REVIEW

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Update in ARDS management: Recent randomized controlled trials that changed our practice

ABSTRACT

In the last 7 years, 14 randomized controlled trials in patients with acute respiratory distress syndrome (ARDS) have shown that:

- Mechanical ventilation with a tidal volume of 6 mL/kg of predicted body weight is better than mechanical ventilation with a tidal volume of 12 mL/kg of predicted body weight.
- Prone positioning improves oxygenation but poses safety concerns.
- A high level of positive end-expiratory pressure does not improve survival.
- High-frequency oscillatory ventilation is in theory the ideal "lung-protective" method, but its benefits have not been proven.
- No drug therapy has been shown to improve survival in patients with ARDS.
- Exogenous surfactant may improve oxygenation but has no significant effect on the death rate or length of use of mechanical ventilation.
- Low-dose inhaled nitric oxide has no substantial impact on the duration of ventilatory support or on the death rate.
- Partial liquid ventilation may be beneficial in young patients with acute lung injury or ARDS, although further study is needed to confirm this.

EVEN THOUGH the acute respiratory distress syndrome (ARDS) still carries a high mortality rate, several advances have been made in the last 10 to 15 years in understanding its pathophysiology and in improving patient care. For example, the idea of "lung-protective" strategies has led to studies that proved the benefit of using low tidal volumes during mechanical ventilation, a finding that has changed our practice. Very encouraging is that the number of randomized controlled trials has increased dramatically in the last 10 years.

ARDS is an acute diffuse lung injury associated with severe hypoxemia.[1] Approximately 10% to 15% of patients admitted to an intensive care unit and up to 20% of mechanically ventilated patients meet the criteria for ARDS.[2] Despite extensive efforts to decrease the mortality associated with this disease, the case-fatality rate in ARDS exceeds 30%.[3]

In recent years, numerous studies have evaluated therapeutic strategies to increase the survival rate. The main principle continues to be supportive care, focusing on improving gas exchange, preventing complications associated with mechanical ventilation, and reducing length of stay in the intensive care unit.

VENTILATORY SUPPORT

The traditional approach in treating ARDS has been supportive care with mechanical ventilation using a tidal volume of 10 to 15 mL/kg,[4] even though this volume is larger than in healthy people at rest.

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In studies in animals[5] and in humans, large tidal volumes disrupted the pulmonary epithelium and caused lung inflammation, atelectasis, hypoxemia, and the systemic release of inflammatory mediators. Thus, large tidal volumes may exacerbate lung injury and increase the risk of nonpulmonary organ failure.

LOW TIDAL VOLUME IMPROVES OUTCOMES

"Lung-protective" ventilation, using a lower tidal volume, may reduce injurious lung stretching and the release of inflammatory mediators.[6] However, using a low tidal volume may cause respiratory acidosis and decrease arterial oxygenation.

In the last 7 years, five randomized, controlled trials focused on lung-protective ventilation strategies.

STEWART TE, MEADE MO, COOK DJ, ET AL.
EVALUATION OF A VENTILATION STRATEGY TO PREVENT BAROTRAUMA IN PATIENTS AT HIGH RISK FOR ACUTE RESPIRATORY DISTRESS SYNDROME. N ENGL J MED 1998; 338:355–361.

Large tidal volumes may worsen lung injury and increase the risk of organ failure

The study. Stewart et al[7] conducted a prospective, randomized, controlled trial in eight tertiary care centers to determine if a mechanical ventilation strategy with specific limits on peak inspiratory pressure and tidal volume in patients at high risk for ARDS would affect the in-hospital mortality rate. Secondary outcomes studied were barotrauma, the highest total multiple organ dysfunction score, dysfunction of individual organs, relevant arrhythmias, dialysis, duration of mechanical ventilation, and length of stay in the hospital and intensive care unit.

A total of 120 patients were assigned to receive assist-control ventilation with either limited pressure and volume or conventional pressure and volume. The average tidal volume in the limited-ventilation group was 7.2 mL/kg, compared with 10.8 mL/kg in the conventional-ventilation group ($P < .001$). The average peak inspiratory pressures were 23.6 cm H_2O vs 34.0 cm H_2O ($P < .001$). There were no differences in the positive end-expiratory pressure, fraction of inspired oxygen (Fi_{O_2}), or minute ventilation.

Findings. The mortality rate did not differ with treatment: 50% in the limited-ventilation group vs 47% in the conventional-ventilation group ($P = .72$). Likewise, there were no differences in the other outcomes.

Interestingly, significantly more patients in the limited-ventilation group needed dialysis (13% vs 5%, $P = .04$) or paralytic drugs (23% vs 13%, $P = .05$).

