Editorial

High positive pressure at end expiration and recruitment maneuvers—is there a place for this therapy in acute respiratory distress syndrome?

Roberto Eduardo Santa Cruz[1,2], **Alvaro Figueroa**[2]

[1]School of Medicine, University of Magallanes, Punta Arenas, Chile; [2]Department of Intensive Care, Hospital Regional Rio Gallegos, Río Gallegos, Argentina

Correspondence to: Roberto Eduardo Santa Cruz. Department of Intensive Care, Hospital Regional Rio Gallegos, Río Gallegos, Argentina. Email: resc.hrrg@gmail.com.

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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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The use of mechanical ventilation (MV) in patients with acute respiratory distress syndrome (ARDS) can exacerbate lung injury, which is usually referred to as ventilator-induced lung injury (VILI). The two most important mechanisms involved in VILI are the excessive volume or pressure that occurs at the end of inspiration, and the repetitive opening and closing of the alveoli. Therefore, lung protective ventilation strategy is based on the use of low tidal volumes and the prevention of intratidal collapse of pulmonary units by providing an appropriate level of positive pressure at end expiration (PEEP). In turn, some authors propose the use of recruitment maneuvers prior to the titration of the PEEP level (1,2) through the conception of open the lung and keep it open (3).

One randomized clinical trial that used small ventilatory volumes and low plateau pressures have demonstrated reduced mortality (4). Regarding the use of PEEP, several studies have evaluated the use of high levels of PEEP, but the results have not shown a benefit (5-7). Through a systematic review, we have pooled studies that compare two levels of PEEP in patients with acute lung injury (ALI) and ARDS without finding significant differences (8).

Lately, a ventilatory strategy more physiologically, "open lung approach" (OLA), aiming at maximal alveolar recruitment has been proposed. In OLA, recruitment maneuvers are applied to overcome the critical "opening pressure" and subsequently PEEP is titrated to match the best compliance (or the best oxygenation) compatible with the lowest PEEP level (9). This strategy has been evaluated in a mathematical (10) and animal model (11) as well as in clinical studies (12,13).

Recently, in the *JAMA*, the Writing Group for the Alveolar Recruitment for Acute Respiratory Distress Syndrome Trial (ART) Investigators *et al.* (14) publish a randomized controlled study to determine if lung recruitment with incremental PEEP, with subsequent titration of the decremental PEEP determined by the best static compliance value (experimental group) decrease 28-day mortality compared with a conventional low-PEEP strategy (control group). The study was conducted in 120 intensive care units in nine countries and included patients with moderate and severe ARDS of less than 72 hours duration. A total of 1,010 patients were included (501 in the experimental group and 509 in the control group). Mortality at 28 days was significantly greater for experimental group [277 of 501 patients (55.3%)] compared to the control group [251 of 509 patients (49.3%)]. The hazard ratio was 1.20 (95% CI, 1.01–1.42; P=0.041). In addition, mortality at 6 months was also higher [65.3% *vs.* 59.9%; HR =1.18 (95% CI, 1.01–1.38; P=0.04)], as the

risk of any barotrauma and death with barotrauma, and the need for vasopressors or hypotension in the first hour. There were no significant differences in the length of ICU stay, length of hospital stay, ICU mortality, and in-hospital mortality.

Among the ventilatory variables during the first day, the difference in PEEP values was 4 cmH_2O in favor of the experimental group, while the driving pressure was lower, both with a statistically significant difference. In addition the plateau pressure was significantly greater in the experimental group, with a greater value of 25 cmH_2O that was prolonged on the third day of MV. Although this elevated plateau pressure could correspond to the higher values of PEEP, it has already been demonstrated that there is a relationship between this variable and mortality. Hager *et al.* (15) analyzing the data of ARDS Network trial of MV with higher versus lower tidal volumes has evaluated the relationship between plateau pressure and mortality and has found that during the first day of MV at a lower plateau pressure mortality is lower.

