Editorial

Intensive alveolar recruitment strategy in the post-cardiac surgery setting: one PEEP level may not fit all

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Low tidal volume ventilation is now a standard of care in ICU patients and in high risk patients in the operating room (OR), since convincing evidence have been provided regarding its benefit on prognosis in these settings (1,2). PEEP setting is less straightforward in ARDS, and, while high PEEP levels are advocated in the more severely hypoxemic patients, the search for a reliable bedside tool to titrate PEEP in an individual ARDS patient is still ongoing (3). In the OR context, the recent PROVHILO trial failed to demonstrate any favorable effect on outcome of high PEEP as compared to low PEEP during open abdominal surgery (4). Recruitment maneuver are even more controversial, either during ARDS where the level of evidence is low, or in the OR where they are often used as a co-intervention in low tidal volume trials. Moreover, a great variability among trials testing recruiting maneuvers exists in terms of timing, frequency, duration, intensity and ventilatory mode, precluding any comparison or generalization of findings. Finally, uncertainties remain regarding the adverse effects of recruitment maneuvers, especially regarding hemodynamic tolerance and risk of ventilation-induced lung injury (VILI).

In the March issue of the Journal of the American Medical Association, Costa Leme *et al.* presented the results of a single-center randomized controlled trial comparing two lung recruitment strategies associated with protective ventilation, in hypoxemic patients after cardiac surgery (5). The aim of their study was to test whether an intensive lung recruitment strategy would decrease the modified semi-quantitative score of Kroenke (a composite endpoint associating post-operative pulmonary complications and mortality), compared to a moderate recruitment strategy (6). Three hundred and twenty post-operative patients with hypoxemia (PaO_2/FiO_2 <250 mmHg at PEEP ≥5 cmH_2O) on ICU admission were enrolled, and recruitment maneuvers were carried out at randomization and 4 hours after. The intensive recruitment strategy (n=157) consisted in 3 inflation cycles (60s each) with PEEP set at 30 cmH_2O and a driving pressure of 15 cmH_2O, followed by PEEP set at 13 cmH_2O. The moderate recruitment strategy (n=163) consisted in 3 sustained inflations of 30 s at 20 cmH_2O, followed by PEEP set at 8 cmH_2O. Both groups were then ventilated until extubation with low tidal volume and PEEP level assigned by randomization. The study showed a significant decrease in the pulmonary complications score in favor of the intensive recruitment strategy [1.8 (95% CI, 1.7–2.0) *vs.* 2.1 (95% CI, 2.0–2.3)]. Hospital and ICU length of stay were significantly lower in the intensive recruitment strategy patients, whereas hospital mortality and incidence of barotrauma did not vary between strategies. Duration of mechanical ventilation was significantly lower in the intensive strategy group, although the 1.1-hour absolute difference may be meaningless. The authors also observed a significant improvement in oxygenation, respiratory system compliance, and driving pressure 4 hours after randomization in the intensive recruitment strategy group. Interestingly, the beneficial effect on lung function of the intensive recruitment strategy was sustained after extubation with a significant decrease in the number of patients meeting the predefined criteria for extended non-invasive ventilation, and a lower use of supplemental oxygen in this group. Hemodynamic monitoring during and after recruitment maneuvers only showed transient, non-severe, hypotension in the intensive strategy group. Finally, in a subgroup of 33 patients studied with electrical impedance tomography (EIT), a homogenization of aeration between dependent and non-dependent lung regions was observed in the intensive strategy group, suggesting reversal of atelectasis in the dependent lung.