Conclusions. In patients at high risk for ARDS, a strategy of mechanical ventilation with limited peak inspiratory pressure and tidal volume did not appear to reduce mortality and may increase morbidity (ie, the need for dialysis and use of paralytic drugs).

BROCHARD L, ROUDOT-THORAVAL F, ROUPIE E, ET AL.
TIDAL VOLUME REDUCTION FOR PREVENTION OF VENTILATOR-INDUCED LUNG INJURY IN ACUTE RESPIRATORY DISTRESS SYNDROME. AM J RESPIR CRIT CARE MED 1998; 158:1831–1838.

The study. This prospective, multicenter, randomized study[8] was performed at 25 hospitals in seven countries to compare conventional assist-control mechanical ventilation with a ventilation strategy that limited the plateau pressure. A total of 116 patients were enrolled, with 58 in each group.

The standard-treatment group received an average tidal volume of 10.3 mL/kg, compared with 7.1 mL/kg ($P < .001$) in the limited-pressure group. The plateau pressure was 31.7 cm H_2O in the standard-treatment group vs 25.7 cm H_2O in the limited-pressure group ($P < .001$). During therapy, the groups differed significantly in their partial pressure of arterial carbon dioxide (Pa_{CO_2}) and pH (both $P < .001$), but they achieved similar levels of oxygenation without significant differences in the positive end-expiratory pressure.

The primary outcome was the mortality rate at 60 days; secondary outcomes were barotrauma, organ system failures, duration of mechanical ventilation, number of ventilation-free days, and length of stay in the intensive care unit.

Findings. The study was terminated after an interim analysis of the first 100 patients when the investigators calculated that pressure limitation would not achieve a beneficial effect within the planned frame of the study (the initial calculated sample was 250 patients). The mortality rates at 60 days were not significantly different between the groups (46.6% in the limited-pressure group vs 37.9% in the standard-treatment group, $P = .38$). Also, no significant differences were seen in

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any of the secondary outcomes, including barotrauma.

Conclusions. Reducing the tidal volume to achieve an end-inspiratory plateau pressure of approximately 25 cm H_2O had no impact on morbidity or mortality.

BROWER RG, SHANHOLTZ CB, FESSLER HE, ET AL.
PROSPECTIVE, RANDOMIZED, CONTROLLED CLINICAL TRIAL COMPARING TRADITIONAL VERSUS REDUCED TIDAL VOLUME VENTILATION IN ACUTE RESPIRATORY DISTRESS SYNDROME PATIENTS. CRIT CARE MED 1999; 27:1492–1498.

The study. Brower et al[9] assessed the safety and efficacy of a mechanical ventilation strategy designed to reduce stretch-induced lung injury in ARDS. Specific variables assessed included the fraction of inspired oxygen (FiO_2), positive end-expiratory pressure, effects on circulation, need for neuromuscular blockers and sedatives, time to reversal of respiratory failure, and mortality rate.

Fifty-two patients were enrolled from eight intensive care units. Assist-control or synchronized intermittent mandatory ventilation was used. Patients were randomized to receive either a low tidal volume (average 7.3 mL/kg), keeping the plateau pressure less than 30 cm H_2O, or a traditional tidal volume (average 10.2 mL/kg), keeping the plateau pressure less than 55 cm H_2O.

Findings. The groups did not differ significantly in their positive end-expiratory pressures; FiO_2 levels; use of vasopressors, sedatives, or neuromuscular blocking agents; rate of reversal of respiratory failure; or mortality rate (46% with a traditional tidal volume vs 50% with a low tidal volume). The incidence of barotrauma was equal. The study was stopped early to permit the patients to participate in another ARDS study.

Conclusions. The low tidal volume ventilation strategy appeared to be as safe as traditional ventilation, but it offered no beneficial effects. This may be due to the small number of patients in the study.

AMATO MB, BARBAS CS, MEDEIROS DM, ET AL.
EFFECT OF A PROTECTIVE-VENTILATION STRATEGY ON MORTALITY IN THE ACUTE RESPIRATORY DISTRESS SYNDROME. N ENGL J MED 1998; 338:347–354.

The study hypothesis was that preventing persistent alveolar collapse and reducing cyclic lung re-opening and lung stretching during mechanical ventilation would result in lower rates of pulmonary complications and mortality at 28 days in patients with ARDS.[10]

Fifty-three patients were prospectively enrolled in two intensive care units in Brazil. Groups received either:

- Conventional ventilation, ie, tidal volume 12 mL/kg (volume-cycled assist-control ventilation), positive end-expiratory pressure 6.9 to 9.3 cm H_2O, and $PaCO_2$ 35 to 38 mm Hg, or
- Protective ventilation, ie, tidal volume 6 mL/kg, positive end-expiratory pressure 13.2 to 16.4 cm H_2O, permissive hypercapnia ($PaCO_2$ 50.8 to 58.2 mm Hg), and preferential use of pressure-limited ventilation mode.

