Editorial

'Lung-protective' ventilation in acute respiratory distress syndrome: still a challenge?

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The acute respiratory distress syndrome (ARDS) is a major cause of morbidity and mortality in the intensive care unit (ICU) (1). It is a life-threating condition characterized by widespread inflammation of the lungs, leading to diffuse injury to alveolar cells, surfactant dysfunction, abnormal coagulation and activation of the immune response (2). Clinically, ARDS presents as a respiratory failure with bilateral opacities on chest imaging, hypoxemia and absence of signs of heart failure or volume overload (3). Usually, patients presenting to the ICU with ARDS are treated with mechanical ventilation and supportive therapies, since ARDS is not a particular disease, rather it is a clinical phenotype which may be triggered by various pathologies.

In the past, traditional approaches to mechanical ventilation use tidal volumes of 10 to 15 mL/kg (4), and these volumes were, in fact, even larger than those in normal subjects at rest (7 to 8 mL/kg) (5). However, a classical study in which animals were ventilated with various tidal volumes sizes at similar airway pressures found that high tidal volumes, and not high airway pressures *per se*, were associated with development of ventilator-induced lung injury (VILI), a condition that mimics ARDS (6). In 2000, a large well-designed randomized controlled trial (RCT) convincingly demonstrated the benefits of ventilation with low tidal volumes in patients with ARDS (7). Patients ventilated with tidal volume ≤6 mL/kg of predicted body weight (PBW) had lower mortality and shorter duration of mechanical ventilation compared to patients ventilated with higher tidal volumes. Indeed, all these findings were confirmed in a subsequent systematic review and meta-analysis polling several studies of mechanical ventilation in patients with ARDS (8).

The presence of non-aerated areas in the lungs of patients with ARDS leads to reduced functional residual capacity, decreasing the functional lung that receives the ventilation (9). Classical studies suggested that, in several patients with ARDS, the normally aerated lung tissue have the dimensions of the lung of child, generating the concept of the 'baby lung' (9). In addition, some lung units located in the boundary of the aerated with the non-aerated areas could suffer from shear stress and lung injury secondary to the repetitive opening and closing during one respiratory cycle (2,9). In this scenario, the application of high inspiratory airway pressures aiming to re-aerate these non-aerated areas, increase the size of the 'baby lung' and avoid this repetitive opening and closing of lung units is appealing. Also, the use of higher levels of positive end-expiratory pressure (PEEP) trying to keep the lung open during the entire respiratory circle could decrease the chance of VILI and improve outcomes in patients with ARDS. Indeed, this was tested in three large RCT comparing strategies using higher levels of PEEP with or without recruitment maneuvers against strategies using lower levels of PEEP (10-12). All these trials failed in demonstrating benefits with the use of higher levels of PEEP regarding mortality, however, this 'open-lung' strategy did appear to improve secondary end-points related to hypoxemia and use of rescue therapies. Indeed, an individual patient data meta-analysis considering these trials found that higher levels of PEEP could benefit patients with more severe ARDS, characterized by a higher degree of hypoxemia (13).

Although higher levels of PEEP could improve alveolar recruitment, reduce lung stress and strain, and prevent atelectrauma, it could also lead to overdistension, increase in tidal and maximal hyperinflation (14), and *cor pulmonale* (15), due to the increase in the pulmonary vascular resistance. When considering the potential benefits of higher levels of PEEP, it is also important to realize that a combination of an individual PEEP titration following an alveolar recruitment maneuver could lead to better outcomes in more severe ARDS patients (16). In fact, two ongoing RCT will provide more insights on the impact of alveolar recruitment on outcomes of patients with moderate-to-severe ARDS (17,18).