While this study meets high methodological standards, several important points and limitations should be further discussed. First, the single-center feature questions study generalizability, and lack of blinding make ascertainment and co-intervention bias uncontrolled. Second, the relevance of the primary judgment criterion is also questionable, as interpretation of the 0.3 difference between groups of the modified Kroenke score is not straightforward, although similar composite complications scores were used in recent RCTs (2,7). Third, we are highly unsettled by the protocol requirement of a negative leg raising test before starting recruiting maneuvers. It suggests that fluid administration was performed post-operatively in some patients without acute circulatory failure, for the only purpose of prevention of hemodynamic intolerance during maneuvers. Surprisingly, while only perioperative fluid balance is reported, we ignore the effects of such a strategy on post-operative fluid administration. As a consequence, such fluid management may have disadvantaged the moderate strategy group, since higher PEEP may have lessened the deleterious pulmonary impact of fluid administration, by reducing pulmonary capillary leak and left ventricle afterload. Furthermore, since positive fluid balance is a strong predictor of ICU death, and a positive leg raising test reflects physiological heart functioning, it is questionable whether any of the tested strategies reflects standard of care (8). Fourth, it should be emphasized that Costa Leme *et al.* selected a particular small subset of postoperative cardiac patients (79% of screened patients being excluded mainly because of lack of hypoxemia, or previous cardiac surgery). Surprisingly, while most of the study patients fulfilled two criteria out of four of the Berlin ARDS definition [namely cardiac pulmonary bypass (CPB) as a risk factor and $PaO_2/FiO_2 \leq 300$ mmHg)], identification of the two other criteria was not specifically reported (9). We may speculate that most of the patients presented with at least a mild form of post-operative ARDS, although pure hydrostatic pulmonary edema cannot be ruled out in this population. Better characterization of the causes leading to hypoxemia could have helped better understand the results. Finally, whether higher PEEP, aggressive recruiting maneuvers, or both explains improved prognosis in the intensive strategy group remains unanswered.

How do the results of this study fit in the current body of evidence regarding prevention of pulmonary complications under mechanical ventilation? VILI has been studied for decades, and the experimental demonstration that an excessive cyclical stretch of lung parenchyma by high tidal volume (volutrauma) is harmful has been undoubtedly confirmed in the clinical setting more than 15 years ago in ARDS patients (1). As a direct translation of experimental research, protective ventilation (i.e., ventilation with low tidal volume, using a minimal amount of PEEP, and plateau pressure control) is now a standard of care in ARDS patients. Avoiding overstretching of lung parenchyma by lowering tidal volume during the perioperative period (i.e., short course mechanical ventilation) of major abdominal surgery also decreases major pulmonary and extrapulmonary complications occurring during the following 7 days (2,10). Finally, a decrease of post-operative complications associated with low-tidal volume was recently confirmed in a meta-analysis of 15 RCT performed in various surgical settings (11).

While the protective effect of low tidal volume ventilation is indisputable, benefits of higher PEEP levels remain unclear. Experimentally, evidence of the lung-protective effect of PEEP has long been demonstrated, probably by promoting alveolar recruitment, by preventing cyclic alveolar collapse (atelectrauma), and by reducing lung regional inhomogeneities that may act as stress raisers on the lung parenchyma (12). However, large randomized trials comparing higher to lower levels of PEEP on unselected ARDS patients were all negative, and a beneficial effect of PEEP on ARDS mortality has only been shown in a meta-analysis of these trials in the subgroup of patients with $PaO_2/FiO_2 \leq 200$ mmHg (3,13-15). On the other hand, critically ill patients without ARDS, or OR patients undergoing abdominal surgery may not benefit from higher PEEP on their outcome (4,11).

To analyze these results, insights on the physiology of VILI become mandatory. Mechanical aggression of the lung by the ventilator may be modelled using bioengineering concepts such as stress, strain and energy load. Lung stress is the orthogonal pressure applied to the lung structures by the distending force, roughly estimated by the transpulmonary pressure. Lung strain is the volumetric deformation of the structure and corresponds to the ratio of the variation in lung volume induced by mechanical ventilation over the lung resting volume [namely the functional residual capacity (FRC) at zero end-expiratory pressure]. Stress and strain are mathematically related by the lung specific elastance. Lung strain may be viewed as a measurement of the adequacy between the volume of gas insufflated by the ventilator and the lung resting volume. Experimental data suggests that measured strain should not exceed the safe limit of 2 (i.e., end-inspiratory aerated volume exceeds two times the FRC) (16). Global strain may be partitioned into a static component (i.e., ratio of PEEP-induced increase in lung volume over FRC) and a dynamic component (i.e., ratio of tidal volume over FRC). It has been demonstrated that, for an equal level of global strain, the combination of high dynamic and low static strains was associated with the development of pulmonary edema in healthy pigs, compared to low dynamic and high static strains (17). These results favor the association of low tidal volumes and high PEEP levels to achieve VILI prevention. More recently, it has been postulated that VILI could be viewed as a consequence of an excessive energy load transferred from the ventilator to the lung (18). By computing mechanical power from the equation of motion, this approach allows the evaluation of the relative contribution of isolated mechanical ventilation settings and respiratory mechanics to the genesis of VILI. Albeit an oversimplification of the reality, two key messages can be extracted from the analysis of the mechanical power equation. First, while compliance augmentation is associated with a linear decrease in mechanical power, PEEP increase is associated with a linear rise in mechanical power that may only be counterbalanced if associated with an increase in compliance related to alveolar recruitment. This implies that a high PEEP strategy may increase mechanical power and hence be harmful if it fails at promoting alveolar recruitment. Second, increases in tidal volume, respiratory rate, and driving pressure produce an exponential raise in mechanical power, theoretically confirming the predominance of volutrauma over atelectrauma in the genesis of VILI.