The primary end point was survival at 28 days. Secondary end points were survival at hospital discharge, barotrauma, and weaning from the respirator.

Findings. The study was stopped at the fifth interim analysis because a significant survival difference was seen. At 28 days, 38% of patients in the protective-ventilation group had died compared with 71% in the conventional-ventilation group ($P < .001$). The weaning rate in the protective-ventilation group was 66% compared with 29% in the conventional-ventilation group ($P = .005$). The incidence of barotrauma was lower in the protective-ventilation group (7% vs 42%; $P = .02$), despite the use of higher positive end-expiratory pressures and higher mean airway pressures. The difference in survival at hospital discharge was not significant ($P = .37$).

Conclusions. Compared with conventional ventilation, a protective ventilatory strategy was associated with a higher survival rate at 28 days, a higher rate of weaning from mechanical ventilation, and a lower rate of barotrauma, although it was not associated with a higher survival rate at discharge.

On the other hand, low tidal volumes may cause respiratory acidosis and decrease oxygenation

THE ACUTE RESPIRATORY DISTRESS SYNDROME NETWORK.
VENTILATION WITH LOWER TIDAL VOLUMES AS COMPARED WITH TRADITIONAL TIDAL VOLUMES FOR ACUTE LUNG INJURY AND THE ACUTE RESPIRATORY DISTRESS SYNDROME. N ENGL J MED 2000; 342:1301–1308.

The study. The ARDS Network conducted this prospective, randomized trial in 10 university centers from 1996 through 1999 to determine whether the use of low tidal volumes would improve important clinical outcomes in ARDS.[11]

A total of 861 patients were randomized; 432 received mechanical ventilation with a

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TABLE 1

Studies of low vs high tidal volumes in ARDS

INVESTIGATORS	NO. OF PATIENTS	MEAN TIDAL VOLUMES		
		HIGH TIDAL VOLUME	LOW TIDAL VOLUME	DIFFERENCE*
Stewart et al[7]	120	10.8 mL/kg	7.2 mL/kg	3.6 mL/kg
Brochard et al[8]	116	10.3 mL/kg	7.1 mL/kg	3.2 mL/kg
Brower et al[9]	52	10.2 mL/kg IBW	7.3 mL/kg IBW	2.9 mL/kg
Amato et al[10]	53	12 mL/kg	6 mL/kg	6 mL/kg
ARDS Network[11]	861	12 mL/kg PBW	6 mL/kg PBW	6 mL/kg

*Approximate difference based on averages
IBW = ideal body weight; PBW= predicted body weight

low tidal volume (6 mL/kg of predicted body weight), and 429 received a traditional tidal volume (12 mL/kg of predicted body weight). Plateau pressures were less than 50 cm H_2O in the traditional-tidal-volume group and less than 30 cm H_2O in the low-tidal-volume group. All other ventilation procedures, including weaning protocols, were identical. Volume-assist/control mode was used. The baseline characteristics were similar, except for a slightly higher positive end-expiratory pressure used in the low tidal-volume group.

The first primary outcome was death before the patient was discharged home and breathing without a ventilator. The second primary outcome was ventilator-free days. Other outcomes were the number of days without organ failure and barotrauma. Serum samples were obtained on days 0 and 3 to measure plasma interleukin 6 (IL-6) concentrations as a marker of inflammation.

Findings. The trial was stopped after the fourth interim analysis because the use of low tidal volume was found to be beneficial.

The mortality rate before the patient was discharged home and breathing without assistance was 31.0% with low tidal volume vs 39.8% with traditional tidal volume (P = .007). By day 28, 65.7% of the patients on low tidal volume were breathing without assistance, compared with 55% of patients on traditional tidal volume (P < .001). The number of ventilator-free days at 28 days was significantly higher with low tidal volume (P = .007), as was the number of days without failure of nonpulmonary organs (P = .006).

The groups did not differ in the incidence of barotrauma or in the use of neuromuscular blocking agents. The levels of IL-6 were similar at baseline in both groups, but the decrease by day 3 was greater in the low-tidal-volume group (P < .001).

Conclusions. Although the earlier studies had somewhat equivocal results, the ARDS Network study was the conclusive study on this issue. The low-tidal-volume group enjoyed a 22% lower mortality rate, more ventilator-free days, a higher rate of breathing without assistance, and a lower incidence of nonpulmonary organ failure. These results, coupled with the reductions in plasma IL-6 concentrations, suggest that the patients treated with lower tidal volume had less lung inflammation and systemic inflammation.

The ARDS Network trial was stopped early because low tidal volumes were beneficial

WHY DID THE TRIALS HAVE DIFFERENT FINDINGS?

