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Maximal Lung Recruitment in Acute Respiratory Distress Syndrome: A Nail in the Coffin

The traditional way to reverse hypoxemia in acute respiratory distress syndrome (ARDS) is the use of positive end-expiratory pressure (PEEP). Ideally, PEEP is to be used to maximize alveolar recruitment and to minimize alveolar overdistension during tidal ventilation, more than for improving gas exchange. The notion of recruitment implies aeration of previously nonaerated lung regions. There is no uniform definition of recruitment (1). Recruitment has been estimated from gas entering either nonaerated or nonaerated and poorly aerated regions when using thorax computed tomography (CT) scanning (1, 2) or from gas entering previously nonaerated and poorly inflated regions using lung mechanics or gas dilution (1).

The CT scan imaging shows that ARDS lungs are heterogeneous. This means that nonaerated, poorly aerated, normally aerated, and overdistended regions coexist in ARDS lungs. In addition, the overall effects of PEEP on recruitability are complex. In patients with ARDS, the percentage of potentially recruitable lung when going from 5 to 45 cm H_2O airway pressure is highly variable, and 24% of the lung could not be recruited at this high pressure (3). Other authors (4), however, have found that the lungs of selected patients with ARDS can be fully recruited with maximal recruitment maneuvers (i.e., PEEP up to 45 cm H_2O and 60 cm H_2O end-inspiratory airway pressure).

In the last years, numerous investigators have compared different PEEP setting strategies in patients with ARDS. These studies have essentially compared low/moderate PEEP levels with higher PEEP levels. Different methods have been used: comparison of PEEP levels according to high/low PEEP–$F_{I_{O2}}$ tables with or without recruitment maneuvers (5, 6), individual PEEP titration to reach a plateau airway pressure of 28–30 cm H_2O (7), PEEP titration based on respiratory system compliance after performing maximal recruitment maneuvers (8, 9), and PEEP titration based on end-expiratory transpulmonary pressure (10). Very disappointingly, these trials have shown no benefits in terms of relevant patient-centered outcomes. Yet signals of harm have emerged from the maximal recruitment trials.

The PHARLAP (Permissive Hypercapnia, Alveolar Recruitment and Low Airway Pressure) study in this issue of the *Journal* by Hodgson and colleagues (pp. 1363–1372) is a well-conducted randomized clinical trial in patients with moderate to severe ARDS, comparing a maximal recruitment strategy with a control group managed with low V_T and moderate PEEP (11). The maximal recruitment strategy was a combined open lung procedure that included a staircase recruitment maneuver using 15 cm H_2O pressure control ventilation and stepwise increases in PEEP up to 40 cm H_2O, a PEEP titration maneuver in which the PEEP was decreased in steps of 2.5 cm H_2O until a derecruitment PEEP was reached (defined as a decrease in Sp_{O_2} by 2% or more or a PEEP of 15 cm H_2O was reached), and when derecruitment PEEP was reached, a new brief (2 min) recruitment maneuver was again repeated. These maneuvers were conducted from the day of randomization to day 5. A total of 102 combined open lung procedures were performed in 56 patients in the intervention group, and 12 patients in the control group received nonprotocolized recruitment maneuvers. The enrollment in the study was aborted when the results of the Alveolar Recruitment Trial were published (9) because of safety concerns and perceived loss of equipoise, and after 115 of 340 planned patients had been randomized.

Although the study by Hodgson and colleagues is negative, the authors are to be commended for rigorously conducting and reporting this important trial. No differences were found in ventilator-free days (the primary outcome) or mortality rate, barotrauma, new use of hypoxemia adjuvant therapies, and length of stay (secondary outcomes) between the intervention and the control groups. Importantly, a significantly higher rate of new cardiac arrhythmias, defined as rapid atrial fibrillation, ventricular tachycardia, or ventricular fibrillation, was found in the intervention group (29%) compared with the control group (13%). Performing the combined open lung procedure was not simple, and during the maneuvers, transient episodes of hypotension and desaturation often occurred in spite of patients' optimization in terms of vascular volume before the maneuvers. In 13% of instances, the hypotension during the maneuvers was severe enough to trigger an increase in the vasopressor infusion rate. The whole process was complex and time consuming, and safety issues were relevant. Of note, very few patients (less than 10%), received ventilation in prone position. The PHARLAP trial strongly suggests that the cardiovascular consequences and, quite likely, the overdistension induced by the procedures outweigh the

Originally Published in Press as DOI: 10.1164/rccm.201908-1615ED on September 18, 2019

possible benefits of the maximal lung recruitment strategy. This adds to previous knowledge suggesting that a systematic lung recruitment approach may not be advisable, as it may harm the patient (9). Even if the PHARLAP study was lacking power for meaningful outcomes, a negative cardiovascular impact emerged.

