Editorial Commentary

The tidal volume fix?

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Prior to publication of the ARDSNet trial of tidal volumes (VT) (1), traditional mechanical ventilation often employed VT of 10–15 mL/kg of unadjusted body weight. While these volumes had long been noted to exceed those of healthy subjects [who usually breathe at 6–8 mL/kg of predicted body weight (PBW)], they were considered necessary for intubated and mechanically ventilated patients to prevent progressive atelectasis, avoid dyspnea and maintain appropriate ventilation. A frequent consequence of using larger VT was the application of abnormally high airway pressures and alveolar forces, especially in patients with acute lung injury, a condition in which the functioning lung is small and both lung collapse and edema are prevalent. Elevated airway pressures potentially incur damaging stretch in those lung units that remain aerated. Animal studies that employ large VT associated with high airway pressures reveal regional disruption of the blood-gas interface, together with inflammation, atelectasis, and hypoxemia, especially in pre-injured lungs. Lung damage secondary to large VT [ventilator-induced lung injury (VILI)] has also been linked experimentally to injury of remote organs (1-3).

The National Institutes of Health (NIH)-sponsored ARDSNet study that compared 6 to 12 mL/kg of PBW (ARMA trial) convincingly demonstrated that the use of relatively low VT in patients with diverse forms and severities of Acute Lung Injury and Acute Respiratory Distress Syndrome (ARDS) may reduce mortality, presumably by reducing injurious lung stretch and systemic release of inflammatory mediators or toxins (1). It should be noted, however, that this presumed causal link between ventilator settings and outcome has never been proven. Nonetheless, the bulk of clinical data now available do support the use of lower VT and de-emphasize prioritizing normal $PaCO_2$ and pH. In fact, it has been reported that using lower VT confers benefit even when the plateau and driving pressures are relatively low. However, this latter contention is still hotly debated. Reported benefit from lower VT apparently extends to patients making spontaneous breathing efforts as well. Taken together, such observations have encouraged important revision of the ventilation support paradigm. 'Low tidal volume ventilation', often paired with adjustments of PEEP and frequency, has been labelled as 'lung protective' and extended to become a standard in the management of patients with various forms of hypoxemic respiratory failure, and even to those without lung disease or dysfunction (4,5).

Following the seminal ARMA trial of low VT in ARDS, another randomized controlled trial reported reduced development of ARDS in intensive care unit (ICU) patients allocated to low VT ventilation (1,6). However, the implications of these findings that implied prophylaxis were limited by small study size and early termination of data collection, possibly leading to overestimation of benefit associated with using low VT. Nonetheless, subsequent data analyses supported the benefit of using lower VT in patients without a diagnosis of ARDS (7). Large meta-analytic studies and individual patient analyses of mechanically ventilated ICU patients without ARDS provided evidence for a protective effect of low VT with

respect to development of ARDS and/or pneumonia. Further, a dose-response relationship between VT size and development of pulmonary complications was suggested (4-6). Beyond reduction in pulmonary complications, this data evaluation suggested greater numbers of ICU-free and hospital-free days as well as reduced all-cause mortality risk. The use of lower VT has also been investigated in the operating room, where randomized trials have associated lower intraoperative VT with reduced occurrence of postoperative pulmonary complications, including ARDS. A plausible mechanism (if any) for such purported benefit from preventing short-term exposure to larger VT has not yet been elucidated. The airway pressures employed in these studies were well below those in the ARDS Network trials that reported benefit from using lower VT and dramatically lower than those producing experimental harm in previously healthy lungs. A sharp pressure threshold that mandates VT adjustment in patients without ARDS has not been identified, and it remains unlikely that similar numerical limits and guidelines for ventilator settings would apply both in patients with and without ARDS.

