Adequate Tidal Volume Ventilation to Minimize Ventilator-Induced Lung Injury

The potentially injurious effect of positive pressure mechanical ventilation on the lungs of patients with ARDS has been broadly recognized for more than 25 years.[1] Recognizing that the application of high distending pressures to the injured lungs results in lung injury indistinguishable from that observed in patients with ARDS led to the widespread implementation of lung-protective ventilation strategies by using low tidal volumes (V_T).[2] However, applying lung-protective strategies to patients without ARDS has failed to consistently show a benefit in terms of reducing mortality.[3] The key underlying concept here is that high V_T does not induce ventilator-induced lung injury (VILI) per se, with the actual driver of VILI being the excessive lung stress and strain that a given V_T generates.[4] Driving pressure represents the distending pressure of the respiratory system with tidal ventilation and, therefore, is a surrogate of the effect of a given V_T on these determinants of VILI.[5] Driving pressure was shown to determine the effect of a low V_T ventilation strategy on mortality in subjects with ARDS,[6] and a driving pressure $<$ 15 cm H_2O is proposed as a target when setting the ventilator[5] (although this hypothesis has never been evaluated in a clinical trial). Previous studies failed to show an association between driving pressure and mortality in subjects without ARDS.[7,8]

In this issue of Respiratory Care, Roca et al[9] provide evidence that driving pressure is also associated with the risk of developing ARDS, which contributes to the growing literature that suggests that driving pressure is in the causal pathway of VILI. The investigators analyzed data from a multi-center prospective observational study on 1,575 subjects without ARDS who were receiving controlled mechanical ventilation.[9] They found that higher driving pressure in the first 2 days of mechanical ventilation was associated with an increased risk of developing ARDS in the subsequent days.[9] Importantly, their results were robust across several sensitivity analyses and by using bootstrap validation. Unlike other studies that explored the same question in which an association between driving pressure and mortality was not observed,[7,8] this is the first report in which subjects who progressed to ARDS actually had

See the Original Study on Page 1505

higher driving pressure versus those who did not progress to ARDS (mean $\pm$ SD driving pressure, 15 $\pm$ 5 cm H_2O vs 12 $\pm$ 5 cm H_2O).[9] The study by Roca et al[9] is important because it provides evidence that ARDS can be induced in non-injured lungs when injurious mechanical ventilation is applied. These findings have implications for clinical practice and for future research.

Prevention is better than cure. Until now, lung-protective ventilation is recommended for patients with established ARDS. The notion that ARDS can be generated de novo by injurious mechanical ventilation settings can shift the paradigm of lung-protective ventilation to prevention of VILI rather than focusing on mitigating the deleterious effects of positive-pressure ventilation in patients once lung injury is established. If elevated driving pressure causes VILI, then proactive measures to limit driving pressure could be implemented. Given that $>$ 95% of the patients who require mechanical ventilation do not have ARDS at the onset of respiratory support,[10] the potential benefit of a reduction in the risk of VILI in this population is substantial.

Importantly, the diagnosis of ARDS is often missed by clinicians.[11] The Berlin definition of ARDS[12] has moderate inter-observer reliability, and even experienced clinicians disagree with regard to the presence or absence of ARDS in a given patient.[13] Interestingly, mortality among patients in which there is consensus in the diagnosis of ARDS is similar to that when expert physicians disagree on ARDS diagnosis,[14] which suggests that the biology of ARDS is different than what the Berlin definition says ARDS is.[12] Failure to recognize the presence of ARDS could lead to the underutilization of inexpensive, readily available, and lifesaving lung-protective ventilation strategies. Adhering to a driving pressure-limited ventilation strategy in most patients who received mechanical ventilation could ensure that safe mechanical ventilation is delivered regardless of clinician recognition of ARDS,[12] which reduces the risk of iatrogenic complications.

