

## Ventilation Strategies for Acute Lung Injury and Acute Respiratory Distress Syndrome

To the Editor: Limiting plateau pressures in the respiratory system of patients with acute lung injury and acute respiratory distress syndrome (ALI/ARDS) to 28 to 30 cm H<sub>2</sub>O may help guarantee lung protection.<sup>1</sup> In the large multicenter Express trial, Dr Mercat and colleagues<sup>2</sup> set positive end-expiratory pressure (PEEP) as high as possible to avoid plateau pressure above 28 to 30 cm H<sub>2</sub>O (mean, 27.5 cm H<sub>2</sub>O). In the lower PEEP (minimal distention) group in the Express trial, plateau pressure was kept as low as possible to maintain oxygenation targets (mean, 21 cm H<sub>2</sub>O). There was no difference in mortality between the 2 groups, but the higher PEEP/plateau pressure (increased recruitment) group showed a greater number of ventilator-free and organ failure-free days. Plateau pressure in the increased recruitment group dropped to 24 cm H<sub>2</sub>O within the first week.

Two smaller trials (n=53<sup>3</sup> and n=103<sup>4</sup>) showed that higher PEEP levels, comparable with the Express trial (14-16 cm H<sub>2</sub>O), can reduce mortality in ARDS, despite using plateau pressures that have been considered unsafe. Both studies started out with a plateau pressure of 32 and 31 cm H<sub>2</sub>O, respectively, but within 1 week they only needed a plateau pressure of 24 to 26 cm H<sub>2</sub>O.

There are 2 main differences between these studies and the Express trial. In the smaller trials, plateau pressure before lung protective ventilation was 30 to 32 cm H<sub>2</sub>O compared with 23 cm H<sub>2</sub>O in the Express study, at comparable PEEP levels (8 cm H<sub>2</sub>O) and tidal volumes. Also, both smaller studies used standardized ventilator settings with the patients to see whether ARDS criteria (ratio of partial pressure of arterial oxygen over fraction of inspired oxygen [PaO<sub>2</sub>:FiO<sub>2</sub>] < 200 mm Hg) were maintained over a set time period.

Alterations in chest wall mechanics may also result in marked differences in the real transpulmonary pressure, leading to progressive lung derecruitment and ventilator-induced lung injury (VILI).<sup>5</sup> Recruitment maneuvers may improve lung function by allowing ventilation on the deflation limb of the pressure-volume curve, resulting in higher end-expiratory lung volumes at similar airway pressures and potentially minimizing VILI.<sup>5</sup>

Arbitrarily limiting plateau pressure without individualized settings, with potential resultant progressive lung derecruitment, may prevent advances in lung protective ventilation. An individually titrated recruitment maneuver leading to an early short-term increase in plateau pressure, especially in more severely hypoxemic patients with altered chest wall mechanics, may result in better oxygenation, rapid lowering of plateau pressure in the first week, and possibly improved outcome.

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To the Editor: I believe that the design of the Lung Open Ventilator Study by Dr Meade and colleagues<sup>1</sup> made an error by adjusting PEEP according to FiO<sub>2</sub>, leading to overdistention of alveoli as evidenced by lower static compliance (tidal volume/[plateau pressure–end-expiratory pressure]) in the high PEEP group than in the lower PEEP group.<sup>2</sup> The mean levels of compliance in the high and low PEEP groups were 0.41 and 0.42 mL/kg/cm H<sub>2</sub>O on day 3 and 0.37 and 0.41 mL/kg/cm H<sub>2</sub>O on day 7, respectively. Despite a similar protocol, the same phenomenon was not observed in the ALVEOLI study,<sup>3</sup> possibly due to the difference in patient population. The protocol change in the middle of the study allowing higher PEEP levels in the Lung Open Ventilator Study might have negatively affected the study results.

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**Letters Section Editor:** Robert M. Golub, MD, Senior Editor.

The results of the Express study by Dr Mercat and colleagues<sup>4</sup> could also have been different if the PEEP level had been adjusted according to compliance instead of plateau pressure, given the non-statistically significant increased mortality and duration of mechanical ventilation with higher levels of PEEP in the group with ALI but without ARDS. Aiming for the same level of plateau pressure in patients with mild lung injury might have led to more adverse effects by overextending the alveoli.

Although in their editorial Drs Gattinoni and Caironi<sup>5</sup> suggested the direct assessment of lung recruitability by a dynamic lung imaging technique, getting a computed tomographic scan in all patients with ALI and ARDS seems impractical and may not be efficient because recruitability can change very quickly.<sup>2</sup> Achieving maximal lung recruitment without overextending the alveoli could easily be done at the bedside by titrating PEEP to the greatest compliance while not exceeding a certain level of plateau pressure. For example, PEEP can be increased gradually on pressure control ventilation until a tidal volume declines or a plateau pressure exceeds 28 to 30 cm H<sub>2</sub>O, whichever comes first.