Several explanations for the benefits of ventilating with low VT have been proposed. Ventilation with low VT in the appropriate setting, such as acute lung injury/ARDS could reduce or prevent injurious mechanical lung stress and strain because it limits alveolar over distention, driving pressure and inflation energy input (8,9). Several studies demonstrate that avoidance of VT that produce damaging pressures reduces adverse effects in animals without injured lungs. Additional findings from recent retrospective work suggest that to be effective, protective low VT ventilation should be used early in the course of patient management, presumably because deleterious effects depend, in part, on the duration of ventilatory support. Furthermore, key mechanical characteristics of injured tissue, such as tidal recruitability and tendency for re-collapse, fade over time. Except in very obese patients or those with abdominal hypertension, the levels of positive end expiratory pressure (PEEP) used in patients without ARDS typically are low (~6 cm/H_2O), whatever the VT under study. The role of PEEP titration in patients without ARDS who receive low VT remains unclear. Because peak airway pressure increases with rising VT, it may not be easy to distinguish the effects of reducing VT itself from those of reducing the associated alveolar (plateau airway pressure).

In theory, using low VT could increase dyspnea and prompt deeper analgesia or sedation (6). However, a consistent pattern of increased sedative use has not been reported in managing patients with or without ARDS receiving low VT. Furthermore, it has been argued that the use of higher respiratory rates to compensate for lower VT delivers equivalent mechanical power with lung-injuring potential or causes respiratory muscle fatigue in those who maintain spontaneous efforts. If true, those factors could offset the benefits of ventilation with lower VT, particularly in patients without ARDS. Importantly, the patient without ARDS is not at comparable risk for ventilator-associated lung injury. Ultimately, we have lacked convincing and confirmatory RCTs that compare low VT with more traditional VT in patients without hypoxemic respiratory failure.

While clear statistical differences has been reported between the use of low and high VT with respect to pulmonary complications, published differences associated with low and intermediate VT strategies have not achieved statistical significance. One reasonable conclusion might be that there is no consistent additional benefit from reducing VT below the intermediate range (7–10 mL/kg PBW). Another possibility is that the number of patients in these trials has been too small to confer sufficient statistical power to effectively test this question. Finally, data regarding intermediate VT has come primarily from observational studies, as compared to the more rigorous study designs directed toward low versus high VT (4-6).

Treatments used in current practice that potentially contribute to outcomes associated with ventilation were identified in the recently published LUNG SAFE survey (10). This international study was undertaken in 459 intensive care units (ICUs) in 50 countries on five continents. In addition to documenting the epidemiology, LUNG SAFE was intended to examine factors associated with outcomes in patients with ARDS diagnosed in the era following the 2012 release of the Berlin Definition. Of particular interest were modifiable risk factors. A comparable dataset is not available in patients without ARDS who received VT of various amplitudes. Nonetheless, certain results are worthy of comment.

Retrospective data were stratified according to ARDS severity, according to the Berlin criteria: mild (PaO_2/FiO_2 ratio 201–300 mmHg), moderate (PaO_2/FiO_2 ratio 101–200 mmHg), and severe (PaO_2/FiO_2 ratio ≤100 mmHg). ICU and hospital survival were evaluated. ARDS was further categorized regarding presumed cause of ARDS: pulmonary (pneumonia or aspiration) or extrapulmonary (sepsis, burn, blood transfusion, etc.). Driving pressure (defined as plateau pressure minus PEEP) was examined in patients with no evidence of spontaneous ventilation.

In each category of ARDS severity, risk associations at the onset of ARDS were examined for ICU and hospital mortality according to VT employed, PEEP level provided, driving pressure, and plateau pressure.

As expected, these investigators confirmed that older patient age, neoplastic disease, severity of illness markers (such as lower pH, lower PaO_2/FiO_2 ratio), and higher non-pulmonary organ failure scores were associated with worse patient outcomes. Modifiable factors associated with increased hospital mortality included lower PEEP, increased respiratory rate, and higher peak inspiratory, plateau, and driving pressures.

That using higher PEEP in patients with moderate or severe ARDS was independently associated with improved hospital survival, supported prior findings from a variety of trials. Lack of a relationship between VT and outcome in this dataset has been interpreted to reflect the relatively limited range of VT employed (centered near 7 mL/kg PBW). Association of peak, plateau, and driving pressure with both hospital and ICU outcomes was consistent with prior reports of smaller size. Another important finding was a positive association between lower respiratory rate and improved patient outcome. This observation is consistent with experimental data indicating that cumulative energy transferred to the lung per unit time (power)—not simply the characteristics of the individual tidal cycle, is an important determinant of iatrogenic pulmonary injury (10).