Recently, Fan *et al.* published a guideline concerning the mechanical ventilation of patients with ARDS (19). For all patients with ARDS, the recommendation is strong for mechanical ventilation using lower tidal volumes (4–8 mL/kg PBW), and lower inspiratory pressures (plateau pressure ≤30 cmH_2O). The guideline also recommends the use of recruitment maneuvers and higher rather than lower levels of PEEP in patients with moderate-to-severe ARDS. Also, for patients with moderate-to-severe ARDS the prone positioning should be strongly considered. Finally, according to the guideline, high frequency oscillatory ventilation should not be routinely used and additional evidence is necessary to make a definitive recommendation for or against the use of extracorporeal membrane oxygenation in patients with severe ARDS.

Recent evidence from an observational study suggests that the practice of ventilation in patients with ARDS around the world is slightly different from those recommended by the guideline (1). Less than two-thirds of the patients with ARDS receive a tidal volume <8 of mL/kg PBW. In fact, the mean tidal volume size used in patients with ARDS included in this study is comparable to those of critically ill patients receiving mechanical ventilation for other causes than ARDS (20). Also, plateau pressure was measured only in 40% of the patients with ARDS, and 83% of these patients received a PEEP <12 cmH_2O (1). Besides, despite the potential benefits, prone positioning was used only in 16% of the patients with severe ARDS (1). Finally, one critical point is that ARDS remains under-recognized by physicians, delaying the initiation of potential therapies and the use of protective ventilation (1).

Driving pressure, defined as the difference between the pressure at end-inspiration and the pressure at end-expiration (e.g., plateau pressure minus PEEP) is gaining attention in recent years. In a large cohort of patients with ARDS the driving pressure appeared to be strongly and independently associated with mortality (21). The role of the driving pressure could be explained by the fact that driving pressure itself is an important driver of the energy delivered by the ventilator to lung in each breath (22). With every artificial breath, the lung conserves some energy, as the elastic recoil returns less energy during exhalation than that absorbed during inspiration. In other words, there is considerable dissipation of energy, probably resulting in heat and lung tissue damage during each breath. This phenomenon is known as 'lung hysteresis', and the 'hysteresis area' may represent the energy dissipated across the parenchyma. Interestingly, driving pressure is closely related to the 'hysteresis area' and this mean that the total amount of energy transferred from the ventilator to the lung is, at least in part, a function of the driving pressure.

Despite the potential benefits of controlling driving pressure in patients with ARDS it could be very difficult to precisely measure and control it in current clinical settings. Also, the ability of driving pressure to predict outcome could be attributable to the fact that the variables that define it are themselves highly predictive of survival (23). Thus, it remains uncertain how to achieve a low driving pressure in an individual patient. One possible strategy is to aim for even lower tidal volumes. So-called 'ultra-protective ventilation' combining very low tidal volumes (~3 mL/kg PBW) with extracorporeal CO_2 removal has the potential to further reduce VILI compared with a standard protective ventilation (24). Another way to achieve a low driving pressure is to titrated PEEP according to the driving pressure. For example, the best response to an increase of PEEP would be a decrease in the driving pressure, meaning that the intervention resulted in recruitment of lung tissue without causing overdistension. In fact, a recent study suggested that the increase of PEEP resulting in higher driving pressure was associated with worse outcomes in surgical patients (25). Also, the use of the 'open-lung' strategy in patients with ARDS was associated with decreased driving pressure in a small RCT (26).

Thus, higher levels of PEEP, with or without recruitment maneuvers, should not be seen as a goal in itself, but as a way to achieve the lowest driving pressure.

One remarkable finding is that the incidence of hospital-acquired ARDS has decreased over the years (27), suggesting that ARDS could be prevented through strategies limiting risk factors potentially associated with its development. Among these factors, the use of protective ventilation in patients without ARDS can play a role. A RCT comparing low tidal volume to high tidal volume in patients without ARDS found that the use of low tidal volume protected against the development of ARDS during the follow-up (28). This finding was confirmed in several meta-analyses (29,30) and individual patient data meta-analysis (31,32). Also, despite these potential benefits, since ARDS is poorly recognized by physicians, the wide adoption of low tidal volume for the ventilation of all critically ill patients is appealing and could avoid the exposure of patients with unrecognized ARDS to higher tidal volumes.

