CME CREDIT

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Acute respiratory distress syndrome: Low-stretch ventilation improves survival

ABSTRACT

In a recent major study, patients with acute respiratory distress syndrome or acute lung injury were randomly assigned to have their respirators set to deliver tidal volumes of either 6 mL/kg or a more-traditional 12 mL/kg. Mortality in the low-tidal-volume group was 31.0%, compared with 39.8% in the traditional-tidal-volume group, a 22% difference ($P = .007$).

WE CAN DECREASE the mortality rate in the acute respiratory distress syndrome (ARDS) by about one fifth from current rates of 40% to 50%,[1–3] according to a recent study sponsored by the National Institutes of Health.[4] Remarkably, the decrease does not involve any new high-tech device or drug. Rather, it involves setting the respirator to deliver smaller volumes of air with each breath (ie, a lower tidal volume) than are currently used, and correcting acidosis if necessary by increasing the frequency of breaths.

So striking were the findings that the researchers terminated the trial early. Moreover, the editors of *The New England Journal of Medicine* thought the results so significant that they released the findings 2 months before the scheduled publication date of May 4, 2000.

This article describes the pathogenesis and management of ARDS and reviews and comments on the highlights of the ARDS Network study.

PATHOPHYSIOLOGY OF ARDS

The acronym ARDS stands for acute respiratory distress syndrome, but also serves as a mnemonic for its key features:

Acute. ARDS begins with a precipitating event that injures the alveoli. Sepsis is the leading cause; others include pneumonia, trauma, burns, gastric aspiration, multiple blood transfusions, and pancreatitis.

Restrictive. The injury in turn leads to inflammation, pulmonary edema, and loss of lung compliance.

Diffuse. Radiographs frequently show infiltrates in all five lobes. However, and of importance, the involvement is not homogeneous; normal lung units are interspersed among damaged ones.

Shunt. The hypoxemia of ARDS is due to shunting of unoxygenated blood past the fluid-filled alveoli.

Progress—not from a new drug or high-tech device, but from a new ventilator strategy

COURSE

ARDS progresses through three stages: exudative, fibroproliferative, and fibrotic. However, the pace of events varies widely among patients. In fact, all three of these stages can exist simultaneously in a single patient.

Symptoms arise relatively late. The lung injury does not become evident until pulmonary edema occurs—up to 48 hours after the precipitating event. Researchers are trying to identify sensitive and specific markers of the earliest stages of lung injury, but success has been elusive, and we must deal as best we can with patients already in a fairly late stage.

MOST DEATHS ARE NOT DIRECTLY LUNG-RELATED

In the premodern era, almost all patients with ARDS died. Even now, the mortality rate is 40% to 50%. But survivors usually achieve near-normal lung function.[5]

Only about 16% of ARDS deaths are caused by respiratory failure per se—that is, severe hypoxemia, hypercapnia, and respiratory acidosis.[6] The other 84% of deaths are due to nonlung causes: specifically, organ failure brought on by the spread of inflammatory cytokines through the circulation.

Mortality is not associated with the length of time that a patient spends on a ventilator. For this reason, any decisions pertaining to withdrawal from life support should not be based solely on the duration of therapy. Only when organs begin to fail can we consider that further therapy might be futile.

RENEWED INTEREST IN LUNG-SPECIFIC THERAPIES

Do not base decisions about withdrawing life support solely on duration of therapy

Over the years, investigators have looked for ways to lower the mortality rate. But because respiratory failure is responsible for only a minority of deaths, researchers eventually turned their attention elsewhere, ie, to systemic therapies, and interest in lung-specific therapies waned.

Enthusiasm for lung-specific strategies was renewed when researchers began to more fully understand that the fatal multiple organ failures in ARDS patients were caused in large part by cytokines induced by lung inflammation. The emerging theory was that if lung inflammation could be dampened or prevented altogether, the incidence of systemic organ dysfunction might be reduced. Therefore, a number of lung-specific therapies are under investigation, including inhaled nitrous oxide, surfactant, partial liquid ventilation, and lung-protective ventilator strategies.

IS TRADITIONAL TREATMENT HARMFUL?

The traditional ventilation strategy is to maintain adequate oxygenation (eg, a PaO_2 between 55 and 60 mm Hg) and a normal carbon dioxide level (eg, a $PaCO_2$ of approximately 40 mm Hg) by using volume-cycled ventilation with a tidal volume of 10 to 15 mL/kg, a minimal amount of positive end-expiratory pressure, or PEEP (5–10 cm H_2O), and an FIO_2 as low as possible, preferably less than 0.6.

