO_2 denotes the partial pressure of arterial oxygen to the fraction of inspired oxygen; [b]definition of the American-European Consensus Conference on the acute respiratory distress syndrome was used; [c]the 80-ppm dose was stopped because of the consensus that the dose was likely to be higher than the peak of the dose-response curve; [d]there were significant differences in this outcome between the control group and the group receiving inhaled nitric oxide; [e]of 268 patients with a response to nitric oxide, 180 underwent randomization; [f]the group receiving inhaled nitric oxide had an increased incidence of acute failure (as defined by a serum creatinine concentration of >3.5 mg/dL or the need for renal replacement therapy) ($p < .03$).

Reprinted with permission from Griffiths MJD, Evans TW: Inhaled nitric oxide therapy in adults. *N Engl J Med* 2005; 353:2683–2695.

Safety and Monitoring Boards for futility at interim analyses (70, 71).

A Cochrane Database Systematic Review of pharmacologic therapy for adults with ALI and ARDS reviewed 33 trials that randomized 3,272 patients and concluded that two interventions were beneficial in single small trials: corticosteroids given for late-phase ARDS reduced hospital mortality (n = 24) and pentoxifylline reduced 1-month mortality (n = 30). Individual trials of nine additional pharmacologic interventions failed to show a beneficial effect, concluding that effective pharmacotherapy for ALI and ARDS is extremely limited (72).

Most recently, alterations in coagulation and fibrinolysis in the pathogenesis of ALI and ARDS have been examined, particularly related to alveolar fibrin deposition. Increased local tissue factor-mediated thrombin generation and depression of local fibrinolysis related to increased plasminogen activator inhibitors have been reported (73). Pulmonary coagulopathy may be a prominent feature of ARDS and ventilator-induced lung injury, just as microvascular thrombosis is a common feature of sepsis. Additional studies in this important area are warranted.

Corticosteroids

Because ARDS is pathologically associated with persistent inflammation and excessive fibroproliferation, previous studies investigated the use of corticosteroids. Four trials of high-dose, short-course corticosteroids for early ARDS failed to show improvements in survival (74–77). In contrast, several small case series (78–83) and a single-center randomized trial (n = 24) (84) reported improved lung function and survival with moderate-dose corticosteroids in patients with persistent (7 days) ARDS.

The multicenter trial (n = 180) from the National Heart, Lung and Blood Institute ARDS Clinical Trials Network randomized patients with ARDS of at least 7 days duration to receive either methylprednisolone or placebo in a double-blind manner (85). A complete description of the protocol and methods is available at www.ardsnet.org.

Methylprednisolone therapy was associated with increased ventilator-free and shock-free days, improved oxygenation, and improved pulmonary compliance during the first 28 days. There was no significant difference in 60-day (28.6% vs. 29.2%) and 180-day mortality (31.9% vs. 31.5%) rates in the entire study cohort. As compared with placebo, methylprednisolone was associated with significantly increased 60- and 180-day mortality rates in patients enrolled at least 14 days after