Mechanical ventilation also acts as a trigger of pro-inflammatory molecular and cell-mediated pathways (namely biotrauma), with potentially harmful consequences on the lungs and extrapulmonary organs (19). Volutrauma may induce higher lung inflammation when compared to atelectrauma, favoring the prevention of the former by low tidal volume ventilation, than of the latter by applying high PEEP levels (20). The study by Futier *et al.*, proving the beneficial effect of a protective ventilatory strategy (associating low tidal volume, a PEEP between 6 and 8 mmHg and recruitment maneuvers) on an extrapulmonary composite outcome variable, which incorporated sepsis, is an indirect clinical demonstration of the relevance of the biotrauma concept (2,21).

PEEP is a two-edged sword, as beneficial effect on alveolar recruitment and compliance are counterbalanced by potential lung hyperinflation and worsened hemodynamics. The more severely hypoxemic ARDS patients may benefit from higher PEEP, since they have the highest potential for recruitment, although this may not be true on an individual basis (22). Furthermore, recent data on ARDS patients using computed tomography suggests that reduction of atelectrauma and spatial reduction of stress raisers would require PEEP levels far higher than the ones commonly applied in severe ARDS, while the awaited beneficial effects of PEEP may be outweighed by deleterious effects (23). The study by Costa Leme *et al.* apparently provides contradictory results, since they considered mildly hypoxemic patients for inclusion (PaO_2/FiO_2 <250 mmHg). It may be speculated that the selected population of the study presented high potential for recruitment (as shown by improvement in oxygenation, driving pressure, and hence compliance, and improved aeration in the dependent lung in EIT), possibly because patients were studied immediately after lung aggression by CPB. Also, respiratory improvement in the intensive strategy group may be partly related to its counteraction on hydrostatic edema.

Futures studies should aim at tailoring PEEP to individual patient characteristics and response to therapy, given the harmful potential of high PEEP in some patients. Unfortunately, response to PEEP assessed by easily available bedside tools (PaO_2/FiO_2, $PaCO_2$, compliance of the respiratory system, dead space) is poorly related to alveolar recruitment (22). Of note, changes in driving pressure in response to PEEP is not expected to outperform compliance assessment in the detection of PEEP-induced alveolar recruitment, since they are inversely proportional when tidal volume is kept constant. EIT is a promising tool to assess alveolar recruitment at the bedside, but crippled by several limitations, among which is limited regional assessment, poor spatial resolution, and has yet to prove its effectiveness in selecting an adequate level of PEEP in ICU patients. Esophageal pressure represents an appealing option to determine optimal PEEP levels during ARDS, but diffusion of this tool in the clinical setting awaits confirmation of the preliminary results of a large RCT currently under way (24). To finish with, lung ultrasound exploration allows the detection of changes in lung aeration during a PEEP trial, and may allow the detection of patients with high recruitment potential (25).

In conclusion, systematic use of an intensive recruitment strategy may be an option in a specific and selected population with expected high potential for recruitment, given its efficiency and security are confirmed in a multicenter RCT. Personalizing PEEP levels as a function of alveolar recruitment potential seems a more relevant option in a general population, but awaits the advent of a reliable bedside tool helping to prevent the harmful consequences of VILI in some patients.

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Footnote

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

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