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**To the Editor:** The study of PEEP settings in adults with ALI and ARDS by Dr Mercat and colleagues<sup>1</sup> did not find a mortality benefit in patients in the increased recruitment (high-PEEP) group compared with patients in the minimal distension arm. Lungs of patients with ARDS are likely to be less compliant, with resulting higher plateau pressures during volume-controlled ventilation.<sup>2,3</sup> In the increased recruitment group, patients with ARDS, compared with patients with less ALI and more compliant lungs, would receive lower levels of PEEP at the target plateau pressure of 30 cm H<sub>2</sub>O. This PEEP level may have been close to that applied in the minimal distension group in which the PEEP level was restricted between 5 and 9 cm H<sub>2</sub>O. It is therefore possible that in patients with severe forms of lung injury, there may not have been meaningful differences between the actual PEEP levels achieved in the 2 groups. A protocol

that required the PEEP level to be decreased with increasing severity of lung injury may have diluted the potential benefit of “high” PEEP in the increased recruitment group.

Analysis comparing the mean PEEP levels in the subgroups of patients with ARDS vs ALI without ARDS may provide some insight into whether this contributed to the negative study results.

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**To the Editor:** Dr Mercat and colleagues<sup>1</sup> reported the results of the Express trial comparing a minimal alveolar distention strategy with a strategy aiming for maximal alveolar recruitment while limiting hyperinflation. Although there was no difference in the primary end point (28-day mortality rate), the maximal alveolar recruitment strategy resulted in more ventilator-free days, more organ failure-free days, and less frequent use of rescue therapy. However, there are certain points that merit attention.

First, the screening for PEEP weaning was determined by the PaO<sub>2</sub>:FIO<sub>2</sub> ratio. This ratio depends on the PEEP level, which was by design not equal between groups. Higher PEEP level will result in higher PaO<sub>2</sub>:FIO<sub>2</sub> ratio, favoring early weaning in the increased recruitment group and possibly contributing to the reduced time spent on mechanical ventilation in this group.

Second, the amount of alveolar recruitment and alveolar hyperinflation by PEEP is a trade-off.<sup>2</sup> The patients in the minimal alveolar distention group may have actually been treated with an unusually low PEEP level, lower than in the 2 trials that showed a beneficial effect with low tidal volume ventilation.<sup>3,4</sup> In the ARDS Network trial,<sup>3</sup> even the set PEEP (excluding intrinsic PEEP) was higher (9.4, 9.2, and 8.1 cm H<sub>2</sub>O on days 1, 3, and 7, respectively) than the total PEEP (including intrinsic PEEP) in this trial (8.4, 8.1, and 8.0 cm H<sub>2</sub>O on days 1, 3, and 7, respectively).

Although the strategy in the maximal alveolar recruitment strategy is appealing, hyperinflation may still occur in certain patients despite plateau pressure being below 30 cm H<sub>2</sub>O.<sup>2</sup> This may result in a local and systemic inflammatory response syndrome, which could result in a worse outcome.<sup>2,3</sup> Another strategy for individual titration of PEEP could be the simultaneous measurement of dead space.<sup>5</sup> A combination of maximal compliance with the lowest dead

space fraction could be another practical way to optimize the balance between derecruitment and hyperinflation.

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**To the Editor:** The studies by Dr Meade and colleagues<sup>1</sup> and Dr Mercat and colleagues<sup>2</sup> were intended to test a strategy aimed at maximizing alveolar recruitment while limiting hyperinflation. To guarantee applicability at the bedside, both studies made use of fixed targets such as plateau pressures or PEEP/FiO<sub>2</sub> ratios with PEEP levels adjusted accordingly. Because PEEP levels were not primarily titrated, the question is how much this approach compromised the test of an “optimum-PEEP” in favor of a “feasible-PEEP.”

In the Lung Open Ventilation Study,<sup>1</sup> patients demonstrating easy lung recruitment, possibly those in whom the FiO<sub>2</sub> could be immediately reduced to 40% (after recruiting maneuvers and an initial PEEP of 20 cm H<sub>2</sub>O), may have been immediately submitted to a PEEP of only 10 cm H<sub>2</sub>O. In contrast, patients not easily achieving recruitment, requiring FiO<sub>2</sub> levels at or above 50% after the recruitment maneuver, were submitted to PEEP levels at or above 18 cm H<sub>2</sub>O for many days. Whereas a PEEP of 10 cm H<sub>2</sub>O was likely too low to stabilize the recently open tissue in the first case, a PEEP of 18 cm H<sub>2</sub>O might be too high for the already open lung tissue in the second case. The insistence on a high PEEP level is not an efficient strategy for recruiting those collapsed units,<sup>3</sup> especially after observing failure with an inspiratory pressure of 40 cm H<sub>2</sub>O. This binary treatment may have wasted an opportunity for those who could benefit the most from the recruitment maneuver while adding risk for those who could not get a clear benefit.