In conclusion, ARDS is still a condition associated with high morbidity and mortality, and remains under-recognized by physicians around the world. Mechanical ventilation in ARDS is still the cornerstone of the treatment, but it should never be seen as a simple and safe intervention. In the era of protective ventilation, physicians should focus on the use of low tidal volumes for all patients with ARDS and consider higher levels of PEEP and prone positioning in the most severe. Also, potential therapies for the future should considering driving pressure and energy as a target. Despite the advance in the field, additional studies are warranted to guarantee the safety of care of this group of patients.

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Footnote

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

References

1. Bellani G, Laffey JG, Pham T, et al. Epidemiology, Patterns of Care, and Mortality for Patients With Acute Respiratory Distress Syndrome in Intensive Care Units in 50 Countries. JAMA 2016;315:788-800.
2. Ware LB, Matthay MA. The Acute Respiratory Distress Syndrome. N Engl J Med 2000;342:1334-49.
3. ARDS Definition Task Force, Ranieri VM, Rubenfeld GD, et al. Acute respiratory distress syndrome: the Berlin Definition. JAMA 2012;307:2526-33.
4. Bendixen HH, Hedley-White J, Laver MB. Impaired oxygenation in surgical patients during general anesthesia with controlled ventilation. A concept of atelectasis. N Engl J Med 1963;269:991-6.
5. Tenney SM, Remmers JE. Comparative quantitative morphology of the mammalian lung: diffusing area. Nature 1963;197:54-6.
6. Dreyfuss D, Soler P, Basset G, et al. High inflation pressure pulmonary edema. Respective effects of high airway pressure, high tidal volume, and positive end-expiratory pressure. Am Rev Respir Dis 1988;137:1159-64.
7. Brower RG, Matthay MA, Morris A, et al. Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. N Engl J Med 2000;342:1301-8.
8. Putensen C, Theuerkauf N, Zinserling J, et al. Meta-analysis: ventilation strategies and outcomes of the acute respiratory distress syndrome and acute lung injury. Ann Intern Med 2009;151:566-76.
9. Gattinoni L, Pesenti A. The concept of "baby lung". Intensive Care Med 2005;31:776-84.
10. Brower RG, Lanken PN, MacIntyre N, et al. Higher versus Lower Positive End-Expiratory Pressures in Patients with the Acute Respiratory Distress Syndrome. N Engl J Med 2004;351:327-36.
11. Mercat A, Richard JC, Vielle B, et al. Positive end-expiratory pressure setting in adults with acute lung injury and acute respiratory distress syndrome: a randomized controlled trial. JAMA 2008;299:646-55.
12. Meade MO, Cook DJ, Guyatt GH, et al. Ventilation strategy using low tidal volumes, recruitment maneuvers, and high positive end-expiratory pressure for acute lung injury and acute respiratory distress syndrome: a randomized controlled trial. JAMA 2008;299:637-45.
13. Briel M, Meade M, Mercat A, et al. Higher vs lower positive end-expiratory pressure in patients with acute lung injury and acute respiratory distress syndrome: systematic review and meta-analysis. JAMA 2010;303:865-73.
14. Retamal J, Borges JB, Bruhn A, et al. High respiratory rate is associated with early reduction of lung edema clearance in an experimental model of ARDS. Acta Anaesthesiol Scand 2016;60:79-92.
15. Lhéritier G, Legras A, Caille A, et al. Prevalence and

