Editorial

Recruitment and titrated positive end-expiratory pressure in acute respiratory distress—have we reached the ceiling?

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Comment on: Writing Group for the Alveolar Recruitment for Acute Respiratory Distress Syndrome Trial (ART) Investigators, Cavalcanti AB, Suzumura ÉA, *et al.* 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 2017;318:1335-45.

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Acute respiratory distress (ARDS) is a serious medical condition having significant mortality, the management of which hinges primarily on appropriate ventilator management. The different aspects of management have been a matter of intense research over the last several decades which have led to better understanding of the disease process as well as periodic modifications in ventilator strategies. Over the years, the two aspects of ventilator strategies that have been accepted as standard-of-care are low tidal volume (LTV) strategy and suitable high positive end expiratory pressure (PEEP) ventilation. However, the exact "quantum" of PEEP has been ardently debated and has not been yet determined even after scores of trials. The evidence in favour of either an arbitrary "higher" or "lower" PEEP has been largely equivocal.

Much of the strategies for mechanical ventilation in ARDS has emphasized the importance of "opening" up of alveoli and "maintaining the alveoli open" for which recruitment manoeuvres and PEEP have been used respectively (1,2). This has led to the concept of open lung ventilation (OLV), which refers to the combination of LTV ventilation, with a recruitment manoeuvre and titration of PEEP to a level that prevents the de-recruitment of opened-up alveoli thus resulting in better oxygenation (3). In theory it has been an appealing approach which seemed to address the pathophysiology of hypoxemia in ARDS but it effectiveness in bringing about better clinical outcome has not been unequivocally and consistently validated by trials. On a similar note, the search for an "ideal" PEEP has remained elusive. Whether PEEP should be "higher" or towards the "lower" side has been a subject of intense research. Use of "higher" PEEP as a part of OLV was investigated previously in a few studies which showed some benefits, but had small sample sizes, heterogeneity in patient population, technical errors and a higher mortality than expected in ARDS (4,5). A meta-analysis analysed the three trials which had tested high PEEP strategy with low PEEP strategies in patients with ARDS (6). In the individual trials as well as in the meta-analysis, there was no significant mortality reduction in favour of either strategy (7-9). Subgroup analyses of this study however suggested that in patients with moderate and severe ARDS (PiO_2/FiO_2 ratio <200), there was mortality reduction with higher PEEP strategies. Subsequently another meta-analysis in 2013 further supported reduced mortality in subgroup of participants with PiO_2/FiO_2 ratio <200 (10). Thus, the necessity, to prospectively validate the effectiveness of high PEEP in moderate and severe ARDS, was earnestly perceived.

In a recent issue of JAMA, a trial conducted by the Writing Group for the Alveolar Recruitment for Acute Respiratory Distress Syndrome Trial (ART) Investigators was published which strived to gauge the effects of recruitment manoeuvres and PEEP titration on 28-day

mortality of patients with moderate to severe ARDS (11). It was a multicentre randomised clinical trial spanning over 6 years, conducted in nine countries recruiting patients from over 120 intensive care units. The included patients were randomised to two arms, one managed according to the conventional PEEP protocol (n=509) and the other received recruitment manoeuvres and PEEP titration according to the best respiratory compliance (n=501). The predominant cause for ARDS in the study was pulmonary (around 62%) and two-thirds of the patient had septic shock. Other aspects of management in both arms were kept similar, including use of fluids and neuromuscular blockers. A tidal volume of 6 mL/kg was used, allowing a maximum inspiratory plateau pressure of 30 cmH_2O. The recruitment manoeuvre included an incremental pressure of up to 45 cmH_2O over 4 minutes followed by decremental PEEP (in steps of 3 cmH_2O starting at 23 cmH_2O) to determine optimal PEEP. This was followed by repeat recruitment (at 45 cmH_2O) before maintaining a PEEP of 2 cm above optimal PEEP, in the experimental group. This recruitment manoeuvre was used for the first 555 patients, but was modified from the 556th patient with lowering of pressures with shortening of time in each phase, after three episodes of cardiac arrest occurred, possibly associated with experimental group treatment.