However, several lines of evidence indicate that this ventilator strategy may in fact superimpose an injury we term "volutrauma"—overdistention of the alveoli due to excessive tidal volumes. The tidal volumes traditionally used—10 to 15 mL/kg—are higher than what normal people breathe at rest—6 to 7 mL/kg.

Furthermore, lung injury in ARDS is relatively nonuniform, despite the diffuse bilateral infiltrates typically seen on the chest x-ray. Large tidal volumes may therefore overdistend the small fraction of relatively normally compliant lung that is still capable of gas exchange.

Finally, studies in animals[7–13] showed that large tidal volumes could disrupt the pulmonary epithelium and endothelium and lead to lung inflammation, atelectasis, and release of inflammatory cytokines, which in turn could increase lung inflammation and injure other organs.[8,13]

A NEW, LOW-STRETCH STRATEGY

These insights led investigators to wonder if they could prevent inflammation and thus lower mortality by using lower tidal volumes (a "low-stretch" strategy).

But low tidal volumes could result in hypercapnia and subsequent acidosis. This presented a dilemma. If investigators tried to prevent hypercapnia by increasing the rate of ventilation, they might also be damaging the lung by subjecting some of the collapsed alveoli to repeated opening and closing.

The alternative, however, was to simply allow hypercapnia and respiratory acidosis to occur, even though acidosis might have deleterious effects. Ultimately, the ARDS Network investigators decided that if hypercapnia occurred, they would increase the ventilation rate to as high as 35 cycles per minute and give bicarbonate to keep the pH above 7.30.

STUDY DESIGN

The ARDS Network trial was a prospective, randomized, controlled study of patients hospitalized for ARDS and acute lung injury (a less-severe variant) between March 1996 and March 1999. Ten hospitals across the United States participated.

Our purpose was to test the efficacy of low-stretch ventilation by comparing it with traditional ventilation for 28 days in each patient enrolled in the study. The two primary outcomes measured were in-hospital mortality and the number of days out of the 28 that patients were able to breathe without assistance for more than 48 hours consecutively (ventilator-free days).

Patients

Intubated and mechanically ventilated patients were eligible for this study if they met all three inclusion criteria:

- A PaO_2/FIO_2 ratio of less than 300 (this level was adjusted for patients in the high-altitude cities of Denver and Salt Lake City)
- Findings of bilateral pulmonary infiltrates on roentgenograms that were consistent with edema
- No clinical evidence of left atrial hypertension.

Exclusion criteria included a duration of acute lung injury or ARDS of 36 hours or more, age less than 18 years, severe chronic respiratory disease or neuromuscular disease that could impair spontaneous breathing, comorbid conditions with high mortality (> 50%), chronic liver disease, pregnancy, severe obesity (> 1 kg/cm of height), and several others.

Traditional-stretch group

The conventional-therapy group consisted of 429 patients (mean age 52 years; 41% women). Approximately 36% of them had been admitted for pneumonia, 26% for sepsis, 14% for aspiration, 9% for trauma, 11% for other causes, and 3% for multiple causes. Approximately 85% had PaO_2/FIO_2 ratios of 200 or less.

The traditional-stretch strategy called for an initial tidal volume of 12 mL/kg of predicted (or "ideal") body weight (TABLE 1). Body weight is related to lung volume in both sexes, but predicted body weights are used rather than actual weights because they correspond more closely to actual lung volume. For example, using the actual body weight in a patient with significant obesity or edema would overestimate the actual lung volume and lead to overstretching of the lungs. In fact, it was later determined that the measured weight of the ARDS Network patients exceeded their calculated weight by approximately 20%.

TABLE 1

Formula for 'ideal' body weight (used in setting the tidal volume)

In men:

Weight (in kg) = 50 + 0.91(cm of height – 152.4)

In women:

Weight (in kg) = 45.5 + 0.91(cm of height – 152.4)

When necessary, the tidal volume was increased or decreased in increments of 1 mL/kg to maintain end-inspiratory plateau pressures between 45 and 50 cm H_2O. Plateau pressures were allowed to exceed 50 cm H_2O in patients who received only 4 mL/kg and in patients whose arterial pH levels fell below 7.15. But regardless of plateau pressure, the tidal volume did not fall below 4 mL/kg or exceed 12 mL/kg.

