Refining Ventilatory Treatment for Acute Lung Injury and Acute Respiratory Distress Syndrome

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ACUTE RESPIRATORY DISTRESS SYNDROME (ARDS) IS the clinical manifestation of inflammatory lung edema originating from a variety of insults. Since its first description 40 years ago,[1] the mainstays of management have been institution of mechanical ventilation to ventilate the incompliant lungs, inspired oxygen for hypoxemia, and when hypoxemia is severe, the addition of positive end-expiratory pressure (PEEP) to increase end-expiration lung volume, which facilitates O_2 gas exchange.[2]

Early on, physicians recognized that the high intrathoracic pressures of mechanical ventilation caused parenchymal stress or rupture, known as barotrauma.[3] However, it took several years to identify the local injury resulting from intratidal opening and closing of parts of the lung (atelectrauma)[4] and the inflammatory reaction of the lung to nonphysiological stress (biotrauma).[5,6] Subsequently computed tomographic scanning showed that the lung fraction open to gas exchange in ARDS is small, equivalent in size to that of a young child (baby lung model[7]). This observation provided the anatomical basis for the concept of volutrauma,[8] focused on the excessive strain within the baby lung induced by tidal ventilation. Taken together, these multiple potentially damaging factors are now called ventilator-induced lung injury (VILI). In the last decade, prevention of VILI through gentle lung treatment,[9] by adjusting either tidal volume or PEEP, has become the major goal of mechanical ventilatory support not just for ARDS but for the broader population of patients with acute lung injury (ALI).

With regard to tidal volume, this line of reasoning and research was most conclusively supported by the National Heart, Lung, and Blood Institute ARDS Network trial demonstrating an improvement in survival for patients with ALI or ARDS who were ventilated with low tidal volumes (6 mL/kg of predicted body weight) compared with those ven-

See also pp 637 and 646.

tilated with higher tidal volumes (12 mL/kg of predicted body weight).[10] Although many argued that the tidal volume in the control group might have been higher than existing practice, the tidal volume in the interventional group marked a stark departure from usual care and has resulted in a dramatic change in the approach to tidal volume setting for ALI and ARDS.[11]

The optimal PEEP strategy, however, has remained unresolved. Evidence from animal studies suggested that higher PEEP (in the range of 10-15 cm H_2O) could prevent VILI.[12,13] Thus, many clinicians were surprised when the first large randomized clinical trial comparing higher levels of PEEP with lower levels of PEEP in patients with ALI and ARDS, the National Heart, Lung, and Blood Institute's ARDS Network Assessment of Low Tidal Volume and Elevated End-Expiratory Lung Volume to Obviate Lung Injury (ALVEOLI) study,[14] was stopped for futility.

In this issue of the *JAMA*, 2 new large international randomized trials[15,16] examining the effects of PEEP on outcome in patients with ALI and ARDS are presented. In the Lung Open Ventilation (LOV) trial,[15] the level of PEEP administered, either lower or higher, was selected according to an oxygenation scale conceptually similar to the one used in the previous ALVEOLI study.[14] In the Expiratory Pressure (Express) trial,[16] PEEP selection was based on a more subtle and refined approach, using bedside assessment of lung mechanics instead of gas exchange. This method identified a minimal distention strategy (lower level of PEEP) and an increased recruitment strategy (higher level of PEEP).

Despite the different criteria used for PEEP selection, the PEEP levels tested were similar in the 2 studies. In the LOV study,[15] mean PEEP levels on day 1 were 15.6 cm H_2O and 10.1 cm H_2O, and the subsequent hospital mortality rates were 36.4% and 40.4%. In the Express study,[16] mean PEEP levels on day 1 were 15.8 cm H_2O and 8.4 cm H_2O, and the

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subsequent hospital mortality rates were 35.4% and 39.0%. In neither instance was the difference in mortality significant. In the ALVEOLI study,[14] mean PEEP levels on day 1 were 14.7 cm H_2O and 8.9 cm H_2O, and the subsequent hospital mortality rates were 27.5% and 24.9%. Taken together, these 3 studies enrolled a total of 2299 patients, randomizing 1136 to higher PEEP and 1163 to lower PEEP, and the crude pooled hospital mortality rates were 33.9% and 36.3%, which are not significantly different.

Thus, the conclusion might appear straightforward: the random application of either higher or lower levels of PEEP in an unselected population with ALI and ARDS does not significantly improve outcome. However, this is not the end of the story. Important considerations include: why should higher levels of PEEP improve survival in ARDS, why is there a sharp contrast between the results of experimental studies and of these large clinical trials, and in the end, which level of PEEP should be used in clinical practice?

A patient's lung with ARDS is (or should be) characterized by inflammatory edema.[17] Computed tomographic scanning has shown that increased lung weight due to edema compresses the more dependent lung regions, which collapse under that weight. At end-expiration, if PEEP is not sufficient to counterbalance these gravitational compressive forces, the collapsed lung regions remain closed and will open up only during the next inspiration when the ventilator provides a sufficient pressure.[18] This cycling collapse and decollapse process acts as a local stress amplifier,[19] and is a recognized cause for lung injury. Higher PEEP levels, by preventing this process,[20] theoretically should decrease VILI and mortality. It is therefore intuitive that if edema and the related regional lung collapse are not present, the mechanism by which PEEP should function will be lacking, and a higher level of PEEP will be at best useless.