Reasons for the different findings in these trials include:

- The ARDS Network[11] used a lower tidal volume in the experimental group, with a greater difference (6 vs 12 mL/kg) between the groups (**TABLE 1**).
- The earlier studies lacked statistical power. The four earlier studies[7–10] were smaller and were designed to detect larger differences in mortality. Hence, they lacked power to detect the effects on survival of low tidal volume seen by the ARDS Network.[11]

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- The ARDS Network protocol allowed for more aggressive management of acidosis, with an increase in the ventilator rate and bicarbonate infusions to correct mild or moderate acidosis. Thus, the treatment groups differed only slightly in their $PaCO_2$ and pH values. The earlier studies allowed more acidosis, which may have counteracted the possible protective effect of low tidal volume. Previous data suggested that hypercapnic acidosis ("permissive hypercapnia") might have a protective effect; however, this has not been proven.
- The ARDS Network used a slightly higher positive end-expiratory pressure in the group receiving low tidal volume. In view of the concept that lung injury may in part be due to excessive lung stretching plus repeated opening and closing of small airways, the higher positive end-expiratory pressure may have prevented these types of injury. This concept was previously studied by Amato et al,[10] who found that higher positive end-expiratory pressure led to favorable clinical outcomes. Nevertheless, another randomized controlled trial performed by the ARDS Network subsequently argued against these finding (see below).

The ARDS Network trial treated acidosis more aggressively than earlier trials did

HIGHER END-EXPIRATORY PRESSURE DOES NOT IMPROVE SURVIVAL

Positive end-expiratory pressure has been used mainly to improve oxygenation in acute lung injury and ARDS. The "keep the lung open" hypothesis implies that positive end-expiratory pressure may have a role in limiting ventilator-induced lung injury by preventing collapse of the alveoli at the end of expiration.

Ventilator-induced lung injury may also occur in portions of the lung that are not aerated at end-expiration owing to atelectasis, flooding, or consolidation. The proportion of unaerated lung may be reduced by applying positive end-expiratory pressure. Most patients with acute lung injury or ARDS are treated with a positive end-expiratory pressure of 5 to 12 cm H_2O.

Would a higher positive end-expiratory pressure decrease ventilator-induced lung injury by reducing the proportion of the lung that is not aerated?

BROWER RG, LANKEN PN, MACINTYRE N, ET AL; NATIONAL HEART, LUNG, AND BLOOD INSTITUTE ARDS CLINICAL TRIALS NETWORK.
HIGHER VERSUS LOWER POSITIVE END-EXPIRATORY PRESSURES IN PATIENTS WITH THE ACUTE RESPIRATORY DISTRESS SYNDROME. N ENGL J MED 2004; 351:327–336.

The study. Brower et al[12] conducted a randomized, controlled trial in 23 hospitals in the United States to determine whether using a higher positive end-expiratory pressure with lower tidal volumes and lower inspiratory airway pressures would improve clinical outcomes. Positive end-expiratory-pressure levels were set according to the FiO_2. The ventilatory mode was volume-assist/control. All patients received a tidal volume of 6 mL/kg and inspiratory plateau pressures of 30 cm H_2O or less.

The study was stopped at the second interim analysis after 549 patients were enrolled, 273 in the group with a low positive end-expiratory pressure (8.3 ± 3.2 cm H_2O) and 276 in the group with a higher positive end-expiratory pressure (13.2 ± 3.5 cm H_2O).

Findings. There were no significant differences between groups in the mortality rate or the number of ventilator-free days, intensive care unit-free days, or organ-failure-free days.

Conclusions. The use of higher or lower positive end-expiratory pressure does not influence the clinical outcome in patients receiving mechanical ventilation with low tidal volumes and low end-expiratory plateau pressures.

It is important to attempt to balance the beneficial effect of positive end-expiratory pressure on arterial oxygenation and its adverse effects such as circulatory depression and increased airway pressures.

PRONE POSITION DOES NOT IMPROVE SURVIVAL

In theory, the prone position may improve oxygenation in acute lung injury and ARDS by increasing alveolar recruitment; redistributing ventilation toward areas that are well perfused; homogenizing the distribution of tidal volume by better fitting of the lungs in the thoracic wall; increasing the end-expiratory volume; redirecting the compressive forces of the heart weight on the lungs; and facilitating the drainage of respiratory secretions.

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GATTINONI L, TOGNONI G, PESENTI A, ET AL.
EFFECT OF PRONE POSITIONING ON THE SURVIVAL OF PATIENTS WITH ACUTE RESPIRATORY FAILURE. N ENGL J MED 2001; 345:568–573.