Use 'ideal' weight—not measured weight—in calculating ventilator settings

Low-stretch group

The low-stretch group consisted of 432 patients (mean age 51 years; 40% women). The cause of ARDS was pneumonia in 33%, sepsis in 27%, aspiration in 15%, trauma in 13%, other causes in 10%, and multiple causes in 2%. Approximately 82% had PaO_2/FIO_2 ratios of 200 or less.

The patients in the low-stretch group received 6 mL/kg of tidal volume, and this amount was adjusted to maintain plateau pressures between 25 and 30 cm H_2O. Plateau pressures were also allowed to exceed 30 cm H_2O in patients who received only 4 mL/kg and in those whose arterial pH levels fell below 7.15. Again, regardless of plateau pressure, the tidal volume did not fall below 4 mL/kg or exceed 6 mL/kg, except for patients

In ARDS, survival is higher when tidal volume is lower

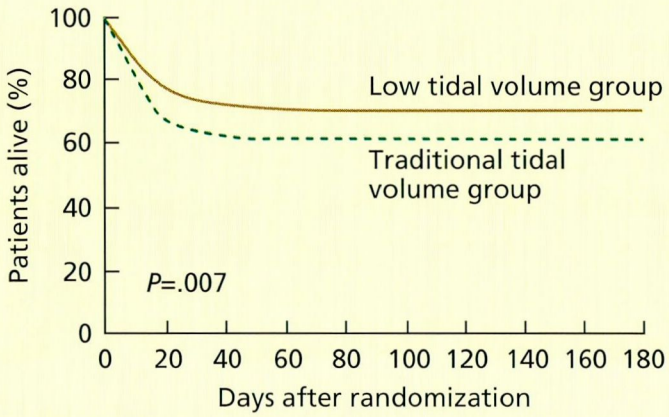

FIGURE 1. Kaplan-Meier estimates of survival in patients with acute respiratory distress syndrome or acute lung injury randomized to treatment with low tidal volume (6 mL/kg) or traditional tidal volume (12 mL/kg).

FROM 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.

with severe dyspnea, who were allowed to receive 7 or 8 mL/kg as long as their plateau pressure did not exceed 30 cm H_2O.

Monitoring

All other procedures were identical in the two groups. Patients received their assigned treatment for 28 days following randomization or until they could be weaned off ventilation and breathe unassisted. Plateau pressures were measured during 0.5-second inspiratory pauses at 4-hour intervals and after each change in tidal volume or PEEP.

Patients were monitored for organ failure for 28 days, regardless of how long they had required mechanical ventilation. Survivors continued to be followed for 180 days or until they could breathe unassisted and be discharged.

STUDY RESULTS

The ARDS Network investigators had planned to enroll 1,000 patients, but they halted the study after only 861 patients when it became evident that low-stretch ventilation improved the chances of survival.

Mortality

In the traditional-stretch group, 39.8% of the patients died, compared with 31.0% in the low-stretch group, a 22% difference (P = .007).

The divergence in mortality rates between the two groups occurred gradually over the course of the 28 days rather than abruptly (FIGURE 1), as one would expect if ventilator-induced injury was in fact contributing to mortality.

Ventilator-free days

The low-stretch group also experienced significantly more ventilator-free days than the traditional-stretch group (mean: 12 vs 10 days; P = .007). Even so, the number of days that each group did require ventilation was similar (8 days in both groups, and 10 vs 10.5 days among those who died), reflecting the lower mortality rate in the low-stretch group.

Moreover, 65.7% of the low-stretch group were breathing without assistance by day 28, compared with 55.0% of those in the traditional-stretch group (P < .001).

Organ failure

The low-stretch group experienced significantly less circulatory, coagulation, and renal failure (mean number of organ failure-free days: 15 vs 12; P = .006).

For the first 4 days of the study, there was no difference in the mean serum creatinine levels in the two groups. But thereafter, we saw a fairly significant divergence. Patients on traditional-stretch ventilation had more renal dysfunction, while those on low-stretch therapy experienced a progressive improvement in renal status.

INTERPRETING THE ARDS TRIAL

Importance of inflammatory cytokines

ARDS is characterized by presence in the lungs of inflammatory cytokines such as interleukins IL-1, IL-6, and IL-8 and tumor necrosis factor. Studies have almost uniformly shown that ARDS patients have high levels of

inflammatory cytokines in the bronchoalveolar lavage fluid and frequently in the systemic circulation. This was the primary indication that led researchers to believe that lung inflammation is probably the most important factor in ARDS, and that this inflammation sometimes extends to the circulation and causes organ failure.

A large body of evidence suggests that high levels of these cytokines are linked to a poor prognosis. Moreover, studies also show that patients who have low levels of the anti-inflammatory cytokine IL-10 in the bronchoalveolar lavage have a relatively poor prognosis.