Most animal models of ARDS are characterized by substantial lung edema, and higher level of PEEP is consistently effective.[13] In contrast, the lack of benefit of a higher level of PEEP observed in these large clinical trials may indicate that, in a substantial proportion of patients, the extent of lung edema and collapse were modest. Unlike in animal models, ALI with ARDS, by current definition, is a heterogeneous syndrome, and patients with abundant edema, collapse, and lung recruitability (ie, the best theoretical candidates for the beneficial effects of a higher level of PEEP) often represent only a minority of enrollees in clinical trials of ALI and ARDS.[21]

Were such patients included in the LOV and Express trials? Did they behave differently at a lower level than at a higher level of PEEP? Firm data, which would have required edema measurements,[22] are not available to answer these questions. However, in both trials, there were subgroups of patients who had severe hypoxemia and need for rescue therapies, such as prone positioning or use of inhaled nitric oxide. In both instances, those developing severe hypoxemia, and for which an alternative rescue treatment was allowed or adopted, were significantly more frequent in the group receiving a lower level of PEEP than in the group receiving a higher level of PEEP (almost twice as frequently in each study). In both studies, these patients were defined a priori: patients with PaO_2 lower than 60 mm Hg for at least 1 hour at a fraction of inspired oxygen (FIO_2) of 1.0 in the LOV study[15] and patients with PaO_2 lower than 55 mm Hg or arterial oxygen saturation (SaO_2) lower than 88% for 1 hour at a FiO_2 of 0.80 or higher in the Express study.[16] Taking the 2 studies together, the numbers of patients with severe hypoxemia requiring rescue therapy were 94 (10.9%) in the higher level of PEEP group and 184 (20.7%) in the lower level of PEEP group. Although mortality was similar (60.6% and 58.2% in the higher and lower PEEP groups, respectively), the difference in incidence suggests that the rate of these pulmonary deaths was much lower in the group receiving a higher level of PEEP (6.6% vs 12.0%). One possible inference is that a higher level of PEEP may prevent a large number of pulmonary deaths, which may be the reason for the 3% to 4% mortality difference favoring the group receiving a higher level of PEEP observed both in the LOV study and in the Express study.

Which patients might benefit from a higher level of PEEP? It is tempting to speculate that they are the fraction of the population with ALI and ARDS who has more lung edema and recruitabilty, either at the time of enrollment or during the course of the trials. If treated with a higher level of PEEP, many pulmonary deaths may be prevented because higher PEEP may reduce the pulmonary damage associated with mechanical ventilation by keeping the lung open. In contrast, if treated with lower PEEP, patients with similar degrees of lung edema and recruitability will progress more easily to a further lung injury, as suggested by refractory hypoxemia. A post hoc analysis reported in the Express study showed a nonsignificant increase in survival in the subset of patients with ALI with more severe disease (ARDS), and is consistent with this line of reasoning because patients with ARDS have more edema and greater recruitability than patients with ALI but without ARDS.[21]

The LOV study[15] and the Express study[16] not only should conclude the era of comparing PEEP levels in unselected populations with ALI and ARDS, but also underscore the need for a new definition of ARDS aimed at identifying patients with greater lung edema and larger recruitability (ie, with a greater lung injury).[23] Higher and lower levels of PEEP should be tested in this more selective population to obtain a definitive answer. In the meantime, the data from these 2 studies favor the use of higher levels of PEEP in the early phase of ALI and ARDS. Ideally, the direct assessment of lung recruitability by a dynamic lung imaging technique would allow the best physiological titration of PEEP.

Until such an approach is widely available, setting PEEP at the highest level compatible with a plateau pressure of 28 to 30 cm H_2O and a tidal volume of 6 mL/kg of predicted body weight seems to be a reasonable alternative. This

approach probably accounts for individual lung recruitability better than an arbitrary oxygenation scale. The Express study demonstrated that such an approach could be incorporated in the protocol and disseminated across multiple centers. It also is reassuring that a higher level of PEEP with plateau pressure limitation (in the ranges used in these 2 studies) does not induce harm. In contrast, the findings of these 2 studies do not support a strategy of using a lower level of PEEP. A lower level of PEEP produces a greater number of patients with severe hypoxemia at high risk of death and for whom clinicians feel pressed to embark on rescue therapy. The Express study suggests lower PEEP is associated with fewer ventilator-free and organ failure–free days.

Thus, strategies with higher levels of PEEP, as tested in these 2 clinical trials, appear safe and probably beneficial, especially in patients with ALI and ARDS who are the most sick, whereas strategies with lower levels of PEEP may worsen outcomes.

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Testing Protocols in the Intensive Care Unit
Complex Trials of Complex Interventions for Complex Patients

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IN THIS ISSUE OF *JAMA*, MEADE AND COLLEAGUES[1] AND Mercat and colleagues[2] report the results of 2 large international trials of alternative strategies for setting positive end-expiratory pressure (PEEP) in ventilated patients with acute lung injury or acute respiratory distress syndrome. Both trials asked whether higher PEEP would reduce mortality, and both concluded it did not. Many read-

ers not familiar with intensive care might reasonably wonder why such a seemingly innocuous intervention would deserve such attention, but the story behind PEEP is a long one, and these latest, largest trials do not provide a conclusion. They do, however, serve to demonstrate that answer-

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