Mechanical Ventilation in Acute Respiratory Distress Syndrome Insights into Opening the Lung and Driving Pressure

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Recommended Reading from the NIH Critical Care Medicine Fellows; Nitin Seam, M.D., Associate Chief and Head of Training

Writing Group for the Alveolar Recruitment for Acute Respiratory Distress Syndrome (ART) Investigators. Effect of Lung Recruitment and Titrated Positive End-Expiratory Pressure (PEEP) vs. Low PEEP on Mortality in Patients with Acute Respiratory Distress Syndrome: A Randomized Clinical Trial. JAMA (1)

Reviewed by Souvik Chatterjee

An open lung approach (OLA) minimizing atelectrauma consists of recruitment maneuvers (RMs) to open collapsed lung tissue followed by high positive end-expiratory pressure (PEEP) to keep lung tissue open. Though three large randomized trials failed to show a mortality benefit of higher PEEP, a meta-analysis of these studies revealed that the higher PEEP strategy reduced mortality in patients with $\text{PaO}_2/\text{FiO}_2$ less than or equal to 200 (2–5).

The study by the Alveolar Recruitment for Acute Respiratory Distress Syndrome Investigators (1) is the largest to date comparing OLA with a conventional low- V_T and -PEEP strategy. The investigators enrolled 1,010 patients with moderate to severe acute respiratory distress syndrome (ARDS) ($\text{PaO}_2/\text{FiO}_2 \leq 200$) from 120 ICUs in nine countries. Patients were not assessed for recruitment responsiveness before enrollment, and all patients received low- V_T ventilation (mean, 5.8 ml/kg ideal body weight). The OLA group ($n = 501$) received a 4-minute pressure control RM with incrementally increasing PEEP from 25 to 45 cm H_2O while driving pressure (DP) was maintained at 15 cm H_2O , followed by decremental PEEP titration until lung compliance was optimized. A second 2-minute RM at highest pressure from the prior RM was performed, and optimal PEEP was maintained for at least 24 hours. Halfway through the trial, after three resuscitated cardiac arrests in the OLA group, this protocol was modified with slightly lower RM airway pressures and shorter decremental PEEP titration. The control group ($n = 509$) received PEEP based on the ARDS Network PEEP/ FiO_2 table from the ARMA (Lower Tidal Volume) trial (6).

Both 28-day (primary study endpoint) and 6-month mortality were higher in the OLA group than in the control group (55.3% vs.

49.3% and 65.3% vs. 59.9%, respectively; $P < 0.05$). The OLA group had more barotrauma than the control group in the first week (5.6% vs. 1.6%; $P = 0.001$) and increased or new vasopressor requirements within 1 hour of recruitment (34.8% vs. 28.3%; $P = 0.03$). The OLA group maintained PEEP 3–4 cm H_2O higher than the control group over the first week ($P < 0.001$), and it maintained plateau pressure (Ppl) 2–3 cm H_2O higher than the control group in the first 3 days ($P < 0.001$). Oxygenation was better in the OLA group throughout the first week, with mean $\text{PaO}_2/\text{FiO}_2$ 47–57 higher in the OLA group than in the control group at Days 1, 3, and 7 ($P < 0.001$ at all time points). Though the OLA group had lower DPs than the control group ($P < 0.001$), the mean difference was only 1.5 cm H_2O over the first week. The minimal change in DPs suggests that OLA resulted in relatively little lung recruitment across the groups.

Study limitations include the use of an aggressive recruitment strategy, variable rates of neuromuscular blockade (97% in recruitment vs. 73% in control; $P < 0.001$), high control group mortality, and exclusive use of volume-control ventilation. In this multicenter randomized trial, OLA improved hypoxemia but resulted in more hypotension and barotrauma, as well as higher mortality, than in control subjects, suggesting that OLA should not be adopted in unselected patients with moderate to severe ARDS. However, this study did not determine the effect of opening the lung on outcome in patients with ARDS with confirmed alveolar recruitment from increased PEEP, the group most likely benefit to from OLA (7). ■

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Cressoni M, *et al.* Opening pressures and atelectrauma in acute respiratory distress syndrome. *Intensive Care Med* (8)

Reviewed by Dominique J. Pepper

An open lung strategy is a popular approach to modern-day mechanical ventilation in ARDS. This strategy combines the use of RMs, low V_T , and high PEEP to decrease ventilator-induced lung injury by minimizing atelectrauma and stress/strain maldistribution (9, 10).

The recent publication by Cressoni and colleagues (8) challenges this paradigm. In their prospective observational study, they measured lung recruitment, intratidal collapse and lung ventilation inhomogeneities in 33 adults with ARDS: mild ARDS ($n = 5$), moderate ARDS ($n = 10$), or severe ARDS with ($n = 9$) or without ($n = 9$) extracorporeal support. Each patient underwent a series of PEEP interventions and computed tomographic (CT) scans performed either during an inspiratory or expiratory hold. RMs were performed at specified time points, and respiratory mechanics, hemodynamics, and blood gas data were collected. With these data, investigators calculated lung recruitment and estimated intratidal collapse (i.e., atelectasis) and lung ventilation inhomogeneities. Investigators defined recruitment as the difference in lung tissue noted on CT scans at PEEP and Ppl (mean Ppl, 19, 28, and 40 cm H_2O for mild, moderate, and severe ARDS, respectively).

