Higher vs. lower PEEP in ARDS: just one part of the whole

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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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Throughout the years the target of mechanical ventilation in acute respiratory distress syndrome (ARDS) patients has shifted from the maintenance of vital gas exchange to the protection of the lung from ventilator induced lung injury (VILI) (1,2). The unphysiological stress and strain of the "baby lung parenchyma", the intra-tidal collapse of pulmonary and lung inhomogeneities units are the main determinants of VILI during mechanical ventilation resulting in inflammatory responses and mechanical lesions up to the lung rupture (3). The "open lung theory" is based on these two key concepts: avoiding barotrauma and volutrauma applying low tidal volume, limiting plateau pressure and preventing atelectrauma providing positive end-expiratory pressure (PEEP) sufficient to keep the lung open throughout the respiratory cycle (4). However, while ventilation at low tidal volume per se has been shown to increase survival in acute lung injury and ARDS patients, up to now the application of higher PEEP to low tidal volume has not increased survival except in animal studies or in patients with severe ARDS (4-6). However, the meta-analysis of the three main trials comparing higher versus lower levels of PEEP suggested that higher levels of PEEP were associated with improved survival among patients with a ratio of arterial oxygen partial pressure to fractional inspired oxygen (PaO₂/FiO₂) <200 (7-10). Two subsequent randomized trials comparing stepwise recruitment maneuvers performed using peak pressure up to 60 cm of water and PEEP of 25-35 cm of water followed

by a decremental PEEP trial versus a low PEEP strategy suggested beneficial effects in oxygenation, driving pressure value, inflammatory biomarkers and a small but nonsignificant improvement in survival. However, they were not large enough to analyze this outcome (11,12).

Cavalcanti et al. conducted a large randomized clinical trial involving 120 intensive care units (ICU) in nine countries, enrolling 1,010 patients comparing the open lung approach (OLA) with a control strategy based on lower PEEP set using the FiO₂-PEEP table proposed by ARDSNet and without recruitment maneuvers (13). The OLA group received recruitment maneuvers with PEEP as high as 45 cm of water and plateau pressure in pressure control mode as high as 60 cm of water, then followed immediately by a decremental PEEP titration to identify the PEEP level at which respiratory system compliance was maximal, hypothetically representing the best balance between recruitment and overdistension. Alveolar recruitment maneuver was performed in three steps, with PEEP of 25 cm of water and delta pressure above PEEP of 15 cm of water for the first minute, then PEEP increased to 35 for the second minute and to 45 cm of water for the third minute. After the identification of the optimal PEEP level, that was the PEEP value at maximum compliance plus 2 cm of water, a new alveolar recruitment, with PEEP of 35 and delta pressure above peep of 15 cmH₂O for 1 minute, was performed. Alveolar recruitment maneuver can be repeated every 24 hours only if the first

maneuver was considered successful that is an increase of $PaO_2/FiO_2 \ge 50 \text{ mmHg}$, then it was allowed to repeat it in case of disconnections from the ventilator circuit in patients with high levels of PEEP $\ge 12 \text{ mmHg}$ and in case of decrease of the oxygenation target.

Contrary to the initial hypothesis they didn't found any beneficial effects from their open lung approach. In fact, the OLA group showed a significantly higher 28-day and 6-month mortality (55.3% vs. 49.3% and 65.3% vs. 59.9% respectively), a higher rate of barotrauma (5.6% vs 1.6%), a higher need of vasopressors or incidence of hypotension in the first hour of the protocol, and a decrease in ventilator-free days (5.3 vs. 6.4 days in OLA vs. control group) (13).

Differently from the three previous trials the authors enrolled patients with established moderate to severe ARDS, with a PaO_2/FiO_2 less than or equal to 200 ventilated with FiO_2 100% and PEEP of 10 or more cm of water for 30 minutes, within 72 hours since the first diagnosis. In fact, the main speculation regarding the lack of benefit from higher PEEP levels in the previous trials is that many patients did not have an established ARDS and these patients could have been damaged by high levels of PEEP (8,9). Furthermore, differently from the trials included in the meta-analysis, the authors did not mention among the exclusion criteria patients intubated as a result of an acute exacerbation of chronic pulmonary disease (chronic obstructive pulmonary disease, asthma, fibrosis).

The overall severity of the enrolled patients at ICU admission was higher as demonstrated by the reported mean value of SAPS III (score 63.5 vs. 62.7—OLA vs. control group) in this trial corresponding to an estimated probability of mortality of 75%, compared with the median value of probability of death from SAPS II, 49% in both groups of the meta-analysis and with the mean values of APACHE II score reported in both groups of the OLA pilot trial (18 vs. 17), the latter two associated with a lower predicted mortality rate (12).

Probably as a consequence, mortality rates were higher than those previously reported in the literature (death in ICU 60.6% vs. 55.8% OLA vs. control group in the Cavalcanti trial; 30.3% vs. 36.6% higher vs. lower PEEP group in the meta-analysis) (6,13).

However, the authors found even higher mortality rate in the OLA group than in the control group. Let's assume the causes of what.

