Low Tidal Volumes for All?

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CLINICIANS ARE CONTINUALLY STRIVING TO IMPROVE the quality of care in medicine. In the intensive care unit (ICU) environment, the focus on quality has been on avoidance of iatrogenic complications. Mechanical ventilation provides a specific example; treatment goals have changed remarkably in the last 20 years—from maintaining "normal" blood gas values to supporting acceptable gas exchange while avoiding or minimizing ventilator-induced lung injury.[1] Previously, ventilator-induced lung injury was only recognized when overt barotrauma such as pneumothorax occurred. Today, however, a more insidious form of ventilator-induced lung injury is recognized, one that arises through cyclic alveolar overdistension (*volutrauma*) and other mechanisms and can produce local and systemic inflammatory reactions leading to multiorgan failure and death.[2] The National Heart, Lung, and Blood Institute Acute Respiratory Distress Syndrome Network clinical trial demonstrated that the use of low tidal volumes in patients with established acute respiratory distress syndrome (ARDS) results in a considerable reduction in mortality.[3] Until now, the focus of lung-protective ventilation has remained on treatment of ARDS.

In this issue of *JAMA*, the study by Serpa Neto and colleagues[4] helps shift thinking from treatment to prevention and raises the question of whether all patients receiving mechanical ventilation should receive low tidal volumes around 6 mL/kg predicted body weight. Several factors favor this proposition. First, there is a strong preclinical database supporting the concept of tidal volume limitation to prevent volutrauma. In animal experiments, the only insult required to produce severe clinical lung injury and diffuse alveolar damage on pathological examination is a relatively short exposure to positive-pressure mechanical ventilation with very large tidal volumes.[5]

Second, extrapolating data from human trials of lung-protective ventilation that show reduced mortality in patients with lung injury (including what is now referred to as mild ARDS[6]) suggests that this approach may be beneficial in a broader population. The combination of the large mortality benefit in the ARDS Network low tidal volume trial,[3] along with the low specificity of the ARDS definition used,[7] supports this notion because it is likely that substantial numbers of patients without diffuse alveolar damage were included in this trial.

A third argument supporting the use of lower tidal volumes in all patients receiving ventilation is that mild ARDS is often unrecognized by clinicians, and life-saving protective ventilation is often not used.[7,8] Applying lung-protective ventilation broadly would reduce the chances of missing patients with mild ARDS.[9]

Fourth, direct data from patients support using lower tidal volumes across a broad range of reasons for mechanical ventilation; it is here that the meta-analysis by Serpa Neto and colleagues contributes.[4] These authors synthesized data from 20 studies involving almost 3000 patients and found large risk ratios (RRs) favoring lower tidal volumes in terms of lung injury development (RR, 0.33; 95% CI, 0.23-0.47), pulmonary infection (RR, 0.45; 95% CI, 0.22-0.92), and mortality (RR, 0.64; 95% CI, 0.46-0.89).

Although these data seem compelling, several factors must be considered in their interpretation. A total of 15 randomized controlled trials were combined with 5 observational studies, but the observational studies (in which inferences of causality may be problematic) account for approximately 85% of both the total number of patients and events in the primary analysis of lung injury prevention. Furthermore, the randomized trials had limitations related to quality, with some trials lacking allocation concealment and many not following an intention-to-treat analysis. In addition, many trials focused on short-term intraoperative ventilation under anesthesia, and these may not be generalizable to other clinical situations. As the authors acknowledge, their findings are not definitive but rather are hypothesis generating and support the need to conduct large randomized trials.

Why should intensive care physicians not simply move immediately to implement low tidal volume ventilation for all patients receiving mechanical ventilation? The medical literature has many examples in which physiological rationale, meta-analyses of small or low-quality studies, or both

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suggested benefit followed by large trials that refuted these findings or even showed harm, such as steroids for traumatic brain injury.[10] More specific to the question at hand, clinicians must be aware of the potential unintended consequences of widespread use of a particular mechanical ventilation strategy. In contrast to the operating room setting, ventilation is often less "controlled" in the ICU. Increasingly, patients receiving ventilation are awake and mobilizing throughout their ICU stay, rendering mandatory low tidal volume ventilation challenging.[11-13]

Although physicians may choose to set higher or lower levels of inspiratory support with resultant tidal volumes, a number of ventilator modes allow patients to "trump" these settings and take larger breaths through their own respiratory muscular efforts. For this reason, it may be difficult to control tidal volumes in the common situation in which patients are receiving pressure support ventilation, allowing them some control over tidal volumes and inspiratory flow rates. Randomized trials of lung protective ventilation in ARDS have typically allowed pressure support ventilation without restriction of tidal volumes during weaning when settings were not excessive (eg, pressure support of ≤10 cm of water with an inspired oxygen fraction of ≤0.4 and positive end-expiratory pressure of ≤10 cm of water).[14] Whether larger tidal volumes generated predominantly with negative pressure through the patient's own respiratory muscle efforts are equally injurious to the same size volumes delivered with positive pressure is unclear.

Clinicians debate the merits of lowering tidal volumes vs minimizing sedation in spontaneously breathing patients even when those patients have moderate to severe ARDS.[15] Mandating lower tidal volumes as a quality marker for all ICU patients at this point may lead to more use of sedation and even paralysis with potential subsequent increases in ICU-acquired delirium, weakness, ventilator-induced diaphragm dysfunction, and duration of ventilation. These "costs" could be acceptable if avoiding high tidal volumes really is associated with decreased rates of lung injury and mortality, but this definitive information is currently lacking.

The meta-analysis by Serpa Neto and colleagues serves as a convincing summary that the current knowledge base about low trial volume ventilation is inadequate. In addition to confirming or refuting the benefit of setting lower vs higher tidal volumes in patients without ARDS, additional trials could address the degree of tidal volume limitation required, the patient populations that may benefit most, and whether to actively seek to limit tidal volumes in spontaneously breathing patients or simply avoid setting higher volumes. The role of intraoperative lung-protective ventilation also needs further study. Given the number of ICU patients receiving mechanical ventilation for whom this question applies (ie, the 95% of patients who do not have ARDS at the time of intubation),[16] such trials would have significant clinical importance and would be highly feasible. Until the results of these or other studies are available, however, the existing data suggest that in the ICU the ventilator should be set to a target tidal volume of 6 to 8 mL/kg in most patients receiving mechanical ventilation. When a patient's spontaneous efforts result in larger tidal volumes, actively controlling tidal volumes through sedation with or without paralysis should be considered in patients with moderate to severe ARDS, but more data are needed before extending this practice to the majority of patients receiving ventilation without ARDS.

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