From a clinical point of view, it seems more important to know whether or not a lung is potentially recruitable before maneuvers such as these are implemented, and then include patients with recruitable lungs and exclude those with nonrecruitable lungs and at high risk for overdistension. Most likely, studies conducted so far have included patients in whom a maximal recruitment maneuver was not needed or useful. It is ironic to see that in these randomized clinical trials of maximal recruitment maneuvers (8, 9, 11), no attempts have been made to assess alveolar recruitment, not even looking at an oxygenation response to increased positive pressure (12). One obvious reason is that the assessment of lung recruitment at the bedside is not easy: the CT scan technique is unfeasible as a routine tool, methods based on pressure–volume curves of the respiratory system and gas dilution are not so practical in clinical routine, and unfortunately, calculation of compliance alone is often misleading (13, 14). As a result, we do not know how patients are to be selected and what is the optimal maximal recruitment maneuver (both in terms of level of pressure and duration), how PEEP is to be adjusted after the maneuver to prevent derecruitment and minimize overdistension (Sp_{O_2} was used in PHARLAP trial and tidal respiratory system compliance in the other trials [8, 9]), how often these maneuvers are to be performed, or how high PEEP is to be weaned off, only to mention a few. Regarding PEEP reduction, for instance, a recent experimental work has shown that abrupt PEEP withdrawal after sustained lung inflation causes lung injury because of increased microvascular endothelial permeability and a surge in lung perfusion (15). Such a scenario is clinically plausible if maximally recruited patients are temporarily disconnected from the ventilator.

What tools available at the bedside do we have now? Analyzing the recruited volume and the response to oxygenation after a change between two levels of PEEP (12, 16) may help to select patients with highly recruitable lungs and those who are the best candidates for a maximal recruitment strategy. Some procedures are relatively easy to perform, although it is needed to take into account the presence of airway closure (17) and understand the fact that oxygenation is not strongly correlated with recruitment. New techniques include lung ultrasound (18) and electrical impedance tomography. Interestingly, electric impedance tomography has been used to individualize PEEP settings by maximizing recruitment and minimizing overdistension in patients with severe ARDS treated with extracorporeal membrane oxygenation (19), and also to provide physiological guidance to wean from high PEEP levels (14). These techniques, however, are still in the research domain, and extensive clinical validation will be required before they can be recommended for routine clinical purposes. Meanwhile, systematic maximal recruitment maneuvers can rest in peace. ■

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

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*J.M. is Associate Editor and L.B. is Deputy Editor of *AJRCCM*. Their participation complies with American Thoracic Society requirements for recusal from review and decisions for authored works.

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The Risk of Hyperoxemia in ICU Patients
Much Ado About O_2

The provision of supplemental oxygen is perhaps the most ubiquitous therapeutic intervention in critical care medicine. To prevent and treat hypoxemia, oxygen is typically administered liberally in the ICU, and patients are often exposed to a high $F_{I_{O_2}}$ and higher than normal Pa_{O_2} (1–3). The association between exposure to hyperoxemia and mortality risk in critical illness has been reported in a number of studies (4–6). However, these studies did not allow for a robust assessment of any dose–response relationship. If such a dose–response relationship were demonstrable, this would increase the probability of a causal relationship between exposure to hyperoxemia and mortality risk.

In this issue of the *Journal*, Palmer and colleagues (pp. 1373–1380) report the findings of an observational study conducted in five university hospitals in the United Kingdom in which they examined the association between longitudinal exposure to hyperoxemia and ICU mortality (7). Hyperoxemia was defined as a Pa_{O_2} >13.3 kPa (100 mm Hg), on the basis that values exceeding this threshold can only be achieved with supplemental oxygen. Patients who stayed in the ICU for 24 hours or less were not included in the analysis. Another important exclusion was patients who had received cardiopulmonary resuscitation in the 24 hours preceding ICU admission. This exclusion is important because the basic science that supports the notion that exposure to hyperoxemia is harmful in hypoxic ischemic encephalopathy is comparatively strong (8) and is supported by prospective observational data (9). The aim of the study was to examine the association between longitudinal exposure to hyperoxemia, defined as time-weighted mean exposure to supraphysiologic Pa_{O_2}, and mortality.

Regrettably, as outlined by the investigators, modeling exposure to hyperoxemia is inherently complicated for several reasons. First, patients can recover and leave the ICU or die and stop contributing data in a nonrandom fashion. Second, to measure the effect of longitudinal exposure to hyperoxemia, a window of time to observe exposure and subsequent effect is needed. Third, patients receiving more vigorous supplemental oxygen therapy are more likely both to be more severely ill and to develop hyperoxemia. Fourth, such patients are also more likely to have arterial blood gas measurements performed (surveillance bias), thus linking the probability of detecting exposure with the likelihood of being both sicker and more frequently monitored at the time of identified exposure and, probably, both before and thereafter. In an effort to account for these complexities, the investigators divided their cohort into groups with different time windows for potential exposure to hyperoxemia. A total of 77.5% of patients were exposed to hyperoxemia by Day 1, increasing to 90.6% by Day 7.

The authors found that exposure to any hyperoxemia was statistically significantly associated with increased mortality risk in patients with 3, 5, and 7 days of potential exposure, but the dose of hyperoxemia was not. In this regard, when considering the data from this study and whether they reflect a "causative pathway" or yet another association between one of the innumerable variables measured in ICU and outcome, one might want to reflect on the canonical Sir Bradford Hill criteria, which can be applied to assess the "functional relationship" between exposure and outcome (10).

In this regard, when relating hyperoxemia to mortality, the strength of association is weak, the consistency of association is limited and the specificity of association is low, the temporality is complex, the biological gradient is absent, the plausibility is unclear, the coherence is uncertain, the experimental data (outside of cardiac arrest models) are lacking, and the presence of an analogy for a

Originally Published in Press as DOI: 10.1164/rccm.201909-1751ED on September 17, 2019