In a recent prospective trial from the PReVENT (PRotective VENTilation) investigators (11), patients without ARDS were prospectively assigned either to low or to intermediate VT groups. The low VT cohort started at a VT of 6 mL/kg PBW and received either volume-controlled (VCV) or pressure support ventilation (PSV). VT was then decreased, if tolerated, by 1 mL/kg every hour to a minimum of 4 mL/kg/PBW. If VT increased to more than 8 mL/kg/PBW while receiving the minimal PSV of 5 cmH_2O, this was accepted. Patients were also allowed larger VT if needed to address patient-ventilator asynchrony. An equal number of subjects were assigned to the intermediate VT group, starting at a VT of 10 mL/kg/PBW. If the plateau pressure exceeded 25 cm/H_2O using VCV, VT was decreased in increments of 1 mL/kg/PBW/h. Those receiving PSV had pressure support level adjusted to reach the target VT while keeping the maximum airway pressure <25 cm/H_2O.

In this trial of adult patients in the ICU without ARDS receiving invasive ventilation (who were not expected to be extubated within 24 hours of randomization), the low VT ventilator strategy described above did not prove more effective than its intermediate VT alternative with respect to ventilator free days and survival to day 28. There were no significant differences regarding length of stay, mortality, or occurrence of pulmonary complications between groups. Low VT was associated with respiratory acidosis. Detailed sedation data were not provided. The authors point out that this is the largest randomized clinical trial to investigate the role of VT management in patients without ARDS that measured clinically relevant, patient-centered outcomes. Perhaps the most important factor, which received relatively little emphasis in the discussion of this report, was the careful control of airway pressure. Patients assigned to higher VT had maximum alveolar pressure carefully constrained, with maximum alveolar pressure not allowed >25 cm/H_2O. Taken together, such results suggest that it is trans-alveolar pressure and strain—not VT that is the key modifiable ventilatory parameter in such patients. Finally, these investigators took care to avoid high compensatory respiratory rates, a power-boosting variable related to VILI that might otherwise have amplified damage risk in the low-VT assigned arm.

Mechanical ventilation strategies using lower end-inspiratory (plateau) pressures, lower VT, and higher PEEP have been collectively described as 'lung protective ventilation'. This approach has been associated with survival benefit in clinical trials involving patients with ARDS (1). The individual components of lung protection bundle, such as lower VT, lower plateau pressure, and higher PEEP, all hold potential to raise or reduce mechanical stress on the lung. When excessive, repeatedly high strain levels may inflict VILI (8). Clinical trials, however, have reported varying responses to the manipulation of separate components of lung protection. Consequently, clinicians often face the dilemma of optimizing one component of risk while negatively affecting the others. Integrating indicators, such as driving pressure, power and driving power represent recent responses to this concern. In current management of ARDS, constraining plateau and driving pressures has emerged as a more influential objective than using a specific VT (12-14). Can a similar lesson be derived from a growing body of data examining differing VT settings in patients without a formal diagnosis of ARDS?

In light of literature suggesting convergence of ventilator strategies for patients with and without ARDS, a number of observations may be made. First, the static transpulmonary pressure (the pressure difference from airway opening to pleural space), not the easily measured airway pressure

