

Should Tidal Volume Be 6 mL/kg Predicted Body Weight in Virtually All Patients With Acute Respiratory Failure?

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Over the last 2 decades, it has become clear that mechanical ventilation itself can cause lung injury and affect outcome. The development of ventilator-induced lung injury is strongly associated with overdistension of lung parenchyma, and limiting lung stretch saves lives in patients with acute lung injury. The debate in this paper is whether all patients on mechanical ventilation should be managed with a tidal volume (V_T) of 6 mL/kg predicted body weight. Current data indicate that reducing lung stretch should be the standard for all patients with acute lung injury and acute respiratory distress syndrome who require ventilatory support. However, insufficient data exist to indicate that a V_T of 6 mL/kg predicted body weight should be the standard for all patients who require mechanical ventilation. Whether V_T is the correct target for therapeutic interventions is debatable. Plateau pressure may be a better target for assessing and preventing alveolar overdistension. As the data evolve, it is conceivable that the actual V_T used should be based on the individual patient's lung mechanics rather than assuming that one V_T will suit all patients. Consensus at this time is not possible, and this paper presents the arguments on both sides of the controversy. *Key words: tidal volume, mechanical ventilation, acute lung injury, acute respiratory distress syndrome.* [Respir Care 2007;52(5):556–564. © 2007 Daedalus Enterprises]

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Introduction

In the not-too-distant past, nearly all patients with acute respiratory failure (ARF) were managed with tidal volume (V_T) of 10–15 mL/kg, and the respiratory rate and V_T were further adjusted to normalize arterial blood gases. Over the last 20 years, a strong body of evidence has been developed that makes it clear that mechanical ventilation has the potential to directly harm the lungs: so-called ventilator-induced lung injury (VILI). The development of VILI is associated with overdistension of lung parenchyma and repetitive opening and closing of unstable lung units. Small (6 mL/kg predicted body weight [PBW]) V_T is used in the management of ARF due to acute lung injury (ALI) and acute respiratory distress syndrome (ARDS) to avoid alveolar overdistension and improve survival.

These data have led clinicians and investigators to postulate that smaller V_T might also be beneficial in other forms of ARF. Data are emerging that patients at risk for ALI/ARDS might be more susceptible to VILI. Patients with obstructive and other restrictive processes might also benefit from so-called lung-protective ventilation. This paper explores the reasons why 6 mL/kg PBW may be the target V_T for most forms of ARF, and will also discuss the evidence for reducing V_T in other forms of ARF. However, in the context of this discussion, the question arises about whether V_T is the bedside variable most reflective of overdistension. Plateau pressure may be a better indicator of transpulmonary pressure and alveolar overdistension, and therefore a better therapeutic target. As a result, this paper will also discuss the reasons V_T should be titrated based on the patient's individual lung mechanics and why V_T greater than 6 mL/kg PBW may be equally acceptable. Thus, this paper explores the relative merits of using a standard V_T approach for all patients, versus a more physiologic, individualized approach based on assessment of the patient's lung mechanics.

Pro: V_T Should Be 6 mL/kg PBW in Virtually All Patients With ARF

Mechanical ventilation is a fundamental component of intensive care for most critically ill patients, particularly those with ALI and ARDS. However, both animal and human studies have found that mechanical ventilation may cause or worsen VILI.¹ Most of the literature on lung-protective mechanical ventilation focuses on patients with ALI/ARDS, in whom V_T reduction improves outcomes. There are several reasons for extrapolating these data to patients without ALI. First, diagnosing ALI/ARDS is at times challenging.² Though the ALI/ARDS consensus criteria seem relatively simple to apply, use of higher positive end-expiratory pressure (PEEP) can improve both the ratio of P_{aO_2} to fraction of inspired oxygen (P_{aO_2}/F_{IO_2}) and ab-

normalities on chest radiograph to the extent that the patient no longer meets the definition of ALI.³ Second, the patient may not yet fulfill ALI/ARDS criteria at the initiation of mechanical ventilation but may develop lung injury during the course of the disease. Third, critically ill patients are constantly at risk for other causes of lung injury (eg, ventilator-associated pneumonia, transfusion-related lung injury, aspiration of gastric contents). Finally, patients with obstructive lung disease are at high risk of developing dynamic hyperinflation (intrinsic PEEP) when managed with high minute volume. Thus, with few exceptions (eg, simple, low-risk postoperative patients without any lung disease, on a short course of mechanical ventilation), most patients on mechanical ventilation should benefit from a lower V_T .