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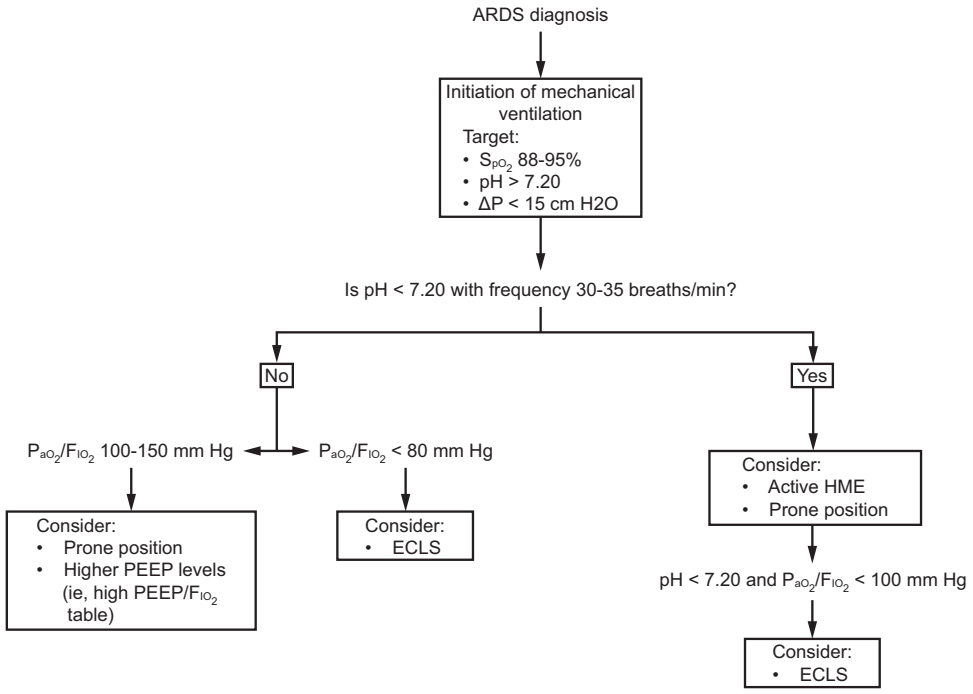

Fig. 1. A potential algorithm for the management of ARDS by incorporating driving pressure. HME = heat-and-moisture exchanger; ECLS = extracorporeal life support.

Moreover, driving pressure could be used not only as a target to provide safe mechanical ventilation but also as a trigger for escalation to rescue interventions in ARDS. Current recommendations suggest the use of oxygenation thresholds to guide the implementation of adjuvant strategies,[15] and the Berlin definition of ARDS does not incorporate any indicator of lung mechanics or of the effect of mechanical ventilation on lung stress and/or strain (respiratory system compliance was originally considered in the draft definition but was later removed from the final criteria because the consensus panel believed that adding this variable did not improve the predictive validity of the definition for mortality). However, a number of considerations support the hypothesis of using driving pressure as a trigger to consider escalation to more complex interventions aimed at enhancing lung protection. In trials that evaluated the effect of a low V_T and high PEEP strategy, reductions in driving pressure more accurately reflected the benefit of adopting this strategy compared with changes in P_{aO_2}/F_{IO_2}.[16] Similarly, in the ARMA trial,[17] which evaluated the effect of low versus high V_T ventilation in ARDS, oxygenation was worse in the low V_T arm throughout the first week, whereas mortality was significantly reduced.

In a secondary analysis of the largest trial that evaluated the effect of prone positioning in ARDS, gas exchange improvement after prone positioning was not associated with increased survival.[18] Finally, in a trial on venovenous extracorporeal membrane oxygenation (VV-ECMO) versus standard lung-protective ventilation strategies, the largest benefit of initiating therapy with VV-ECMO was observed in the subgroup of subjects who required VV-ECMO to facilitate lung-protective ventilation (an effect that was not observed in the subgroup of subjects with oxygenation-driven entry criteria).[19] In this same trial, only driving pressure, and not P_{aO_2}, was improved in the intervention arm, in which a benefit in mortality was observed. Taken together, these observations suggest that high stress and/or strain are the key factors that drive mortality in ARDS and strengthen the hypothesis that the goal of these rescue therapies is to enable lung-protective ventilation. A potential algorithm for the management of ARDS incorporating driving pressure is presented in Figure 1.

Finally, driving pressure could be used to guide enrollment in clinical trials that evaluate strategies to enhance lung-protective ventilation in ARDS. Critical care, unfortunately, has been plagued with underpowered studies that provided indeterminate results. One of the main challenges of conducting research in this field is that ARDS is a markedly heterogeneous entity.[20] This leads to grouping of diseases with potentially significant biologic and clinical differences that could, in turn, result in different responses to treatments. Grouping subjects based on their baseline susceptibility to benefit from a lung-protective strategy (instead of on their baseline risk of dying) could aid in reducing this heterogeneity.[21] Driving pressure provides a simple bedside measurement that could be used to select subjects who may accrue larger benefits from the

intervention, improving trial efficiency with a solid mechanistic rationale.

