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CHEST

The Severe ARDS Generating Evidence (SAGE) Study

A Call for Action in the Daily Clinical Practice

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More than two decades have elapsed since studies have demonstrated that mechanical ventilation with high tidal volume and plateau pressure increases mortality rates compared with a lower volume ventilation strategy in patients with ARDS. Decreasing an inappropriately high tidal volume in clinical practice was a "culmination of an era on research on the acute respiratory distress syndrome" that can lead to saving one of five ARDS patient lives.[1] In more recent years, the use of prone positioning[2] has shown an improvement in survival in patients with moderate-to-severe ARDS. Now, both protective low tidal volume ventilation in all patients with ARDS and prone positioning in patients with severe ARDS are strong recommendations in guidelines.[3] Despite these interventions demonstrating an encouraging benefit in survival in clinical trials, the ARDS mortality rate still remains high in real world clinical practice. The Large Observational Study to Understand the Global Impact of Severe Acute Respiratory Failure (LUNG SAFE), a multicenter worldwide prospective cohort study on the epidemiology of patients with ARDS in 2014, presented a concerning overall hospital mortality rate of 40%.[4] Two key factors were identified as potential targets to improve ARDS outcome: poor clinical recognition of ARDS at onset (ie, 34%) and low adherence to a lung protective, lower tidal-volume ventilation strategy (ie, less than two-thirds of patients with ARDS received ventilation with a tidal volume ≤8 mL/kg of predicted bodyweight, with plateau pressure measured only occasionally). In addition, the use of prone positioning was limited and underused (ie, only 16.3% of patients with severe ARDS).

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In this issue of *CHEST*, Qadir et al[5] provide another key piece of the puzzle to expand our knowledge in the treatment of patients with ARDS in the United States. The authors aimed at understanding whether treatment variability among 29 US academic and community-hospital centers impacted mortality rates in ARDS. They conducted a multicenter observational cohort study in 2,466 mechanically ventilated patients with moderate-to-severe ARDS (ie, Pa_{O_2}/F_{IO_2} ≤150 mm Hg) between October 2016 and April 2017 with 28-day in-hospital death serving as the primary end point. Furthermore, the authors explored the presence of between-centers variation in ventilator management and adjunctive measures application by testing whether these factors could explain the differences seen in mortality rates. The study found that hospital death is still a concern in ARDS, with a rate of 40.7%, and that both patient (ie, age and hepatic or malignant comorbidities) and illness severity factors (ie, baseline Pa_{O_2}/F_{IO_2} and Sequential Organ Failure Assessment score) were both independent predictors of death. Of note, mortality rates ranged from 16.7% to 73.3% across centers. The heterogeneity persisted after expressing mortality rates as standardized mortality ratios (0.33 to 1.98) (ie, adjusted for patient-level factors). Early adherence to lung protective ventilation (LPV), defined as a tidal volume <6.5 mL/kg predicted body weight, inspiratory pressure <30 cmH_2O, was limited (ie, 31.4%). LPV use varied widely across centers (0% to 65%), as did the implementation of adjunctive measures (27.1% to 96.4%). When the authors explored the role of early treatment level factors on standardized mortality ratios, they observed that the initial nonadherence to LPV was the only significant treatment factor that correlated strongly with the variation of standardized mortality ratios across the US centers.

The data reported by Qadir et al[5] describes outcome and ARDS treatment variability in the specific population of the United States. Low adherence to LPV was confirmed

in a secondary analysis of the LUNG SAFE study. Laffey et al[6] reported considerable room for improved compliance with LPV in the high-income countries outside Europe, which includes the United States. Furthermore, the overall use of prone positioning in the Severe ARDS Generating Evidence study (ie, 5.8%) was low and in line with a further focused LUNG SAFE analysis of patients with a similar severity (Pa_{O_2}/F_{IO_2} <150 mm Hg) of hypoxemia, which reported 6.9% use of prone positioning in the first 48 hours of ARDS, reaching 11.6% at 28-day follow-up. In this analysis, Duggal et al[7] suggested that attention to system-level barriers such as the ratio of nurses per beds or the number of physicians per beds are potential factors to take into consideration in the underutilization of these adjunctive measures. Again, similar findings of low adherence to LPV and underutilization of evidence-based adjunctive measures such as prone positioning have been demonstrated in Canadian practice.[8]

