Underuse Versus Equipoise for Low Tidal Volume Ventilation in Acute Respiratory Distress Syndrome: Is This the Right Question?*

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Few interventions have proven effective in the management of patients with acute respiratory distress syndrome (ARDS). Most patients with ARDS require supportive care with mechanical ventilation, and a growing body of research has demonstrated that ventilator-induced lung injury (VILI) is an important contributor to the development of multiple organ failure and death. Indeed, a landmark clinical trial (Acute Respiratory Management in ARDS) from the ARDS Network found a nearly 9% absolute risk reduction in short-term mortality among patients randomized to the low tidal volume (or lung protective) ventilation (LV_T) strategy, with limited plateau pressures (P_{plat}) and tidal volumes (V_T), designed to mitigate VILI (1).

Despite the publication and dissemination of these results, LV_T ventilatory strategies have not been universally applied in patients with ARDS. In this issue of *Critical Care Medicine*, Jaswal et al (2) report their investigation of V_T and P_{plat} practices among studies of patients with acute lung injury (ALI) through a systematic literature review since the publication of the ARMA trial. Twenty-two randomized controlled trials (RCTs) and 71 nonrandomized studies were included in their analysis. The first striking result is how mean V_T has decreased compared with the end of the preceding century. In 1998, the mean V_T used in the first week of ARDS and reported in an international observational study was 8.8 mL/kg measured (not predicted) body weight, and there was great variability in these tidal volumes (SD, 2.0) (3). Mean routine V_T is now consistently below 7 mL/kg predicted body weight (PBW) (not actual) with much smaller variability, which is an extraordinarily large and important change. This mean V_T (6.81 mL/kg PBW; 95% CI, 6.45–7.18) was unchanged over time in ARDS Network centers ($p = 0.75$) but decreased significantly over time in non-ARDS Network centers (6.77 mL/kg PBW; 95% CI, 6.22–7.32; $p = 0.001$). The authors note that all the estimates of routine V_T were significantly greater than 6 mL/kg PBW ($p \leq 0.02$). RCTs that reported the use of a LV_T protocol had significantly lower routine V_T postrandomization ($p \leq 0.01$). Finally, P_{plat} was significantly less than 30 cm H_2O ($p \leq 0.02$) in the 59 studies with routine P_{plat} measurements. The authors conclude that V_T less than or equal to 6 mL/kg PBW may not have been as attainable or important as P_{plat} less than or equal to 30 cm H_2O, and there may be equipoise for the use of V_T less than or equal to 6 mL/kg PBW by clinicians managing patients with ALI. Although these data report a mean V_T (slightly) higher than 6 mL/kg PBW, the reason for this is unclear. Interestingly, in some of the studies mentioned, the actual V_T set by clinicians was lower than what was directed by the protocol. For instance, in a RCT evaluating neuromuscular blockade (4), the set V_T was around 6.5 mL/kg PBW, whereas the study protocol proposed 6–8 mL/kg PBW, suggesting that clinicians preferred to set V_T in the lowest range on average.

Evidence-based therapies are often incompletely translated into clinical practice (5), and when they are, may come after a significant delay (6). A number of studies have demonstrated limited implementation of, and adherence to, LV_T strategies in patients with ARDS (7, 8). Barriers, real or perceived, may limit the use of LV_T ventilation in patients with ARDS in many practice settings (9). Jaswal et al (2) focus on a number of alternative explanations for discrepancy between the available evidence and clinical practice. First, they argue that clinicians may adjust V_T based on airway pressures and may be less concerned with lower V_T when P_{plat} is less than or equal to 30 cm H_2O. Second, they argue that concerns regarding the design and interpretation of the ARDS Network trial may have contributed to the limited adoption of the LV_T protocol. Finally, they posit that the widely advocated goal of V_T 6 mL/kg PBW may not be achievable in many patients with ARDS.

Equipoise for the use of LV_T is only one of many possible explanations for the apparent underuse of LV_T strategies in patients with ARDS. The putative benefits of LV_T have been consistently demonstrated in a number of additional studies and in different populations, and equipoise arising from uncertainty regarding the efficacy of LV_T seems unlikely. A recent meta-analysis (four trials, 1,149 patients) revealed a significant reduction in hospital mortality (odds ratio, 0.75; 95% CI, 0.58–0.96) with the use of a LV_T strategy in patients with ARDS (10). A post hoc analysis of the ARDS Network ARMA trial demonstrated that there is no level of P_{plat} at which lower V_T was not advantageous (11). Data

*See also p. 2278.

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from a large, prospective multisite study reported a significant association between the use of LV_T and 2-year mortality (12). Furthermore, V_T and 2-year mortality exhibited a dose-response relationship, with lower V_T (even < 6 mL/kg PBW) associated with lower mortality. Finally, the benefits of LV_T may extend to patients at risk for ARDS, resulting in a significant reduction in subsequent development of pulmonary complications (including ARDS), as well as short-term mortality (13).

Greater attention might be focused on how to make the "… widely advocated goal of V_T 6 mL/kg PBW …" more attainable in routine practice. As Jaswal et al (2) suggest, studies using qualitative methods (e.g., surveys and focus groups) may be required to elucidate the barriers and facilitators for the use of a LV_T strategy. The implementation and prescription of a LV_T protocol (7) or the development of formal evidence-based guidelines may further enhance the delivery of lung protective ventilation. Participating in clinical trials may also help clinicians to change their practice (14). It should be clearly noted that the development and implementation of clinical protocol and guidelines supporting the use of a LV_T strategy represents a starting point and not the final word in a "one size fits all" approach to ventilatory support in patients with ARDS. For instance, in patients with more severe ARDS, V_T set at 6 mL/kg PBW may still induce important tidal stress and strain, leading to VILI and adverse outcomes (15). A number of proof-of-concept studies have suggested the potential benefits of lowering V_T below 6 mL/kg PBW using extracorporeal CO_2 removal on surrogate outcomes (16, 17). Individualized titration of mechanical ventilation, taking into account the patient's physiological measurements (e.g., transpulmonary pressure and calculation of stress, chest wall compliance, lung volume, and calculation of strain) may yield a more rational (and safer) choice of ventilatory variables, including V_T and P_{plat}. In addition, the feasibility of the routine use of LV_T needs to be better assessed by recording physiological signals. This may help to sort out whether clinical difficulties are real or perceived, and if real, whether they depend on the way the ventilator is set (e.g., mode, inspiratory time, peak flow, synchronization, oxygenation) or on the patient's characteristics. The benefits observed with neuromuscular blockers in ARDS strongly suggest that we do not capture the reality of patient-ventilator interaction (4). We need more physiological studies and a better monitoring for individual decisions. Otherwise, we may continue to propose RCTs which, at best, will test one option versus another (or two others) and then argue about all other options that were not tested. Until better monitoring becomes routine, and clinical protocols incorporating their use are evaluated in clinical trials, targeting lower V_T (i.e., 6 mL/kg PBW) remains an important therapeutic goal in patients with ARDS.

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