GUERIN C, GAILLARD S, LEMASSON S, ET AL
EFFECTS OF SYSTEMATIC PRONE POSITIONING IN HYPOXEMIC ACUTE RESPIRATORY FAILURE: A RANDOMIZED CONTROLLED TRIAL. JAMA 2004; 292:2379–2387.

The studies. Two large randomized trials compared the effect of prone vs supine positioning on mortality.[13,14]

Gattinoni et al[13] enrolled 304 patients, randomizing 152 to be put in the prone position for at least 6 hours daily for 10 days and 152 to conventional supine positioning. Primary end points were the number of patients who died before 10 days, before discharge, and before 6 months. Secondary outcomes were improvement in respiratory failure and in organ dysfunction.

Guerin et al[14] enrolled 802 patients with acute hypoxemic respiratory failure, randomizing 417 to prone positioning (at least 8 hours daily) and 385 to supine positioning. The supine group was kept at a 30-degree angle and could cross over to prone positioning in case of severe hypoxemia. The primary end point was the mortality rate at 28 days. Secondary outcomes were the mortality rate at 90 days, incidence of ventilator-associated pneumonia, duration of mechanical ventilation, and measures of oxygenation.

Findings. Gattinoni et al found no significant improvement in survival at 10 days (21% in the prone group vs 25% in the supine group), at discharge from the intensive care unit (51% vs 48%), or at 6 months (62% vs 59%). Prone positioning improved oxygenation in more than 70% of the patients. However, the prone group had a greater number of pressure sores per patient and a higher proportion of sores at expected sites. The rates of displacement of endotracheal tubes, vascular catheters, or thoracotomy tubes were similar in the two groups.

Guerin et al found no differences between groups in the mortality rate at 28 days (32.4% for the prone group vs 31.5% for the supine group) or 90 days (43.3% vs 42.2%), or in duration of mechanical ventilation (13.7 vs 14.1 days). The prone-positioning group had a higher PaO_2/FiO_2 ratio (an index of oxygenation) and a lower incidence of ventilator-associated pneumonia (1.66 vs 2.14 episodes per 100 patient-days of intubation, $P = .045$). Pressure sores, selective intubation, and endotracheal tube obstruction occurred more frequently in the prone group.

Conclusion. Both studies showed that prone positioning does not improve survival and that it may be associated with harmful effects such as decubitus ulcers and self-extubation. Nevertheless, prone positioning may reduce the incidence of ventilator-associated pneumonia and improve oxygenation in patients with severe hypoxemia.

Given the lack of clear benefit in survival and the potential complications of prone positioning, we believe that there is not enough evidence to support its routine use in all patients with acute lung injury and ARDS.

HIGH-FREQUENCY OSCILLATORY VENTILATION: SAFE, MAYBE BENEFICIAL

High-frequency oscillatory ventilation is, in theory, a "lung-protective" ventilation method. This method oscillates the lung around a constant mean airway pressure that is usually higher than those used in conventional mechanical ventilation with tidal volumes of 10 to 12 mL/kg. The application of a constant mean airway pressure in high-frequency oscillatory ventilation allows the maintenance of alveolar recruitment while avoiding low end-expiratory pressure and high peak pressures.

One must balance the benefit of positive end-expiratory pressure on oxygenation vs its adverse effects

Studies in animals have shown that high-frequency oscillatory ventilation improves gas exchange, inflates the lungs uniformly, reduces histopathological evidence of ventilator-induced lung injury, and reduces levels of systemic inflammatory mediators. Several randomized, controlled trials in children failed to show a significant decrease in the mortality rate but did demonstrate increases in oxygenation without a major increase in barotrauma.

DERDAK S, MEHTA S, STEWART TE, ET AL, AND THE MULTICENTER OSCILLATORY VENTILATION FOR ACUTE RESPIRATORY DISTRESS SYNDROME TRIAL (MOAT) STUDY INVESTIGATORS.
HIGH-FREQUENCY OSCILLATORY VENTILATION FOR ACUTE RESPIRATORY DISTRESS SYNDROME IN ADULTS. A RANDOMIZED, CONTROLLED TRIAL. AM J RESPIR CRIT CARE MED 2002; 166:801–808.

The study. Derdak et al[15] performed a randomized, controlled trial in 13 university-affiliated medical centers from October 1997

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through December 2000 to compare high-frequency oscillatory ventilation (n = 75) vs conventional mechanical ventilation (n = 73) in adults with early-phase ARDS. A Sensormedics 3100B high-frequency oscillatory ventilator (Sensormedics, Yorba Linda, CA) was used. The groups did not differ in baseline characteristics.

The initial settings in the high-frequency oscillatory ventilation group were FiO_2 0.80 to 1.00 and oscillatory frequency 5 Hz; the mean airway pressure was set 5 cm H_2O higher than the mean airway pressure during conventional mechanical ventilation at the beginning and was titrated later on.