Our findings support these concepts. During the first few days of ventilation, plasma IL-6 levels decreased in both groups, but decreased more in the low-stretch group. Analysis of other cytokines is pending.

Tidal volume may be more important than plateau pressure

Before this trial, the consensus among investigators was that as long as the inspiratory plateau pressure was less than 35 cm, the patient was safe, regardless of the amount of tidal volume delivered. And indeed, during the first 4 days, the mean plateau pressure in the low-stretch group was between 20 and 25 cm. However, the mean plateau pressure in the traditional-stretch group was only about 30 cm, and yet their outcomes were much worse.

This finding provides evidence that tidal volume may be more important than plateau pressure, and that plateau pressure levels that were once thought to be safe may not be.

Hypercapnea was avoided

In the low-stretch group, $PaCO_2$ levels were between 40 and 45 mm Hg, which is not particularly high, and their mean pH was not acidotic. (In contrast, the patients in the traditional-stretch group had lower $PaCO_2$ levels [35–40 mm Hg] and their pH levels were slightly alkalotic.)

The explanation behind these results was our decision to minimize hypercapnia by adjusting the inspiratory rate when necessary. In fact, the low-stretch group received an average of 28 breaths per minute, compared with approximately 18 for the traditional-stretch group. The net effect of this difference was that the overall amount of ventilation per minute in the two groups was nearly the same.

Barotrauma

There was no difference in the incidence of pneumothorax, both in cases that required chest tubes and those that did not. This is significant because it supports the concept that ventilator-induced lung injury is not necessarily a sudden traumatic event, but a more insidious and subtle injury. With the tidal volumes used in this study, pneumothorax is not a specific or sensitive marker of stretch-induced injury.

Candidates for therapy

Should we give low-stretch ventilation to all ARDS patients, or only to those whose lungs are already somewhat stiff? In a subset analysis of 502 patients, 25% had a baseline static lung compliance (C_{st}) score of less than 0.4 mL/cm/kg, which indicates that they had the most severe ARDS and that their lungs were the most stiff. The mortality rates in these more seriously injured patients were 32.6% in the low-stretch group and 46.9% in the traditional-stretch group. However, the key point is that there was also a significant reduction in mortality in those low-stretch patients whose ARDS was less severe. Among patients whose static lung compliance was not as poor ($C_{st} \leq 0.4$), mortality rates in the low-stretch and traditional-stretch groups were 27.5% and 35.3%, respectively.

The low-stretch group received more breaths per minute

Conflicts with previous studies

Three previous studies published in 1998 and 1999 failed to show any survival advantage with low-stretch ventilation.[14–16] On the other hand, a trial by Amato et al,[17] also published in 1998, showed that low-stretch ventilation did provide a significant survival benefit.

There are shortcomings in all four of these previous trials, which may explain the seemingly contradictory results. For example, in the Amato study, mortality in the traditional-stretch group was 71%—an extremely high rate. Moreover, the Kaplan-Meier curve

showed a marked difference in mortality during the first 2 days, a finding that is not consistent with the prevailing concept of ventilator-induced lung injury. Another difference between our study and the Amato trial is that we used conventional PEEP therapy, while Amato's group used aggressive PEEP therapy in addition to other maneuvers. Therefore, the Amato results suggested that low-stretch ventilation by itself is not effective; it is only effective when it is combined with high levels of PEEP. The results of our study suggest otherwise.

Another shortcoming of the previous trials was their size. The number of patients in the three negative studies ranged from 52 to 120. These studies appear to be underpowered.

Another important point is that these trials allowed a fair amount of permissive hypercapnia. Their protocol for responding to elevations in $PaCO_2$ levels with low-stretch ventilation was to permit hypercapnia to occur. By contrast, our response was to increase the ventilation rate.

Finally, the tidal volumes used in these three negative trials were not quite as low as ours. Their lung-protective tidal volumes averaged between 7 and 8 mL/kg, while ours averaged approximately 6.2 mL/kg.

UNRESOLVED ISSUES

Many issues remain to be resolved. For example, perhaps high-level PEEP therapy would lower mortality even further than conventional PEEP. In fact, the ARDS Network investigators are currently conducting a trial to test this hypothesis. In the meantime, we believe the evidence from our trial is powerful, and we conclude that every eligible patient with acute lung injury or ARDS ought to be seriously considered for low-stretch ventilation.

Consider low-stretch ventilation for every ARDS patient

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