There are plenty of examples throughout the medical literature in which observational studies or post hoc analyses that used strong physiologic rationale showed promising results only to be later debunked by clinical trials that showed no effect or even harm.[22,23] Therefore, caution is generally advised when interpreting the results of observational studies in which causality cannot be confirmed. So, what are the potential downsides of putting driving pressure in the frontline of management and research in patients with respiratory failure? First, limiting tidal ventilation commonly hinders spontaneous ventilation. Although there is strong evidence that supports restricting V_T in the early stage of ARDS, there is a large knowledge gap with regard to how and, more importantly, when to allow patients to resume spontaneous breathing. On the one hand, the benefits on patient-centered outcomes of minimizing sedation and allowing patients to be awake and breathe spontaneously are clear.[24] On the other hand, results of a recent study suggest longitudinal exposure to elevated driving pressure up to 30 d is associated with an increased risk of death.[25] It is uncertain how these 2 seemingly contradictory pieces of evidence can be reconciled. Second, low pressure/volume ventilation could lead to hypoventilation. Although moderate respiratory acidosis is considered acceptable in patients with ARDS, the effects of permissive hypercapnia on patients without ARDS have not been described.

However, because using the driving pressure-limited approach will actually lead to variable V_T, depending on lung size, it is likely that patients without ARDS (and with theoretically more lung surface available for ventilation) will receive adequate alveolar ventilation. Importantly, these issues pertain to both the accepted standard therapy in ARDS, low V_T ventilation and a driving pressure-limited approach. If and by how much a driving pressure-limited ventilation strategy results in different alveolar ventilation than a V_T limited one is currently unknown. Finally, driving pressure reflects the distending pressure of the whole respiratory system. Patients with increased chest wall elastance may present elevated driving pressure while lung stress is still within safe limits. In cases in which clinicians suspect chest wall mechanics may be impaired, more precise monitoring of specific lung mechanics may be warranted.[26]

The diagnosis and management of patients with ARDS remains a major challenge for clinicians. Using driving pressure to guide ventilator settings can help avoid the need to distinguish between patients with injured and uninjured lungs, and simplify the management of patients who receive mechanical ventilation. Under this paradigm, the delivered V_T will depend on the actual area of the lungs available for ventilation, and tidal ventilation will remain in the physiologic range of lung stretch, minimizing the risk of inducing further lung injury.

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REFERENCES

1. Slutsky AS. Consensus Conference on Mechanical Ventilation —Jan 28–30, 1993 at Northbrook, Illinois, USA. Part I. European Society of Intensive Care Medicine, the ACCP and the SCCM. Intensive Care Med 1994;20(1):64-79.
2. Fan E, Del Sorbo L, Goligher EC, Hodgson CL, Munshi L, Walkey AJ, et al; American Thoracic Society, European Society of Intensive Care Medicine, and Society of Critical Care Medicine. 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(9):1253-1263.
3. Writing Group for the PReVENT Investigators; Simonis FD, Serpa Neto A, Binnekade JM, Braber A, Bruin KCM, et al. Effect of a low vs intermediate tidal volume strategy on ventilator-free days in intensive care unit patients without ARDS: a randomized clinical trial. JAMA 2018;320(18):1872-1880.
4. Gattinoni L, Protti A, Caironi P, Carlesso E. Ventilator-induced lung injury: the anatomical and physiological framework. Crit Care Med 2010;38(10 Suppl):S539-S548.
5. Amato MBP, Meade MO, Slutsky AS, Brochard L, Costa ELV, Schoenfeld DA, et al. Driving pressure and survival in the acute respiratory distress syndrome. N Engl J Med 2015;372(8):747-755.
6. Goligher EC, Costa ELV, Yarnell CJ, Brochard L, Stewart TE, Tomlinson G, et al. Effect of lowering Vt on mortality in acute respiratory distress syndrome varies with respiratory system elastance. Am J Respir Crit Care Med 2021;203(11):1378-1385.
7. Schmidt MFS, Amaral ACKB, Fan E, Rubenfeld GD. Driving pressure and hospital mortality in patients without ARDS a cohort study. Chest 2018;153(1):46-54.
8. Lanspa MJ, Peltan ID, Jacobs JR, Sorensen JS, Carpenter L, Ferraro JP, et al. Driving pressure is not associated with mortality in mechanically ventilated patients without ARDS. Crit Care 2019;23(1):424.
9. Roca O, Peñuelas O, Muriel A, García-de-Acilu M, Laborda C, Sacanell J, et al. Driving pressure is a risk factor for ARDS in