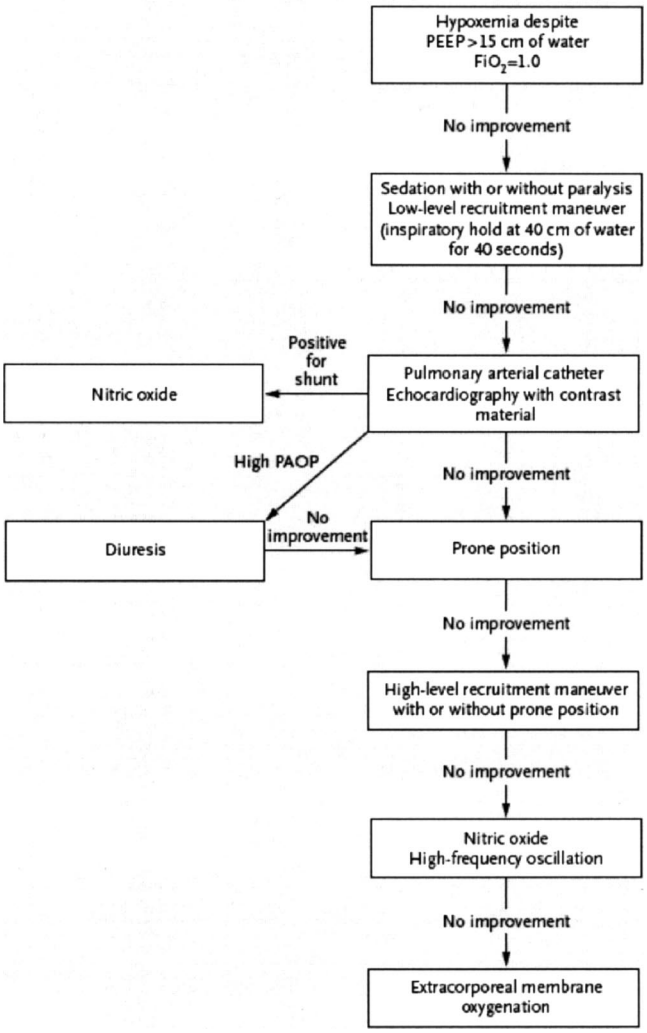

Figure 9. An incremental approach to the management of catastrophic acute respiratory distress syndrome. A high-level recruitment maneuver is used only in patients that are without neurologic disease and bacterial pneumonia and that have adequate blood pressure, filling pressures, and cardiac output. *PEEP*, positive end-expiratory pressure; *PAOP*, pulmonary artery occlusion pressure. Reprinted with permission from Medoff BD, Shepard JO, Smith RN, et al: Case 17-2005: A 22-year-old woman with back and leg pain and respiratory failure. *N Engl J Med* 2005; 352:2425–2434.

the onset of ARDS and with a higher rate of neuromuscular weakness and increased blood glucose concentrations; however, no increase in infectious complications was identified. These results do not support the routine use of methylprednisolone for persistent ARDS.

Surfactant Therapy

Regardless of the cause, a common pathophysiologic feature of patients with ARDS is a dysfunction of the endogenous surfactant system. Exogenous surfactant therapy is an effective standard of care in neonates with ARDS (86, 87). No similar current effective surfactant therapy exists for adult patients with ARDS; however, ongoing and future research efforts suggest that this may eventually be feasible (88, 89).

A multicenter, randomized, blinded trial of calfactant (a natural lung surfactant containing high levels of surfactant-specific protein B) compared with placebo in 153 infants, children, and adolescents with respiratory failure from ALI documented that calfactant acutely improved oxygenation and significantly decreased mortality, although no significant decrease in the course of respiratory failure (duration of ventilation, ICU, or hospital stay) was observed (90). Exogenous surfactant may improve oxygenation, but all clinical studies to date have demonstrated no significant effect on the death rate or length of use of mechanical ventilation in adults.

Nitric Oxide

Inhaled nitric oxide is a selective pulmonary vasodilator, resulting in decreased pulmonary vascular resistance, pulmonary arterial pressure, and right ventricular afterload. The selectivity of nitric oxide for the pulmonary circulation is the result of rapid hemoglobin-mediated inactivation of nitric oxide. Two small single-center studies and four multicenter, randomized, placebo-controlled trials have failed to determine the therapeutic role of inhaled nitric oxide in patients with acute respiratory failure. Low-dose inhaled nitric oxide in ALI and ARDS has been associated with improved short-term oxygenation but has had no substantial impact on the duration of mechanical ventilatory support or on mortality (Table 3) (91–96). The improvement in oxygenation associated with inhaled nitric oxide has not been able to be translated into improved clinical outcome. This may be related to the fact that ARDS is a heterogeneous condition with multiple causes (pulmonary and extrapulmonary) and that only a small minority of patients with ARDS die of respiratory failure—the majority die of multiple organ dysfunction and failure. These data do not support the routine use of inhaled nitric oxide in the treatment of ALI or ARDS, but it may be considered as a salvage therapy in patients who continue to have life-threatening hypoxemia, despite optimization of all other treatment strategies.

Incremental Approach to the Management of Patients with Severe ARDS

In patients with severe refractory hypoxemia, there is potential utility in the incremental approach to ARDS management (Fig. 9). Implementation of the specific strategies we have discussed above may result in improved oxygenation, improved pulmonary compliance, and ultimately, survival in individual patients. There is also the possibility that some of these interventional strategies may have additive effects. It is important to have full knowledge of the results of prospective, randomized trials that have carefully assessed the impact of these treatment strategies on patient outcome in ALI and ARDS. However, faced

with an individual patient with refractory hypoxemia resulting from severe ARDS, it is also important to be comfortable with appropriate bedside implementation of these potential treatment strategies for ALI and ARDS.

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