The primary outcome was the rate of survival without the need for mechanical ventilation at 30 days after study entry; secondary outcomes were new or worsening air leak, mucus plugging requiring changing the endotracheal tube, and the mortality rate at 6 months.

Findings. In the group on high-frequency oscillatory ventilation, the mean airway pressure was significantly higher at all times during the study.

Patients in the high-frequency oscillatory ventilation group showed an earlier improvement in the PaO_2/FiO_2 ratio compared with those on conventional ventilation, although the difference did not persist for more than 24 hours.

At 30 days, the percentage of patients alive and not needing mechanical ventilation was 36% for high-frequency oscillatory ventilation and 31% for conventional ventilation (P = .686). The mortality rate at 30 days was 37% for high-frequency oscillatory ventilation and 52% for conventional ventilation (P = .102).

At 6 months, the mortality rates were 47% vs 59%, respectively (P = .143). No significant differences in mucus plugging, barotrauma, or ventilatory failure were seen.

Conclusions. High-frequency oscillatory ventilation was found to be safe and was not associated with significant hemodynamic effects. The study was not designed to evaluate mortality; however, a trend towards reduced mortality was seen at 30 days and 6 months with high-frequency oscillatory ventilation.

A major problem in this study was that the protocol for high-frequency oscillatory ventilation was compared with conventional mechanical ventilation using tidal volume based on actual rather than ideal body weight. The average tidal volume in the control group was 10 mL/kg of ideal body weight. Further studies should be done to compare high-frequency oscillatory ventilation with current mechanical ventilation strategies using the low tidal volume setting described by the ARDS Network.

PHARMACOLOGIC THERAPY

A number of pharmacologic strategies have been tried in ARDS, but none has been shown to increase the survival rate.

EXOGENOUS SURFACTANT DOES NOT IMPROVE SURVIVAL

Patients with ARDS have decreased production and biochemical alterations of endogenous surfactant. The lack of surfactant in ARDS contributes to atelectasis, shunts, and gas-exchange abnormalities and predisposes to infections and injury from mechanical ventilation.

A recombinant surfactant based on protein C showed favorable effects in preclinical studies, and a trend towards benefit was seen in two phase 2 clinical trials.

SPRAGG RG, LEWIS JF, WALMRATH HD, ET AL.
EFFECT OF RECOMBINANT SURFACTANT PROTEIN C-BASED SURFACTANT ON THE ACUTE RESPIRATORY DISTRESS SYNDROME. N ENGL J MED 2004; 351:884–892.

The study. Two independent, multicenter, randomized, parallel-group, double-blind, controlled, prospective studies[16] were conducted in Canada, the United States, Europe, and Africa. The hypothesis was that giving exogenous surfactant would decrease the need for mechanical ventilation.

Of the 448 patients enrolled, 224 received surfactant and 224 did not. The most common cause of ARDS was sepsis, followed by pneumonia and trauma or surgery. Patients were randomly assigned in a 1:1 ratio to receive standard therapy alone or standard therapy plus up to four intratracheal installations of surfactant within 24 hours.

We believe there is not enough evidence in support of prone positioning to recommend its routine use

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The primary end point was the number of ventilator-free days. Secondary end points were safety, the survival rate at 28 days, and oxygenation.

Findings. Although the surfactant group had better oxygenation, they did not have more ventilator-free days or a lower mortality rate. The gas exchange benefit was seen during the first 24 hours of treatment.

A post hoc analysis of patients with ARDS caused by direct lung injury (pneumonia, aspiration, or both) showed a trend toward a higher survival rate in the surfactant group. In the patients with ARDS due to indirect injury, the post hoc analysis showed worsened survival.

Conclusions. Given the lack of improvement in survival or ventilator-free days, the use of recombinant protein C-based surfactant is not justified.

However, oxygenation was improved within a 24-hour period, with a significant increase in the PaO_2/FiO_2 ratio. The authors speculated that if the treatment were given for more than 24 hours, a potential benefit might have been seen.

In addition, the post hoc analysis showed a trend towards a survival benefit in the direct-injury group that may be related to improvement in gas exchange; this group also had fewer severe coexisting conditions. There was no clear explanation for the lower survival rate in the heterogeneous group of patients with indirect injury-related ARDS.

Further studies need to be conducted to evaluate these findings.

Lack of surfactant in ARDS contributes to atelectasis, shunts, gas-exchange abnormalities, infections, and injuries

LOW-DOSE NITRIC OXIDE IMPROVES O_2 BUT NOT DEATHS

Acute lung injury and ARDS are characterized by pulmonary hypertension and significant right-to-left shunting of venous blood. Inhaled nitric oxide is a selective pulmonary vasodilator that recruits blood flow in the injured lung away from the damaged alveolar units. It has been used in prior trials as an adjunctive therapy to improve gas exchange and oxygenation, although none of the previous studies demonstrated an impact on mortality.

