The Dethroning of 6 ml/kg as the “Go-To” Setting in Acute Respiratory Distress Syndrome

To the Editor:

In the latest of a succession of reanalyses of data from five randomized controlled trials (RCTs) of high versus low Vt in patients with acute respiratory distress syndrome, Goligher and colleagues conclude that clinicians should select Vt on the basis of distending pressure (plateau pressure minus positive end-expiratory pressure [PEEP]) rather than milliliter per kilogram (1). This is the same conclusion I reached when I editorialized on the publication of the ARDSNet RCT in 2000 (2). I recommended that Vt should be set to avoid the plateau pressure that discriminated between life and death (32 cm H2O).

I pointed out that setting Vt in terms of milliliters per kilogram was misguided because it ignores the physiological variable (plateau pressure) that signals alveolar injury. I proffered the analogy of a patient with hypertension-associated stroke for which antihypertensive therapy is based solely on milligram dosage with disregard to changes in arterial pressure. The passage of time demonstrates that my writing was unpersuasive, and I apologize to patients for having failed them.

After the publication of the ARDSNet report, guidelines promoted the use of 6 ml/kg, although 6 ml/kg has never been shown to be superior to 11 ml/kg (or anything in between). Guidelines now recommend 4 ml/kg (3), which translates to an unnatural Vt of 280 ml for an average person.

In patients who are critically ill with inflamed lungs, sensory receptor stimulation produces heightened respiratory drive and dyspnea. Patients react by attempting deeper inspirations. When a low Vt setting impedes this response, intense dyspnea is guaranteed through corollary discharge from the medulla to the cerebral cortex—amplified by hypercapnia that accompanies hypoventilation (4).

Patients rebel against the racking constraint and buck the ventilator. To combat recalcitrance, pharmacological agents are administered to restrain patients on the Procrustean bed of 6 ml/kg. Sedative agents do not relieve air hunger, and neuromuscular blockade aggravates dyspnea by removing behavioral clues that alert caregivers to patient discomfort (4). For those of us caring for ventilated patients over the past four decades, it is disturbing to observe large doses of sedatives and paralyzing agents being administered nonchalantly—undoing the great strides in the 1980s–1990s to limit their use. It contravenes every physiological principle to employ unnaturally low Vts in patients with plateau pressures in the low 20s.

Cleaving to a physiological framework, Vt should be customized in terms of end-inspiratory alveolar volume. It has been known for decades that airway pressure after an end-inspiratory pause during control mechanical ventilation with a flow square wave provides a reasonable estimate of end-inspiratory alveolar volume (5).

Despite the temptation, it would be foolhardy to undertake an RCT based on one numerical pressure target (whether plateau pressure or plateau minus PEEP). Unlike the exactitude with which arterial oxygen tension can be measured with a Clark electrode, instrumentation for measuring respiratory pressure has lower fidelity (6). Technical limitations combined with biological variation in the elastic properties of the lungs and chest wall exceed the concreteness of one single number.

Several of Dr. Goligher’s coauthors are also authors on the recent guidelines (3). It would be beneficial to patients if they published a codicil advising physicians to no longer base Vt on the nonphysiological target of 6 ml/kg.

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**From the Authors:**

We thank Professor Tobin for his thoughtful letter regarding our findings. We share his concern that the application of a low VT in patients with acute respiratory distress syndrome (ARDS) with low respiratory system elastance may sometimes result in an unnecessary risk of dyspnea, respiratory distress, patient–ventilator dyssynchrony, and needless use of sedation and neuromuscular blockade, although this has not been consistently demonstrated (1).

Dr. Tobin suggests that VT should be titrated according to a plateau pressure limit of 32 cm H2O, rather than according to driving pressure (ΔP). Although plateau pressure is an important parameter to monitor, we argue that there are several reasons to prioritize ΔP over plateau pressure. First, experimental studies have demonstrated that the magnitude of injury is more closely linked to the magnitude of dynamic (tidal) strain than the peak static strain (2, 3). Second, owing to variability in chest wall mechanics (e.g., rightward shift of the chest wall pressure–volume curve common in ARDS and obesity), absolute values of airway pressure may be unreliable measures of alveolar distention (4). For example, a patient with morbid obesity may have an airway plateau pressure well above 32 cm H2O without risk of alveolar hyperdistention because of high pleural pressure (5), provided ΔP is kept sufficiently low. On the other hand, some patients with a small “baby lung” volume exhibit substantial alveolar hyperdistention even when plateau pressure is kept below 30 cm H2O (6). The relation between ΔP and dynamic lung stress is relatively unaffected by a rightward shift in chest wall pressure–volume curve. Third, most of the trials included in the analysis (including the largest) targeted a plateau airway pressure of 30 cm H2O or less in the intervention arm, and yet we found substantial heterogeneity of treatment effect related to elastance (7). Attending only to plateau pressure while ignoring ΔP may therefore fail to adequately protect the lung and increase mortality.

To further substantiate our position, we present additional analysis of the comparative associations of ΔP and plateau pressure with mortality in ARDS (Figure 1). This analysis was performed in the same data set used for a previously published report examining ΔP and mortality in ARDS (8), updated to include ART (the Alveolar Recruitment Trial) (n = 4,090) (9). A plateau pressure ≥30 cm H2O was associated with a higher risk of mortality, but only in patients in whom ΔP was >15 cm H2O (relative risk, 1.47; 95% confidence interval [CI], 1.27–1.70). In patients in whom ΔP was <15 cm H2O, a plateau pressure ≥30 cm H2O was not associated with a higher risk of death (relative risk, 1.09; 95% CI, 0.90–1.33; P = 0.015 for interaction). Very similar results were obtained when using a plateau pressure threshold of 32 cm H2O. Note that the use of a ΔP threshold of 15 cm H2O for this analysis is not intended to imply that this is the definitively confirmed safe limit for ΔP, although we found that lowering VT was unlikely to improve mortality when ΔP is <15 cm H2O (7).

Although we are unaware of a process for issuing a codicil to a published guideline, we believe that these findings should be considered in future guidelines for management of mechanical ventilation in ARDS. For the present, we believe it would be prudent for clinicians to incorporate limitation of ΔP in the ventilatory strategy for patients with ARDS.

Figure 1. Association between Pplat and mortality varies according to ΔP. Error bars represent 95% confidence intervals. The association between Pplat and mortality varied according to ΔP; higher Pplat was associated with a substantially increased risk of death only when ΔP was increased (P = 0.015 for interaction). Data are adjusted for age, APACHE/SAPS risk, arterial pH, P/F ratio, and study trial. APACHE = Acute Physiology and Chronic Health Evaluation; P/F ratio = PaO2/FiO2; ΔP = driving pressure; Pplat = plateau pressure; SAPS = Simplified Acute Physiology Score.

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

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