For several years, the use of high PEEP has been studied in patients with ARDS and several ventilatory strategies have been proposed in relation to the use of high PEEP, where the titration was performed according to oxygenation (5,6) or according to mechanical variables (7). These studies used high PEEP in an unselected patient population with ALI and ARDS and they did not obtain favorable results. It was considered that the use of high PEEP could be of benefit in patients with greater lung damage and a systematic review showed a trend towards the decrease in mortality in patients with more severe ARDS (16).

In the last time, two studies have used the OLA in patients with moderate or severe ARDS, with a strategy very similar to ART. Hodgson *et al.* (12) examine the effectiveness of a recruitment maneuver with decremental PEEP, where the level of PEEP was determined by a certain drop in oxygen saturation. In turn, Kacmarek *et al.* (13) used a recruitment maneuver with subsequent titration of the decremental PEEP determined by the best dynamic compliance value. In both studies, the recruitment maneuver was through incremental PEEP. The three studies were very similar in terms of the recruitment maneuver and the PEEP titration.

There were no differences between the groups in the ventilatory parameters, with the exception of higher risk of barotrauma in the experimental group in the ART study. It is noteworthy that this average rate of barotrauma within 7 days in the experimental group from ART study was low (28 of 56 patients, 50%). Recently, Goligher *et al.* (17), assessing studies using recruitment maneuvers associated with high PEEP have found that the median rate of barotrauma across all trials was 10%. Despite these results, this difference between the groups may have influenced the results and differed from the other two studies, since the outcomes of the ART study suggested harm. In addition, some studies have found an association between high PEEP and barotrauma. Eisner *et al.* (18), in a study using data from ARDS Network randomized controlled trials, have found that after controlling for covariants, PEEP was associated with an increased risk of early barotrauma and for every 5 cmH_2O concurrent PEEP increment, the relative hazard (RH) of developing barotrauma increased by 1.67 (95% CI, 1.35–2.07). Meanwhile, Anzueto *et al.* (19) have found a trend towards higher PEEP in patients who experienced barotrauma. Regarding the association between barotrauma and mortality, we could say that it is controversial since Weg *et al.* (20) have found that pneumothorax or other air leaks were not associated with a significantly increased mortality rate, while an old study by Gattinoni *et al.* (21) in patients with ARDS have found higher mortality in patients with barotrauma.

It is important to highlight some common characteristics of these three studies. The first is the elevated plateau pressure (>25 cmH_2O) during the first day, according to what was previously expressed in relation to the association between plateau pressure and mortality. Lung hyperinflation has been previously reported as resulting from MV with PEEP and could be related with high plateau pressure. Nieszkowska *et al.* (22), in an analysis of a previous study found that 32 patients with ALI under VM, expiratory derecruitment was prevented by maintaining a level of PEEP of 15 cmH_2O. But this beneficial effect was obtained at a price of an overinflation of non-dependent pulmonary regions. If this elevated pressure plateau, which as mentioned above could be a consequence of high levels of PEEP, we should reassess the benefit of this ventilatory strategy.

Secondly, none of the studies has assessed the potential recruitment of the included patients. Gattinoni *et al.* (23), have shown that patients with ARDS have a variable degree of potentially recruitable lung and that only those patients with a high degree of recruitment, pulmonary opening maneuvers could decrease VILI.

Given the above, we can affirm in the present that the usefulness of recruitment maneuvers and the optimal level of PEEP in patients with ARDS are still controversial. The

pulmonary heterogeneity in collapsed, occupied and normal alveoli makes it difficult to implement such a strategy, without which more VILI could be generated. Lately driving pressure has been considered, due to its association with mortality (24), but it would be very important, considering one of its components, plateau pressure. For this, a greater evaluation of the patient is necessary through more complex studies (computerized axial tomography, electrical impedance tomography, etc.) that are not easily accessible. We believe that this individual assessment of the severity of lung injury will allow us a better assessment of functional and anatomical recruitment and will help us to improve outcomes in patients with ARDS.

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Footnote

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

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