Mean difference in PEEP in both groups was 3 to 4 cmH_2O in first 7 days. The decrease in driving pressures amongst both groups differed by less than 2 cm in the first 3 days. Higher sedative doses were also used in the experimental group. The primary outcome i.e., 28-day mortality was different among both groups. It was 49.3% in the control group and 55.3% in the experimental group, P value of 0.041 and hazard ratio of 1.2 (1.01–1.42). Similar difference was also seen in 6-month mortality though no difference was seen in the in-hospital mortality. Experimental group also had significantly higher incidence of barotraumas (P=0.007) and need of commencement or increase of vasopressors within first hour (P=0.03). The experimental group had lower ventilator-free days during the first 28 days. Sub group analysis did not reveal any variable treatment effects in the experimental *vs.* control strategy in any of subgroups based on type of ARDS (pulmonary *vs.* extrapulmonary, moderate *vs.* severe, duration of mechanical ventilation before randomization, before and after protocol modification for recruitment etc.).

Several explanations have been solicited to explain the increased 28-day and 6-month mortality in the experimental group *vs.* control strategy group. Foremost, is the tug-of-war between the potential "good" *vs.* "bad" effect of high pressures, causing reduction in driving pressure (by recruiting more number of lung units) and overdistension (causing barotrauma and hemodynamic instability) respectively. In this study, the minimal difference in driving pressure (12) with a similar tidal volume in two groups implies that recruitment and higher PEEP titration in the experimental did not translate in significant recruitment of non-aerated portion of the collapsed lung. This is in contradistinction to the findings of studies that have shown favourable recruitment of diseased alveoli with higher inspiratory pressures and recruitment manoeuvres (13,14). The higher mortality in the experimental group could likely have been driven by the higher incidences of barotrauma and hemodynamic compromise in the experimental strategy group. However, ICU mortality and in-hospital mortality were not different in the two groups, suggesting that perhaps, the increased mortality could not be explained only by acute insults of barotraumas and hemodynamic instability in the "higher" pressure group. Whether this could be linked to increased biotrauma secondary to tidal overdistension?—was not addressed by the authors. Another explanation for the result was the use of LTV ventilation in both the control and experimental and control group with PEEP level higher (by around 3 cm) in the control group as compared to previous studies (6). The use of LTV was hypothesized to lead to decreased driving pressure and reduced lung injury due to volume overdistension and at the same time, "reasonable" PEEP levels had led to reduction of atelectrauma—resulting in good clinical outcome in the control group. Thirdly, the phenomenon of breath stacking may have led to more alveolar distension in patients receiving higher PEEP levels resulting in adverse outcomes.

The major strengths of the study included adequate concealment of allocation, avoiding attrition, multi centric design, strict eligibility criteria and identical management strategies in both the groups (barring the open lung strategy under study). However, this study was not without limitations, which included lack of blinding of patients, physicians and assessors. Also, the baseline responsiveness to PEEP was not assessed which could have potentially lead to identification of recruitable lung and could have avoided use of higher pressures in those not demonstrating recruitability. Sustained inflation has been shown to have higher rates of hypotension, barotraumas without improving oxygenation or reducing intrapulmonary shunting in spite

of having high mean airway pressure (8,15). As the use of recruitment manoeuvres is variable with respect to time and pressure applied, it may be reasoned that the results of this trial may not be generalised to all forms of recruitment manoeuvres and by extension to different methods of OLV. How much of pressure is enough to keep the "lung open" without overdoing it, needs to be further researched.

Recent guidelines like American thoracic society guidelines (which did not incorporate the results of this study) recommend using higher PEEP in moderate-severe ARDS and also the use of recruitment manoeuvre in adult patients with ARDS (16). It however does not give recommendations on type of manoeuvre to be used. However, the results of this study suggest that OLV, relying on rigorous recruitment manoeuvres and "high" PEEP can no longer be blindly advocated. But whether it is the beginning of the end for the strategy as a whole or warrants a suitable "toning down of the pressures"—would depend on further evidence derived from large scale studies focussing on the potential modifications of this strategy.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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