mechanically ventilated subjects without ARDS. Respir Care 2021;66 (10):1505-1513.
10. Adhikari NKJ, Fowler RA, Bhagwanjee S, Rubenfeld GD. Critical care and the global burden of critical illness in adults. Lancet 2010;376(9749):1339-1346.
11. Bellani G, Pham T, Laffey JG. Missed or delayed diagnosis of ARDS: a common and serious problem. Intensive Care Med 2020;46(6):1180-1183.
12. ARDS Definition Task Force; Ranieri VM, Rubenfeld GD, Thompson BT, Ferguson ND, Caldwell E, , et al. Acute respiratory distress syndrome: the Berlin Definition. JAMA 2012;307(23):2526-2533.
13. Sjoding MW, Hofer TP, Co I, Courey A, Cooke CR, Iwashyna TJ. Interobserver reliability of the Berlin ARDS definition and strategies to improve the reliability of ARDS diagnosis. Chest 2018;153(2):361-367.
14. Sjoding MW, Hofer TP, Co I, McSparron JI, Iwashyna TJ. Differences between patients in whom physicians agree and disagree about the diagnosis of acute respiratory distress syndrome. Ann Am Thorac Soc 2019;16(2):258-264.
15. Ferguson ND, Fan E, Camporota L, Antonelli M, Anzueto A, Beale R, et al. The Berlin definition of ARDS: an expanded rationale, justification, and supplementary material. Intensive Care Med 2012;38 (10):1573-1582.
16. Yehya N, Hodgson CL, Amato MBP, Richard J-C, Brochard LJ, Mercat A, Goligher EC. Response to ventilator adjustments for predicting acute respiratory distress syndrome mortality. Driving pressure versus oxygenation. Ann Am Thorac Soc 2021;18(5):857-864.
17. Acute Respiratory Distress Syndrome Network; Brower RG, Matthay MA, Morris A, Schoenfeld D, Thompson BT, Wheeler A. Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. N Eng J Med 2000;343(11):1301-1308.
18. Albert RK, Keniston A, Baboi L, Ayzac L, Guérin C, PROSEVA Investigators. Prone position–induced improvement in gas exchange does not predict improved survival in the acute respiratory distress syndrome. Am J Respir Crit Care Med 2014;189(4):494-496.
19. Combes A, Hajage D, Capellier G, Demoule A, Lavoué S, Guervilly C, et al; EOLIA Trial Group, REVA, and ECMONet. Extracorporeal membrane oxygenation for severe acute respiratory distress syndrome. N Engl J Med 2018;378(21):1965-1975.
20. Santhakumaran S, Gordon A, Prevost AT, O'Kane C, McAuley DF, Shankar-Hari M. Heterogeneity of treatment effect by baseline risk of mortality in critically ill patients: re-analysis of three recent sepsis and ARDS randomised controlled trials. Crit Care 2019;23(1):156.
21. Shankar-Hari M, Rubenfeld GD. The use of enrichment to reduce statistically indeterminate or negative trials in critical care. Anaesthesia 2017;72(5):560-565.
22. Roberts I, Yates D, Sandercock P, Farrel B, Wasserberg J, Lomas G, et al; CRASH trial collaborators. Effect of intravenous corticosteroids on death within 14 days in 10008 adults with clinically significant head injury (MRC CRASH trial): randomised placebo-controlled trial. Lancet 2004;364(9442):1321-1328.
23. Writing Group for the Alveolar Recruitment for Acute Respiratory Distress Syndrome Trial (ART) Investigators; Cavalcanti AB, Suzumura ÉA, Laranjeira LN, de Moraes Paisani D, Petri Damiani L, 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 (14):1335-1345.
24. Ely EW. The ABCDEF Bundle: science and philosophy of how ICU liberation serves patients and families. Crit Care Med 2017;45(2):321-330.
25. Urner M, Jüni P, Hansen B, Wettstein MS, Ferguson ND, Fan E. Time-varying intensity of mechanical ventilation and mortality in patients with acute respiratory failure: a registry-based, prospective cohort study. Lancet Respir Med 2020;8(9):905-913.
26. Diehl J-L, Talmor D. When could airway plateau pressure above 30 cmH_2O be acceptable in ARDS patients? Intensive Care Med 2021 [Online ahead of print].