In the work by Qadir et al,[5] two other relevant points deserve mention. First, despite recommendations to use higher positive end-expiratory pressure levels in moderate-to-severe ARDS,[3] the applied positive end-expiratory pressure levels averaged only 9 cmH_2O. Furthermore, the missing information on plateau pressure in 50% of the sample indicates the lack of focus of monitoring this crucial element of LPV and on the derived driving pressure. Without these, we drastically reduce our ability to prevent ventilator-induced lung injury and our ability to control an independent risk factor for death in patients with ARDS.[9] This becomes even more relevant considering recent insights about a different response to the ventilatory strategy in ARDS according to lung morphologic evidence[10] and subphenotypes.[11]

In this study, we believe that Qadir et al[5] highlight two sides of the same coin with regards to clinical practice in ARDS. The bad side is that, despite two decades since it became known that LPV reduces mortality rates and more than a decade since it became known that prone position is beneficial in patients with severe ARDS, these treatment strategies are not yet part of a widespread standard of care. The inconsistent use of recommended interventions underlies, once more, the gap that exists between clinical trials and clinical practice[12]: the real dilemma between what we should do and what we actually do in our daily care of these critically ill patients with ARDS.

So, what's the good side of the coin? The data used by Qadir et al[5] demonstrate that we can improve the outcome of critically ill patients with ARDS markedly by adopting simple, safe, and unexpensive measures in our clinical practice. We should be thankful to the authors for increasing awareness to what we are missing and for providing some light on interventions we should aim to improve in our practice. Which in turn, highlights things we can do to improve the outcomes of critically ill patients with ARDS. These data represent an ethical call-to-action. In other words, what is the best way to overcome our deficiencies if not standing in front of them and acknowledging the correct path toward improvement?

References

1. Tobin MJ. Culmination of an era in research on the acute respiratory distress syndrome. *N Engl J Med*. 2000;342(18):1360-1361.
2. Guérin C, Reignier J, Richard JC, et al. Prone positioning in severe acute respiratory distress syndrome. *N Engl J Med*. 2013;368(23):2159-2168.
3. 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(9):1253-1263.
4. 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(8):788-800.
5. Qadir N, Bartz RR, Cooter ML, et al. Variation in early management practices in moderate-to-severe acute respiratory distress syndrome in the United States. *Chest*. 2021;160(4):1304-1315.
6. Laffey JG, Madotto F, Bellani G, et al. Geo-economic variations in epidemiology, patterns of care, and outcomes in patients with acute respiratory distress syndrome: insights from the LUNG SAFE prospective cohort study. *Lancet Respir Med*. 2017;5(8):627-638.
7. Duggal A, Rezoagli E, Pham T, et al. Patterns of use of adjunctive therapies in patients with early moderate to severe ARDS: insights from the LUNG SAFE study. *Chest*. 2020;157(6):1497-1505.
8. Duan EH, Adhikari NKJ, D'Aragon F, et al. Management of acute respiratory distress syndrome and refractory hypoxemia. a multicenter observational study. *Ann Am Thorac Soc*. 2017;14(12):1818-1826.
9. Amato MB, Meade MO, Slutsky AS, et al. Driving pressure and survival in the acute respiratory distress syndrome. *N Engl J Med*. 2015;372(8):747-755.
10. Constantin JM, Jabaudon M, Lefrant JY, et al. Personalised mechanical ventilation tailored to lung morphology versus low positive end-expiratory pressure for patients with acute respiratory distress syndrome in France (the LIVE study): a multicentre, single-blind, randomised controlled trial. *Lancet Respir Med*. 2019;7(10):870-880.
11. Calfee CS, Delucchi K, Parsons PE, et al. Subphenotypes in acute respiratory distress syndrome: latent class analysis of data from two randomised controlled trials. *Lancet Respir Med*. 2014;2(8):611-620.
12. Qadir N, Chen JT. Adjunctive therapies in ARDS: the disconnect between clinical trials and clinical practice. *Chest*. 2020;157(6):1405-1406.