Targeting Driving Pressure for the Management of ARDS…Isn't It Just Very Low Tidal Volume Ventilation?

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Acute respiratory distress syndrome (ARDS) remains a worldwide health concern, with a prevalence near 10.4% of all intensive care unit (ICU) admissions and mortality rates as high as 46% (1). Despite these statistics, clinicians still fail to recognize ARDS, and consequently, treatment with lung-protective ventilation to minimize ventilator-induced lung injury (VILI) remains underutilized (1–3). Although mechanical ventilation with low tidal volume (V_T) ventilation (LTVV) endures as the foundation of life-saving treatment for ARDS, decades of research has yielded few treatment alternatives (4). However, researchers continue to look for adjunctive or alternative treatments to reduce ARDS mortality.

In this issue of *AnnalsATS*, Pereira Romano and colleagues (pp. 596–604) present the results of a pilot multicenter randomized trial designed to determine the feasibility of a mechanical ventilation strategy that targets driving pressure (DP) as compared with conventional LTVV (5). Thirty-one patients with predominantly mild ARDS (6) and a qualifying starting DP = ⩾ = 13 and positive end-expiratory pressure (PEEP) = ⩾ = 10 were randomized between the conventional LTVV control and DP groups. A decrease in DP was achieved largely with reductions in V_T and a corresponding and expected increase in respiratory rate. Resulting differences in carbon dioxide tension (P_{CO_2}) and potential of hydrogen between the groups were noted, with a higher mean P_{CO_2} in the DP-limited group on Day 1 (59.5 vs. 49.1; $P = 0.04$) and Day 2 (59.8 vs. 49.8; $P = 0.03$), but the differences disappeared by Day 3. The authors present proof of concept that a DP ventilator management strategy can lower V_T below 6 cc/kg of ideal body weight, and that such values are physiologically tolerated in the management of mild-to-moderate ARDS. The authors executed elegant study procedures that required daily administration of sedation or neuromuscular blockade for accurate measurements of plateau pressure. However, the labor-intensive nature of the study protocol raises concerns about the practicality of such an approach in routine clinical care.

Although Pereira Romano and colleagues present intriguing results, several details likely need to be refined before a large multicenter comparative trial can be successfully executed. First, the heterogeneous nature of ARDS and inherent limitations of the mechanical ventilator render the continuous measurement of DP difficult. Second, spontaneous respiratory efforts alter DP and make it challenging to achieve accurate titration. Third, the clinical implications of daily administration of neuromuscular blockade and sedating medications for DP measurement may be significant and should not be overlooked. Finally, the utility of this protocol for managing patients with severe ARDS, the population most likely to gain benefit from the intervention, remains unknown. Many ICUs lack the considerable collective expertise of these investigators, and may encounter significant obstacles when trying to institute intensive ventilator management protocols in the context of a multicenter randomized controlled trial.

The potential value of DP in the management of patients with ARDS has been discussed since 1998 (7). Given the heterogeneous nature of ARDS and the concept of optimally ventilating only recruitable lung units, clinicians agree that efforts to minimize VILI rely on reducing V_T, limiting plateau pressure, and titrating PEEP (7, 8). DP provides a more accurate picture of optimal lung mechanics in ARDS by estimating V_T corrected for respiratory compliance in the diseased state rather than on the basis of ideal body weight alone. Many studies have reported an association between DP and mortality in ARDS (9, 10), and a secondary retrospective analysis of randomized controlled trials identified DP as the ventilator parameter most closely associated with mortality (11). It is not surprising that in a retrospective analysis the sickest patients with the lowest compliance would have the highest DP and mortality. The assumption that lung compliance remains constant and that a single, daily DP measurement would accurately predict DP throughout the next 24 hours is suspect. Furthermore, inaccuracies in ventilator pressure measurements, and the role of spontaneous breathing efforts in the management of ARDS contribute to the clinical uncertainty about how to optimally calculate and titrate DP at the bedside (12, 13).

During pressure-regulated volume control, adaptive pressure control, synchronized intermittent mandatory ventilation, and pressure support ventilation, spontaneous respiratory efforts will alter the true DP and result in breaths that may not match the DP titration goal. During spontaneous respiratory efforts, the

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pleural pressure decreases, leading to an increase in transpulmonary pressure and increased distending pressure of the alveoli. Therefore, a single, daily DP calculated during an inspiratory hold while the patient is sedated and/or paralyzed, as was done by Pereira Romano and colleagues, will likely underestimate the true distending pressure triggered by spontaneous efforts (14). Furthermore, the effects of DP on clinical outcomes in the background of spontaneous efforts remain unclear. After a DP-directed reduction in V_T, the respiratory rate increases to maintain minute ventilation (as also noted by Pereira Romano and colleagues), which may increase cyclic stretch. There is a strong correlation between cyclic lung stretch during mechanical ventilation and VILI, DP, and mortality in patients with ARDS (11). Increased respiratory rates are also associated with worse outcomes in patients with ARDS, so minimizing DP in exchange for an increase in respiratory rate may not be a clinically desirable trade-off. Although the DP target strategy was physiologically tolerated in this study, the clinical benefits of such an outcome remain elusive.

Several of the patients enrolled in Pereira Romano and colleagues' study were ventilated with pressure support, and all patients were given medications during the study protocol to ensure passive mechanical ventilation and facilitate accurate DP measurements. This rigorous type of study protocol is essential for proof of concept, but daily administration of neuromuscular blockade or deep sedation with the purpose of titrating mechanical ventilation may have unfavorable consequences (15, 16). Continuous neuromuscular blockade in the treatment of patients with ARDS does not provide a mortality benefit and may have associated harms (17). The small size of the study population and the enrollment of patients with largely mild-to-moderate ARDS also raise concerns about the physiologic tolerance of such a strategy in patients with severe ARDS.

Although Pereira Romano and colleagues should be commended for their efforts in demonstrating that a DP ventilator strategy is feasible for the management of mild-to-moderate ARDS, replication of their results in patients with severe ARDS and a clear study protocol that addresses the above issues seem to be the next steps in designing a prospective study to test a mortality benefit. Several unanswered questions remain about the practicality and clinical implications of a DP-targeted ventilator strategy. The authors' results provide important insights into the design of future clinical trials and suggest the importance of detailed protocols with a clear direction in managing cointerventions such as sedation and neuromuscular blockade. The authors used daily DP measurements to set V_T; however, a strategy that merely reduces V_T to target $\leqslant$4 cc/kg of predicted ideal body weight and maximizes PEEP might be more practical. Amid the paucity of clear evidence in support of the routine clinical use of DP, it would seem that Pereira Romano and colleagues have provided a foundation for further investigations into alternative ventilator strategies to determine whether a very low V_T is superior to standard LTVV in the treatment of moderate-to-severe ARDS. ■

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

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