from the ventilator, is the distending pressure most directly relevant to lung stress (8,9,15). In part because of relative difficulty of its measurement, this fact is often overlooked when practitioners focus on plateau or driving pressure without considering the potential effect of the chest wall in confining lung expansion and stress. Very high transpulmonary tidal pressures may produce lung injury resembling ARDS or gross barotrauma with pneumothorax. A significant body of physiologic data demonstrates that using low rather than very high VT (and therefore applying lower plateau and transpulmonary pressures) improves survival. At this point it should be noted that while the inference has been made that the outcome benefit of 'lung protective' ventilation relates to VILI prevention, we have little direct clinical evidence to substantiate that assumption. The adverse vascular, hemodynamic and neuro-reflexive effects of using high airway pressures have seldom been considered or investigated. Without pharmacologic intervention, parameters such as driving pressure limitation may not be applicable in patients who breathe actively and generate wide swings of pleural pressure accompanied by high-amplitude transpulmonary pressures. Micro and regional atelectasis associated with supine body position and/or insufficient PEEP or local ventilation is both a stress-focusing influence and promoter of repetitive tidal collapse and re-expansion of dependent lung units (atelectrauma). Regional lung collapse may occur in commonly encountered conditions characterized by elevated pleural pressures that effectively compress the lung. These include obesity, pleural effusion, and increased abdominal pressure from various causes. In these situations, adequate PEEP and prone positioning may help prevent collapse and reduce the otherwise damaging potential of the ventilation strategy in use. The PREVeNT investigators provided needed data regarding VT manipulation in patients without ARDS. Yet, while limiting VT in all patients is appealing in theory and readily accomplished with current ventilator technology, the question of whether VT must be constrained into the low range for the individual without established lung injury remains. We suggest that studies of mechanical ventilation that examine transpulmonary pressure-focused and energetics-associated issues in patients with varying pulmonary physiology may ultimately be necessary to answer this question with certainty.

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Footnote

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References

1. Acute Respiratory Distress Syndrome Network, Brower RG, Matthay MA, et al. Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. N Engl J Med 2000;342:1301-8.
2. Gattinoni L, Presenti A, Torresin A, et al. Adult respiratory distress syndrome profiles by computed tomography. J Thorac Imaging 1986;1:25-30.
3. Maunder RJ, Shuman WP, McHugh JW, et al. Preservation of normal lung regions in the adult respiratory distress syndrome. Analysis by computed tomography. JAMA 1986;255:2463-5.
4. Neto AS, Simonis FD, Barbas CS, et al. Lung-Protective Ventilation With Low Tidal Volumes and the Occurrence of Pulmonary Complications in Patients Without Acute Respiratory Distress Syndrome: A Systematic Review and Individual Patient Data Analysis. Crit Care Med 2015;43:2155-63.
5. Serpa Neto A, Simonis FD, Barbas CS, et al. Association between tidal volume size, duration of ventilation, and sedation needs in patients without acute respiratory distress syndrome: an individual patient data meta-analysis. Intensive Care Med 2014;40:950-7.
6. Determann RM, Royakkers A, Wolthuis EK, et al. Ventilation with lower tidal volumes as compared with conventional tidal volumes for patients without acute lung injury: a preventive randomized controlled trial. Crit Care 2010;14:R1.
7. Ferguson ND. Low tidal volumes for all? JAMA 2012;308:1689-90.
8. Chiumello D, Carlesso E, Cadringher P, et al. Lung stress and strain during mechanical ventilation for acute respiratory distress syndrome. Am J Respir Crit Care Med 2008;178:346-55.
9. Talmor D, Sarge T, Malhotra A, et al. Mechanical ventilation guided by esophageal pressure in acute lung injury. N Engl J Med 2008;359:2095-104.
10. Laffey JG, Bellani G, Pham T, et al. Potentially modifiable factors contributing to outcome from acute respiratory

distress syndrome: the LUNG SAFE study. Intensive Care Med 2016;42:1865-76.
11. Writing Group for the PReVENT Investigators, Simonis FD, Serpa Neto A, et al. Effect of a Low vs Intermediate Tidal Volume Strategy on Ventilator-Free Days in Intensive Care Unit Patients Without ARDS: A Randomized Clinical Trial. JAMA 2018;320:1872-80.
12. Amato MB, Meade MO, Slutsky AS, et al. Driving pressure and survival in the acute respiratory distress syndrome. N Engl J Med 2015;372:747-55.
13. Loring SH, Malhotra A. Driving pressure and respiratory mechanics in ARDS. N Engl J Med 2015;372:776-7.
14. Guérin C, Papazian L, Reignier J, et al. Effect of driving pressure on mortality in ARDS patients during lung protective mechanical ventilation in two randomized controlled trials. Crit Care 2016;20:384.
15. Grasso S, Stripoli T. Transpulmonary Pressure-based Mechanical Ventilation in Acute Respiratory Distress Syndrome. From Theory to Practice? Am J Respir Crit Care Med 2018;197:977-8.

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