The investigators reported three major findings. First, more lung tissue is recruited with Ppl greater than 30 cm H_2O in worse ARDS, as measured by Hounsfield units on chest CT scans. The amount of lung tissue (mean $\pm$ SD) opened between Ppl 30 and 45 cm H_2O was 10 ± 29 g in mild ARDS, 54 ± 86 g in moderate ARDS, 162 ± 92 g in severe ARDS without extracorporeal membrane oxygenation, and 185 ± 134 g in severe ARDS with extracorporeal membrane oxygenation ($P < 0.05$ for mild vs. severe ARDS). Second, similar intratidal collapse exists for a PEEP of 5 cm

H_2O or a PEEP of 15 cm H_2O . Third, increasing the applied airway pressure up to 45 cm H_2O decreased lung inhomogeneity significantly in mild and moderate ARDS but not in severe ARDS.

These findings have several important limitations. First, the sample size was 33 patients with subgroups having only 5 to 10 patients. Second, it is unclear why the subgroups of mild and severe ARDS had similar baseline respiratory system elastance. Third, potential confounders such as obesity, prior fluid resuscitation, prone positioning, and esophageal pressure monitoring are not described, nor are comorbid illnesses, mortality, or long-term outcomes.

Although study generalizability is affected by these limitations, this study challenges the current open lung paradigm in ARDS. An open lung strategy using high PEEP, low V_T , RMs, and a targeted Ppl less than 30 cm H_2O for all patients is less effective for opening the lung than a strategy where the Ppl exceeds 30 cm H_2O . However, opening the lung further than Ppl 30 cm H_2O increases mortality and barotrauma. Future studies should address these study limitations and also determine 1) whether an open lung strategy that minimizes intratidal collapse is superior to a strategy that aims to reduce barotrauma and volutrauma; and 2) whether personalized, titrated ventilation strategies are superior to a one-size-fits-all strategy (11). ■

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Reviewed by Panagis Galiatsatos

Contemporary management of ARDS involves lung-protective mechanical ventilation strategies with V_T of 4–8 ml/kg predicted body weight, moderate levels of PEEP, and maintaining Ppl less than or equal to 30 cm H_2O (6, 13). However, a retrospective review of nine ARDS trials revealed that DP (Ppl – applied PEEP) was better than Ppl for determining ARDS survival (14).

Villar and colleagues (12) performed a secondary analysis of prior observational studies to determine whether DP was better than Ppl for predicting survival. The authors quantified the risk of hospital mortality on the basis of quantiles of V_T , PEEP, Ppl, and DP 24 hours after ARDS diagnosis. The study was performed in two steps: deriving first a mortality-prediction model, then a validation cohort. The primary outcome was all-cause in-hospital

death. In the derivation cohort ($n = 478$ patients), the authors found that at 19 cm H₂O, an ordinal increment of DP was accompanied by an incremental risk of death. For overall mortality, DP greater than or equal to 19 cm H₂O had a higher mortality than DP less than 19 cm H₂O (66.2% vs. 31.5%; $P < 0.001$), whereas Ppl greater than or equal to 30 cm H₂O had a higher mortality than Ppl less than 30 cm H₂O (69% vs. 27%; $P < 0.001$). The validation cohort (300 separate patients) confirmed these thresholds. Using receiver operating characteristic curves, there was no statistically significant difference in hospital mortality prediction between Ppl (0.724; 95% confidence interval, 0.686–0.761) and DP (0.704; 95% confidence interval, 0.667–0.741).

The findings of the Villar and colleagues study (12) differ from those of the Amato and colleagues study (14); however, there were important design variations between them. First, all patients in the Villar and colleagues study were studied at 24 hours after ARDS diagnosis. In the Amato study, patients may have been randomized up to 96 hours after ARDS onset, resulting in a measurement of pressures not reflecting those at ARDS onset. Second, because DP is derived in part from Ppl, collinearity of these variables must be addressed in any analysis. Whereas Amato and colleagues accounted for collinearity in their adjusted models, it is unclear how Villar and colleagues did so, making definitive conclusions challenging to interpret.

Though lung-protective strategies have resulted in improved outcomes, ARDS remains a high-mortality syndrome. At this point, it is unclear if titrating lung-protective ventilation to DP improves

outcomes compared with Ppl titration, especially without a definitive DP threshold for titration. Because thus far the data on DP versus Ppl originate from past ARDS trials, it is important to prospectively compare titration of V_T and PEEP on the basis of DP threshold versus Ppl threshold before modifying current ARDS management recommendations. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

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