Over the first 7 days, the OLA group has mean PEEP levels higher than only 3–4 cmH₂O compared with control group, mean levels of driving pressure lower of less than

2 cmH₂O and mean values of respiratory system static compliance higher of 3 mL/cmH₂O. These differences though significantly different, are not clinically relevant. Because of the slight increase of the compliance and the slight decrease in driving pressure in the OLA group compared with control group we can suppose much more overinflation than recruitment. Then, after 1 hour from PEEP selection, PaCO₂ was significantly higher in the OLA group, confirming the hypothesis of initial overinflation. Nevertheless, the incidence of barotraumatic events in the OLA group was not higher than in any previous studies using high PEEP (6-9,11). The control group showed PEEP levels, slightly significantly lower than in the experimental group with significantly lower mortality (7-9). We agree with the authors that these higher PEEP levels in the control group compared to previous control groups, could be-due to a very strict adherence to the low tidal volume strategy and to NIH ARDS Network PEEP-FiO₂ table to maintain the oxygenation target and may have contributed to reduce the atelectrauma and maximize the parenchyma homogeneity, having a possible role in the decreased mortality in comparison with the OLA group. However in the control group, not only PEEP levels but also mortality rates were higher than those observed in control groups from previous studies (7-9,12).

As already demonstrated by Gattinoni et al. and Grasso et al. higher levels of PEEP may be more harmful than beneficial in patients with low levels of recruitable lung and only approximately 50% of all ARDS patients respond to higher airway pressure by decreasing the percentage of non-aerated lung tissue (5,14). Moreover, the percentage of potentially recruitable lung varied wildly among patients, from a negligible fraction to more than 50% of the total lung weight, keeping in mind that about 24% of the lung could not be recruited even at 45 cm of water of airway pressure as detected by computed tomography (CT) (5). It follows that the most of PEEP gas volume enters in the already open units causing overinflation (15). Then, as demonstrated, a pressure of 20 cm of water generates an end-expiratory lung volume almost equal to the total lung capacity, when tidal volume is added to the PEEP volume, it becomes extremely easy to overcome the total lung capacity at which the extracellular matrix is at risk of micro fractures or ruptures (16).

Moreover as already demonstrated, the causes of VILI are ventilator related, as components of mechanical power in terms of pressures, tidal volume and flow, and lung's related as consequences of amount of edema (the ARDS severity) (17). We know that in the presence of PEEP, more energy is required to inflate the lung, accordingly the energy needed for tidal volume to reach Plateau pressure is ΔP + PEEP multiplied by the volume displaced from the PEEP volume up to the Plateau volume. Calculating this elastic component of mechanical power, that represents the energy per breath with PEEP corresponding to the area of trapezoid having Plateau and PEEP as basis and tidal volume as height, we found high values of mechanical power in both group, but higher in the treatment group, with differences that seem to be clinically relevant (mean values of mechanical power over 7 days 33, 34 and 28, 31 Joule/min respectively in OLA group and control group). Obviously this calculation doesn't take in to account the PEEP volume, the resistive component and the functional residual capacity and thus the values can be overestimated. The differences between groups can be partly expected because mechanical power increases linearly with PEEP, but we should consider the "ambiguous effect of PEEP" that can also decrease the lung dependent causes of VILI (lung's inhomogeneity and intratidal collapse). The final effect positive or negative will depend on which of two actions prevails and in which patients, for this reason mechanical power to be clinical meaningful must be normalized at least for the lung volume (17).

It follows that because in an unselected patient population, lung recruitability is highly variable, quite low, setting high levels of PEEP without studying lung recruitability can provide little benefit and may be harmful.

These effects don't result only in VILI but mainly in haemodynamic impairment. In Cavalcanti's trial 34.8% of the patients enrolled in the experimental group needed the implementation of vasopressor support or showed severe hypotension within the first hour after the beginning of treatment (13). Furthermore, the authors together with the data monitoring committee, decided to modify the initially proposed recruitment maneuver decreasing the applied pressure, after three cases of resuscitation cardiac arrest associated with the experimental treatment. A possible explanation of these haemodynamic effects is that in absence of significant lung recruitment the application of high airways pressure, in addition to the reduction of versus return and cardiac output, increases right ventricular afterload by increasing pulmonary vascular resistance that can result in acute right ventricular failure and shock.

The significant improvement in the oxygenation observed by the authors in OLA group can be due to the two main haemodynamic effects of PEEP: the decrease of cardiac output that generates a reduction of intra pulmonary

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right-to-left shunt and the opening of previously collapsed and perfused regions that causes an intra pulmonary rightto-left shunt decrease. We don't know which of the two mechanisms prevailed in the improving oxygenation because we don't have any data of central versus hemoglobin versus saturation (ScVO₂) as surrogate for hemodynamics, however we suppose the first mechanism prevailed (18).

Since the percentage of recruiters ARDS patients and the percentage of recruitable lung parenchyma are wildly variable, in the context of a syndrome characterized by lung inhomogeneity, with different lung opening pressures throughout the lung parenchyma, we underline that the main preliminary step before PEEP selection is to assess lung recruitability to avoid harmful haemodynamic effects due to the application of high levels of PEEP in unrecruitable lung tissue. The best tool to measure the recruitability remains the CT scan at different pressure levels because other imaging techniques cannot distinguish between a better overall aeration of the lung and the recruitment of previously gasless tissue (5,15). Moreover, the direct protective effect of PEEP, particularly of higher PEEP, is on doubt (19). In fact, what really matters seems to be the physiological upper limit of the lung expansion that is the mechanical power (20). If PEEP with tidal volume overcomes it, PEEP is harmful in terms of VILI but above all for the hemodynamic impairment, otherwise is irrelevant.

Not only the one PEEP doesn't fit for all, but also looking for the ideal protective PEEP has little meaning because within mechanical power, it is just one part of the whole.

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Footnote

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

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