TAYLOR RW, ZIMMERMAN JL, DELLINGER RP, ET AL.
LOW-DOSE INHALED NITRIC OXIDE IN PATIENTS WITH ACUTE LUNG INJURY: A RANDOMIZED CONTROLLED TRIAL. JAMA 2004; 291:1603–1609.

The study. Taylor et al[17] conducted a multicenter, randomized, placebo-controlled study in the intensive care units of 46 hospitals in the United States. Using a modification of the American-European Consensus Conference definition of ARDS (PaO_2/FiO_2 ratio < 250 instead of < 200), the investigators enrolled 385 patients within 72 hours of the onset of ARDS. Patients with nonpulmonary organ dysfunction or sepsis were excluded.

Patients received placebo (nitrogen gas) or inhaled nitric oxide (5 parts per million) for 28 days or until mechanical ventilation was stopped or they died.

Findings. The mortality rate was similar with either treatment (20% with placebo vs 23% with nitric oxide, $P = .54$). The number of days off mechanical ventilation were also similar (10.6 vs 10.7, $P = .97$), as was the number of days alive and meeting criteria for extubation (17 vs 16.7, $P = .89$). The only positive finding was a temporary (lasting < 48 hours) but statistically significant increase in oxygenation in the nitric oxide group. The groups were comparable in the number of adverse events and side effects.

Conclusions. Inhaled nitric oxide at a dose of 5 parts per million may temporarily improve oxygenation in acute lung injury not due to sepsis but does not influence the duration of ventilatory support or improve outcomes. Currently, there is not enough evidence to support its widespread use, and it should be used only in investigational studies or in a very few selected cases.

PARTIAL LIQUID VENTILATION MAY HELP YOUNGER PATIENTS

Liquid ventilation has been investigated since the 1960s as a method to improve gas exchange and pulmonary function. Recent clinical studies in children and adults focused on partial liquid ventilation, in which perfluorocarbon-filled lungs are ventilated with conventional gas mechanical ventilation. Those studies suggested that partial liquid ventilation may increase gas exchange by recruiting atelectatic lung regions, redistrib-

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uting pulmonary blood flow, and reducing total lung water.

Perflubron (perfluorocarbon) tends to settle in dependent lung regions, which are the areas most commonly affected in ARDS. These areas may be reinflated, providing a protective effect in the setting of lung injury. Also, perflubron may have anti-inflammatory effects, suggested by a reduction in alveolar macrophage function and a decrease in systemic cytokine levels during partial liquid ventilation, although the exact mechanism behind this effect is not clear.

HIRSCHL RB, CROCE M, GORE D, ET AL; THE ADULT PARTIAL LIQUID VENTILATION STUDY GROUP.
PROSPECTIVE, RANDOMIZED, CONTROLLED PILOT STUDY OF PARTIAL LIQUID VENTILATION IN ADULT ACUTE RESPIRATORY DISTRESS SYNDROME. AM J RESPIR CRIT CARE MED 2002; 165:781–787.

The study. Hirschl et al[18] performed a phase 2, prospective, nonblinded, randomized controlled pilot study at 18 centers between July 1995 and August 1996. A total of 90 patients were randomized to receive conventional mechanical ventilation (n = 25) or partial liquid ventilation (n = 65). Those on partial liquid ventilation received perflubron through a side port in the endotracheal tube.

The primary end point was the mean number of ventilator-free days. Secondary outcomes were the mortality rate at 28 days, the calculated Pa_{O_2}/Fi_{O_2} ratio, and the alveolar-arterial oxygen difference.

Findings. Progression to ARDS occurred in 39% of the patients on partial liquid ventilation who entered the study with acute lung injury compared with 82% of the subjects who had conventional mechanical ventilation ($P = .03$). The overall mortality rate was 26% with partial liquid ventilation and 30% with conventional mechanical ventilation ($P = .67$). No significant difference was seen in ventilator-free days or pulmonary-related variables.

In a post hoc analysis of patients younger than 55 years, those on partial liquid ventilation were weaned from mechanical ventilation significantly faster ($P = .045$) and also showed a trend toward more ventilator-free days. Hypoxia, respiratory acidosis, and bradycardia occurred more frequently in those receiving partial liquid ventilation, although the difference was not significant.

