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Lung Recruitment and Titrated PEEP in Moderate to Severe ARDS: Is the Door Closing on the Open Lung?

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Mechanical ventilation is critical for the survival of many patients with the acute respiratory distress syndrome (ARDS) but can also cause ventilator-induced lung injury (VILI). One form of VILI occurs when the lungs exhale to relatively low volumes and airway pressures. This may cause injurious tidal closing and reopening of small bronchioles and alveoli or excessive stress at the margins between aerated and atelectatic airspaces.^{1,2} In animal studies, positive end-expiratory pressure (PEEP) reduced or prevented VILI from exhalation to low volumes and pressures.^{1,3–5} PEEP can also recruit some previously atelectatic or fluid-filled lung regions, allowing more of the lung to be available for inflation during inspiration. This could reduce VILI from overdistention of an otherwise reduced amount of aerated lung.

In some early studies, the levels of PEEP that were applied for lung protection exceeded the levels that most clinicians use when managing patients with ARDS. This led to recommendations to use higher PEEP in patients with ARDS to minimize low volume and low pressure VILI and hopefully to improve clinical outcomes. The “open lung approach” (OLA) aims to achieve high levels of lung aeration in patients with ARDS by first conducting recruitment maneuvers (RMs) to reverse atelectasis and then applying high levels of PEEP to keep recruited alveoli open.⁶ Recruitment maneuvers typically involve a ventilatory approach that transiently increases pulmonary airway pressure to reopen recruitable lung areas. For example, an RM can be conducted by raising inspiratory airway pressures to 50 cm of H₂O for 1 or 2 minutes.

However, 3 large randomized clinical trials of higher PEEP and RMs in patients with ARDS and a Pao₂/Fio₂ ratio of 300 or less did not demonstrate significant reductions in mortality.^{7–9} An individual patient data meta-analysis of these 3 clinical trials suggested that higher PEEP reduced mortality in patients with more severe hypoxemia (Pao₂/Fio₂ < 200), but this

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finding has not been tested in clinical trials.¹⁰ A recent pilot trial of the OLA involved 200 patients and used more aggressive RMs and higher levels of PEEP than in the 3 earlier trials.¹¹ Arterial oxygenation improved and driving pressures decreased in the OLA group compared with the control group in which RMs were not conducted and PEEP was set according to the ARDS Network lower PEEP/Fio₂ table. There were small but nonsignificant differences in mortality and ventilator-free days that favored the OLA group, but the trial was not large enough to analyze these outcomes.¹¹

In this issue of *JAMA*, the Writing Group for the Alveolar Recruitment for Acute Respiratory Distress Syndrome Trial (ART) Investigators¹² report the results of a large randomized clinical trial that was conducted in 120 intensive care units in 9 countries and compared patients treated with the OLA (n = 501) with those managed with conventional PEEP (n = 509). As in the recent pilot OLA trial, patients in this trial had moderate to severe ARDS (Pao₂/Fio₂ < 200). To reduce VILI from overdistention in both study groups, the target tidal volume was 6 mL/kg of predicted body weight with inspiratory plateau pressures of 30 cm H₂O or less, consistent with the National Institutes of Health (NIH) ARDS Network protocol.¹³ Patients in the OLA study group received RMs with PEEP as high as 45 cm H₂O and peak airway pressures as high as 60 cm H₂O.¹⁴ These were followed immediately by a decremental PEEP titration to identify the PEEP at which lung compliance was maximal, presumably representing the best balance between recruitment and overdistention. The control group used the NIH ARDS Network lower PEEP/Fio₂ table without RMs.⁷

As the authors report, the OLA was associated with a significantly higher 28-day mortality and 6-month mortality (55.3% vs 49.3% and 65.3% vs 59.9%, respectively). A small but statistically significant difference in ventilator-free days favored the control group (5.3 days in the OLA group vs 6.4 days in the control group), and there was a higher rate of barotrauma among patients in the OLA group (5.6%) than among those in the control group (1.6%).

The difference in mean levels of PEEP between the OLA and the control group in the study by the ART investigators was only 3 to 4 cm H₂O over the first 7 days. The lung protection that results from these differences in PEEP is probably small. Also, the difference between study groups in driving pressure over the first 3 days was less than 2 cm H₂O. Because tidal volumes were similar in the 2 study groups, the differences in driving pressure reflect primarily the differences in volumes of aerated lung. The small differences in driving pressures suggest that the OLA protocol did not result in much recruitment. Additionally, higher PEEP in the OLA group may have caused more overdistention, which would tend to increase driving pressures, offsetting the decreases that might have resulted from additional recruitment of aerated lung.