In the Express study,<sup>2</sup> the healthiest patients, probably those with the lowest impairment in lung compliance, were by protocol design exposed to highest levels of PEEP (because the fixed 6 mL/kg tidal volume would have produced low driving pressures, requiring the clinician to further increase PEEP levels until achieving plateau pressures of 28 cm H<sub>2</sub>O). In contrast, the sickest patients presenting with lowest compliance likely received a much lower PEEP.

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**In Reply:** Drs Haitsma and Pelosi state that oxygenation may be improved by a recruitment maneuver that leads to a short-term increase in plateau pressure. Oxygenation, which we do not consider a solid end point in patients with ALI/ARDS,<sup>1</sup> was already markedly improved in the high PEEP group of the Express trial. Recruitment maneuvers can have severe adverse effects, and in the absence of evidence that fully recruiting the lung is clinically important, we preferred not to recommend such maneuvers in our trial.

Dr Oba suggests that a PEEP titration based on the static compliance of the respiratory system could result in a better outcome than the method we used. Our experience is that compliance is difficult to use at the bedside for PEEP titration. The changes in compliance induced by increased PEEP are often quite small, and recruitment can be associated with a decrease in linear compliance measured at a given airway pressure.<sup>2,3</sup> In addition, the sigmoidal shape of the pressure-volume curve makes it difficult to interpret such measurement. We therefore remain unsure whether compliance could improve PEEP titration.

Drs Divatia and Ranganathan are correct that the method we used to titrate PEEP in the increased recruitment group could have resulted in moderate levels of PEEP in patients with very low compliance. However, only 23 patients (6%) in this group had a PEEP level on day 1 lower than 10 cm H<sub>2</sub>O. The use of higher levels of PEEP in these patients would have resulted in high levels of plateau pressure and an increased risk of overdistention. Patients with ALI with or without ARDS had similar mean levels of PEEP on day 1.

Drs Heunks and van der Hoeven suggest that the better oxygenation in the increased recruitment group could have accelerated the weaning process. The mean (SD) PEEP level in the minimal distension arm (6.7 [1.8] cm H<sub>2</sub>O at day 3) was very close to the 5 cm H<sub>2</sub>O level chosen for PEEP weaning trials. The oxygenation threshold for testing PEEP weaning was by design relatively low (PaO<sub>2</sub>:FiO<sub>2</sub> > 150) to avoid favoring one group vs the other. The PEEP-weaning process might have been achieved at a similar rate in both groups

if high PEEP had altered nothing but oxygenation in the high PEEP group. However, the earlier PEEP-weaning test success in the increased recruitment group suggests a specific effect of high PEEP, perhaps allowing a better reopening or recruitment of the lung and a better tolerance of a decreased PEEP level.

In the low PEEP group, the goal was to minimize alveolar distension by all means. The mean PEEP level in this arm was very close to the PEEP levels reported in a recent international survey.<sup>4</sup> Three studies have shown no mortality difference using 4 to 5 cm H<sub>2</sub>O differences in PEEP levels,<sup>5</sup> and it is unlikely that less than 1 cm H<sub>2</sub>O of PEEP makes a substantial difference in outcome. Dead space measurement may help individual titration. However, dead space is greatly influenced by its alveolar component in ARDS. Alveolar dead space may increase because of hyperinflation caused by increasing pressures but may also decrease because of shunt reduction. Therefore, a decrease or no change in dead space may mask a real hyperinflation. It therefore remains to be tested whether assessing dead space is sensitive enough in severely hypoxemic patients with high shunt.

In response to Dr Borges and colleagues, our post hoc analyses based on the quartiles of oxygenation or ALI vs ARDS suggest that our increased recruitment approach may not work in the less severe patients (eg, ALI without ARDS), resulting in excessive PEEP levels in these patients. The use of higher levels of PEEP in patients with very low compliance would have resulted in excessively high levels of plateau pressure and potentially an increased risk of overdistention. The beneficial effect on outcome of such a strategy remains to be demonstrated. We are not aware of simple validated bedside tools to better individualize the ventilator therapy.

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**In Reply:** In response to Dr Oba and Drs Borges and colleagues, we agree that the ability to identify those patients with ALI and ARDS who are most likely to benefit from an open-lung approach is a laudable goal. We hope that our experimental approach to PEEP titration, while taking into consideration lung protection, oxygenation, hemodynamics, and barotrauma, will be improved on in the future with more sophisticated methods of individualizing ventilatory management.