Conclusions. Although a significant reduction in progression to ARDS was noted with partial liquid ventilation, no differences in ventilator-free days, overall mortality, or pulmonary function were observed. The post hoc analysis in patients younger than 55 years showed that partial liquid ventilation may be beneficial in increasing ventilator-free days and speeding the discontinuation of mechanical ventilation, although it did not show a reduction in mortality. The side effects of partial liquid ventilation were transient, self-limited, and, with appropriate vigilance, manageable. No attempt was made to control the tidal volume in either group (8–9 mL/kg).

A larger prospective, randomized trial with more patients was recently accepted for publication.[19]

KETOCONAZOLE IS NOT USEFUL FOR EARLY TREATMENT

Ketoconazole is a synthetic antifungal imidazole that has anti-inflammatory properties. It inhibits enzymes implicated in the development of acute lung injury and ARDS, including thromboxane synthase (which catalyzes the conversion of prostaglandin G_2 to thromboxane A_2) and 5-lipoxygenase (which converts arachidonic acid to leukotrienes). Clinical studies have suggested that ketoconazole may be effective in preventing ARDS, and one of those trials showed a significant reduction in mortality.

Use of recombinant protein C-based surfactant is not justified

THE ARDS NETWORK.
KETOCONAZOLE FOR EARLY TREATMENT OF ACUTE LUNG INJURY AND ACUTE RESPIRATORY DISTRESS SYNDROME: A RANDOMIZED CONTROLLED TRIAL. JAMA 2000; 283:1995–2002.

The study. The ARDS Network[20] conducted a multicenter, randomized, double-blind, placebo-controlled trial that enrolled 234 patients: 117 received ketoconazole 400 mg/day, and 117 received placebo.

Primary end points were the proportion of patients who could breathe without assistance at discharge and the number of ventilatory-free days. Secondary outcomes were the proportion of patients achieving unassisted breathing for 48 hours or more, number of organ-failure-free days, and changes in plasma levels of IL-6 and urinary thromboxane metabolites.

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Findings. No difference between groups was noted in the in-hospital mortality rate, the median number of ventilator-free days, or the number of organ-failure-free days. The same proportion of patients in each group achieved unassisted breathing within 28 days. No difference was seen in the lung injury score, the PaO_2/FiO_2 ratio, lung compliance, or the positive end-expiratory pressure. The IL-6 plasma levels were not altered, and thromboxane metabolites did not differ.

Conclusions. This large, randomized trial showed that ketoconazole is not useful for the early treatment of acute lung injury and ARDS. Ketoconazole failed to increase survival or the number of days free of mechanical ventilation or free of organ failure, and it failed to improve any other secondary end points.

The reason the trial did not confirm the findings of the previous studies of ketoconazole may be in part due to the heterogeneous population studied by the ARDS Network (medical and surgical) compared with the predominantly surgical patients enrolled in other trials.

Ketoconazole is not useful for the early treatment of acute lung injury/ARDS

SIVELESTAT: NO BENEFIT, AND MAY INCREASE LONG-TERM MORTALITY

ARDS is a complex disorder in which neutrophils and neutrophil elastase are believed to play a key role in injuring the endothelium and increasing vascular permeability. Sivelestat is an inhibitor of neutrophil elastase and has a low molecular weight. A phase 3 study in Japan demonstrated improved pulmonary function, significant reduction in duration of intensive care unit stay, and favorable trends in the mortality rate and duration of mechanical ventilation. In fact, this neutrophil elastase inhibitor is approved in Japan for treatment of acute lung injury associated with the systemic inflammatory response syndrome.

ZEIHER BG, ARTIGAS A, VINCENT JL, ET AL.
STRIVE STUDY GROUP. NEUTROPHIL ELASTASE INHIBITION IN ACUTE LUNG INJURY: RESULTS OF THE STRIVE STUDY. CRIT CARE MED 2004; 32:1695–1702.

The study. The Sivelestat Trial in Acute Lung Injury Patients Requiring Mechanical Ventilation (STRIVE),[21] a prospective, randomized, double-blind, placebo-controlled, multiple center trial, assessed whether sivelestat could reduce the 28-day all-cause mortality rate and increase ventilator-free days in patients with acute lung injury managed with low tidal volume.

The study was stopped during a scheduled interim analysis. At that point, 487 patients had received the study medication (246 placebo and 241 sivelestat).

Findings. There was no significant difference between the groups in the all-cause mortality rate and number of ventilator-free days at 28 days. No difference was noted in any of the secondary outcomes. The study was stopped early due to a trend toward increased all-cause mortality in the long term in the sivelestat group.

Conclusions. This large study showed that sivelestat does not offer benefits in the treatment of acute lung injury and ARDS. The differences between this trial and the previous Japanese trials may be in part due to a more genetically homogenous population, to a tighter age distribution, and to patients being less severely ill.

Although the increased long-term mortality rate seen in the sivelestat patients seems not to be related to the drug, a relationship cannot be excluded.

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