prognostic value of acute cor pulmonale and patent foramen ovale in ventilated patients with early acute respiratory distress syndrome: a multicenter study. Intensive Care Med 2013;39:1734-42.
16. Suzumura EA, Figueiro M, Normilio-Silva K, et al. Effects of alveolar recruitment maneuvers on clinical outcomes in patients with acute respiratory distress syndrome: a systematic review and meta-analysis. Intensive Care Med 2014;40:1227-40.
17. ART Investigators. Rationale, study design, and analysis plan of the Alveolar Recruitment for ARDS Trial (ART): study protocol for a randomized controlled trial. Trials 2012;13:153.
18. Australian and New Zealand Intensive Care Research Centre. A Multi-centre Trial of an Open Lung Strategy Including Permissive Hypercapnia, Alveolar Recruitment and Low Airway Pressure in Patients With Acute Respiratory Distress Syndrome (PHARLAP). Bethesda, MD: National Library of Medicine; 2000. Available online: http://clinicaltrials.gov/show/NCT01667146. Cited 20 June 2017.
19. Fan E, Del Sorbo L, Goligher EC, et al. An Official American Thoracic Society/European Society of Intensive Care Medicine/Society of Critical Care Medicine Clinical Practice Guideline: Mechanical Ventilation in Adult Patients with Acute Respiratory Distress Syndrome. Am J Respir Crit Care Med 2017;195:1253-63.
20. Neto AS, Barbas CS, Simonis FD, et al. Epidemiological characteristics, practice of ventilation, and clinical outcome in patients at risk of acute respiratory distress syndrome in intensive care units from 16 countries (PRoVENT): an international, multicentre, prospective study. Lancet Respir Med 2016;4:882-93.
21. Amato MB, Meade MO, Slutsky AS, et al. Driving pressure and survival in the acute respiratory distress syndrome. N Engl J Med 2015;372:747-55.
22. Serpa Neto A, Amato MB, Schultz MJ. Dissipated Energy is a Key Mediator of VILI: Rationale for Using Low Driving Pressures. In: Vincent JL. editor. Annual Update in Intensive Care and Emergency Medicine 2016. Cham, Switzerland: Springer International Publishing, 2016:311-21.
23. Loring SH, Malhotra A. Driving pressure and respiratory mechanics in ARDS. N Engl J Med 2015;372:776-7.
24. Bein T, Weber-Carstens S, Goldmann A, et al. Lower tidal volume strategy (approximately 3 mL/kg) combined with extracorporeal CO2 removal versus 'conventional' protective ventilation (6 mL/kg) in severe ARDS: the prospective randomized Xtravent-study. Intensive Care Med 2013;39:847-56
25. Neto AS, Hemmes SN, Barbas CS, et al. Association between driving pressure and development of postoperative pulmonary complications in patients undergoing mechanical ventilation for general anaesthesia: a meta-analysis of individual patient data. Lancet Respir Med 2016;4:272-80.
26. Kacmarek RM, Villar J, Sulemanji D, et al. Open Lung Approach for the Acute Respiratory Distress Syndrome: A Pilot, Randomized Controlled Trial. Crit Care Med 2016;44:32-42.
27. Li G, Malinchoc M, Cartin-Ceba R, et al. Eight-year trend of acute respiratory distress syndrome: a population-based study in Olmsted County, Minnesota. Am J Respir Crit Care Med 2011;183:59-66.
28. Determann RM, Royakkers A, Wolthuis EK, et al. Ventilation with lower tidal volumes as compared with conventional tidal volumes for patients without acute lung injury: a preventive randomized controlled trial. Crit Care 2010;14:R1.
29. Serpa Neto A, Cardoso SO, Manetta JA, et al. Association between use of lung-protective ventilation with lower tidal volumes and clinical outcomes among patients without acute respiratory distress syndrome: a meta-analysis. JAMA 2012;308:1651-9.
30. Serpa Neto A, Nagtzaam L, Schultz MJ. Ventilation with lower tidal volumes for critically ill patients without the acute respiratory distress syndrome: a systematic translational review and meta-analysis. Curr Opin Crit Care 2014;20:25-32.
31. Neto AS, Simonis FD, Barbas CS, et al. Lung-Protective Ventilation With Low Tidal Volumes and the Occurrence of Pulmonary Complications in Patients Without Acute Respiratory Distress Syndrome: A Systematic Review and Individual Patient Data Analysis. Crit Care Med 2015;43:2155-63.
32. Serpa Neto A, Simonis FD, Barbas CS, et al. Association between tidal volume size, duration of ventilation, and sedation needs in patients without acute respiratory distress syndrome: an individual patient data meta-analysis. Intensive Care Med 2014;40:950-7.

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