The mean PEEP in the control group of the ART investigators' trial was approximately 3 cm H₂O higher than the mean PEEP levels in the control groups of the other 3 large clinical trials. The authors suggest that the reason for higher PEEP levels in their control group was stricter adherence to the lower tidal volume protocol resulting in tidal volumes that were lower in their control group compared with the other control groups. The authors suggest

that these lower tidal volumes could have caused hypoxemia from atelectasis, which could have triggered the use of higher PEEP to maintain the arterial oxygenation goal. It is possible that the lower tidal volumes, rather than the higher PEEP, contributed to the lower mortality in their control group.

Therapies are intended to improve patient outcomes, but all therapies have the potential to cause harm. PEEP can reduce VILI from injurious tidal opening and closing. However, PEEP also raises intracardiac pressures, including right atrial pressure, which impedes venous return and cardiac output. Moreover, especially in the absence of significant lung recruitment, PEEP increases right ventricular afterload by compressing alveolar septal capillaries, increasing pulmonary vascular resistance. Many critically ill patients experience shock from acute right ventricular failure, and high levels of PEEP may contribute to this.¹⁵ In the study by the ART investigators, patients in the OLA group required more vasopressors within 1 hour of beginning the protocol, and 3 patients experienced cardiac arrests. PEEP also causes higher inspiratory pressures and volumes, increasing the risk of barotrauma and VILI from overdistention. The only way to know with confidence that beneficial effects of a therapy outweigh the detrimental effects is to conduct a randomized clinical trial and monitor important clinical outcomes. In the trial by the ART investigators, the detrimental effects of the OLA exceeded the beneficial effects. A mechanical ventilation strategy that is designed to be lung protective may not be “patient protective.”

Despite abundant evidence in experimental models that the OLA can reduce VILI, 4 large randomized clinical trials of higher PEEP and RMs have now failed to demonstrate improved clinical outcomes, and the trial by the ART investigators suggested actual harm. In other studies, only approximately 50% of all patients with ARDS responded to higher airway pressures by recruiting previously atelectatic or flooded alveoli.^{16,17} It follows from this observation that the OLA is more likely to have overall beneficial effects among patients whose affected lung segments can be recruited. As in the previous large randomized clinical trials of higher PEEP, the ART investigators did not attempt to identify PEEP responders and exclude the nonresponders. It is possible that there were different effects of the OLA in this trial among the subsets of patients whose involved lung areas were more or less recruitable.

The ART investigators have conducted a rigorous, large, multicenter, international trial that demonstrated that an OLA improves arterial oxygenation and driving pressure compared with the control group, similar to findings from the recent pilot trial,¹¹ but appears to worsen patient outcomes including mortality. The results are not only disappointing but will be unexpected for many intensive care physicians and researchers working on VILI and lung-protective ventilation. However, such results frequently lead to greater insights and more productive directions for the future. The results of the trial by the ART investigators were different than what would have been predicted from the individual patient data meta-analysis.¹⁰ The harmful effects of the OLA observed in the trial by the ART Investigators may have been due to the aggressive RMs and decremental PEEP titration.

PEEP has been used during mechanical ventilation since the landmark description of ARDS 50 years ago.¹⁸ However, the best method for setting PEEP levels has still not been established. Perhaps further refinements in the OLA strategy with less aggressive attempts at

lung recruitment and a focus on identifying patients who recruit in response to PEEP will lead to more favorable results and leave the door to the OLA cracked open.^{19,20} On the other hand, now that 4 large, randomized clinical trials of strategies designed to promote lung recruitment have failed to demonstrate improved mortality, perhaps the door on the OLA should be allowed to close so that the clinical and research community can move on to other, potentially more effective strategies. Because tidal volume reduction is a powerful tool to prevent VILI¹³ and because lower tidal volumes reduce VILI from both overdistention and from opening-closing injury, perhaps future studies should push the limits of lowering tidal volume below 6 mL/kg of predicted body weight. Ultimately, allowing part of the lung to stay closed with permissive atelectasis may be more patient-protective than aggressive efforts to keep the lung open.

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