We agree with Borges et al that our approach may have led to an open lung in some patients and overdistention in others. To this extent, the modification in our protocol may have increased the potential for a negative study, as Oba suggests, although our analyses do not detect this effect. Our experimental approach was based on a consensus of individuals, considering current research evidence and routine clinical practices at that time. From our perspective, this choice was not mistaken. Many approaches to PEEP titration have been suggested, including pressure-volume curve analyses, assessment of the stress index, application of various imaging techniques, the specific methods referred to by Borges et al and several others. To date, however, there is no consensus on the optimal strategy for individualized PEEP titration. We look forward to further research addressing these fundamental issues for patients with ALI and ARDS.

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**In Reply:** Dr Oba proposes an approach to setting PEEP during ALI/ARDS based on the following conceptual model: by applying higher levels of PEEP the lung will be recruited and, with the tidal volume distributed across a greater portion of lung parenchyma, the plateau pressure will decrease; ie, the compliance of the respiratory system will increase. After the recruitment, a further increase of PEEP would lead to alveolar overdistention, and the compliance of the respiratory system would decrease accordingly. Indeed, the “best PEEP” would coincide with the “best compliance.”

Investigators have been approaching this issue for more than 35 years<sup>1,2</sup> without having reached a solution. In 1975, Suter et al<sup>3</sup> formulated the same proposal (best PEEP = maximum oxygen transport = maximum compliance). Unfortunately, things are not so simple for a number of reasons. First, lung recruitment is a continuous in-

spiratory phenomenon occurring up to total lung capacity<sup>4</sup>; it is impossible to dissociate lung recruitment from lung overdistension. Second, this mixture of phenomena is present at different degrees according to the maximal lung recruitability, and the recruitability of the lung in ALI/ARDS may vary from 0% to 30% or 40% of the lung parenchyma.<sup>5</sup> Third, the mechanical characteristics of the chest wall greatly affect the transpulmonary pressure, the real “distending force” of the lung.<sup>6</sup> The compliance of the respiratory system depends on both the chest wall and the lung. It follows that the same plateau pressure may mask completely different transpulmonary pressures.

Each patient is unique. We realize that computed tomographic scanning may sound impractical, but we do not know of better current approaches to characterize the pulmonary pathophysiology of each patient.

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## Randomized Controlled Trials in Critical Care Medicine

**To the Editor:** Randomized controlled trials (RCTs) are often considered the highest form of clinical evidence. However, RCTs providing evidence for reduced mortality using a treatment for patients in intensive care units (ICUs) are scarce. The few trials demonstrating survival advantage were incorporated in the Surviving Sepsis Campaign.<sup>1</sup> However, even some of these trials have been challenged.<sup>2</sup> We are aware of no large RCTs in the ICU setting with beneficial results that have been confirmed by a second RCT. Given that there are also studies with survival disadvantage in the treatment arm,<sup>2</sup> it is possible that the outcome of these studies reflects chance: 2.5% negative, 2.5% positive, and 95% no association.

Two very sophisticated trials were designed to test a survival advantage of an open lung strategy for patients receiv-

ing mechanical ventilation.<sup>3,4</sup> Although based on sound physiological reasoning and preclinical data, both studies failed to find a benefit. An accompanying editorial by Drs Chiche and Angus<sup>5</sup> highlighted the problems of conducting an RCT in critically ill patients. I would like to raise 1 issue that they did not discuss.

Many ICU studies are powered to show a relative reduction in mortality of 20% or absolute reduction of 10%.<sup>3,4</sup> However, mortality in ICU patients is multifactorial, and treating only 1 factor is unlikely to result in such a substantial improvement. Conversely, trying to prove smaller benefits will require either more homogeneous patient populations and treatments or numbers of participants comparable with outcome studies in cardiac disease, hypertension, and diabetes. Neither option seems feasible. Perhaps redirecting some of the enormous effort put into RCTs toward redesigning standards for evidence-based intensive care medicine would allow movement forward. In the meantime, the expert clinician mentioned by Chiche and Angus remains indispensable.

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**In Reply:** We appreciate the high esteem in which Dr Zijlstra and colleagues place RCTs and join them in wishing that more trials would be undisputedly positive. They suggest changing, and possibly lowering, the standards of evidence on which intensivists should base care because the interventions tested in RCTs generally target only 1 of many problems; thus, outcomes such as mortality are hard to modify and, by extension, the trials will always have a high likelihood of failure.

Although we do not believe that RCTs should be abandoned, we do agree that RCTs should continue to test interventions better designed to influence important clinical outcomes. The 2 particular trials we discussed,<sup>1,2</sup> although attempting to manipulate a rather narrow spectrum of the wide set of physiologic derangements seen in critically ill