V_T in Patients With ALI

Numerous animal investigations have shown that excessive mechanical stretch during overinflation of the lungs with high inspiratory pressure and large V_T results in increased epithelial and endothelial permeability.^{4–7} In a seminal study, Webb and Tierney were the first to demonstrate this phenomenon. They reported that rats ventilated with high distending pressure, resulting in high V_T , developed pulmonary edema and diffuse alveolar damage that was histologically indistinguishable from ARDS.⁴

Dreyfuss and associates later published convincing evidence that volume overdistension, rather than airway pressure, is the principal cause of the tissue injury. By comparing rats that had their chests and abdomens banded to those that did not, they were able to deliver high and low V_T with identical high peak airway pressure.^{8,9} Pulmonary edema developed in the high-pressure/high- V_T and low-pressure/high- V_T groups, whereas there was no edema in the high-pressure/low- V_T animals.

Excessive volume with alveolar overdistension may be the most important mechanism in VILI, and the term “volutrauma” has been used to describe the sequelae. In the setting of ALI, the distribution of ventilation may be uneven because of the heterogeneity of injury.¹⁰ Many years ago, Mead and colleagues suggested that, at a transpulmonary pressure of 30 cm H₂O, the regional distending pressure across an atelectatic or fluid-filled region of lung surrounded by fully expanded lung would be nearly 140 cm H₂O.¹¹ Thus, V_T are preferentially directed to more normal or recruitable lung units, and these areas may be more susceptible to overinflation, overdistension, and tissue injury, even at apparently “safe” plateau pressures.

More recently, following on the heels of those observations, several seminal human studies provided strong evidence for VILI.^{12–16} The largest of these studies was the National Institutes of Health/National Heart, Lung, and Blood Institute ARDS Network phase III study of lower

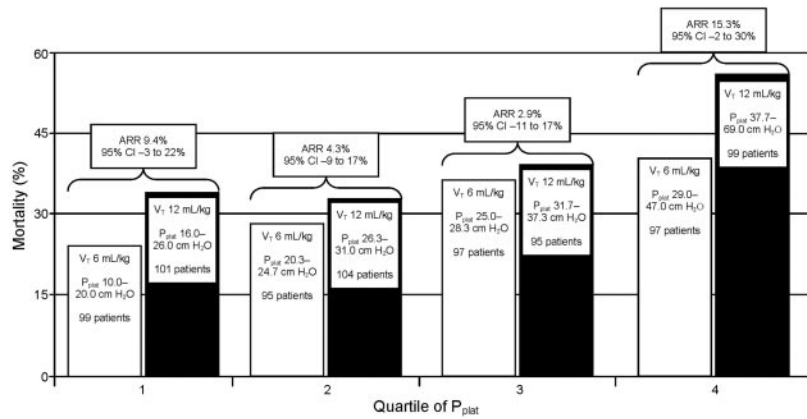


Fig. 1. Mortality versus quartile of day-1 plateau pressure at tidal volume (V_T) of 6 mL/kg or 12 mL/kg. The bars show the V_T, the plateau pressure range, and the number of patients in each category. ARR = absolute risk reduction. CI = confidence interval. (Data from Reference 17.)

versus traditional V_T ventilation in patients with ALI.¹⁶ In that trial, 861 patients with ALI were randomized to receive volume-controlled ventilation with either conventional V_T of 12 mL/kg PBW or lower V_T of 6 mL/kg PBW. In the lower-V_T group, the goal plateau pressure was ≤ 30 cm H₂O, and if the plateau pressure was > 30 cm H₂O, V_T was decreased to a minimum of 4 mL/kg PBW. The mean plateau pressures were 25 cm H₂O and 33 cm H₂O in the intervention and control groups, respectively. The study was stopped early for efficacy; mortality was reduced from 39.8% to 31% (p = 0.007) with the low-V_T intervention.

Some authors have questioned the value of V_T reduction in patients with ALI/ARDS whose plateau pressure is already below 30–35 cm H₂O. However, in their secondary analysis of the ARDS Network database, Hager and colleagues found that there was a beneficial effect of V_T reduction, from 12 mL/kg PBW to 6 mL/kg PBW, regardless of the plateau pressure before the V_T reduction.¹⁷ In their model, patients in both arms of the study were divided into quartiles of plateau pressure. In addition to V_T assignment and plateau pressure quartile, they included in their multivariable logistic regression model any baseline characteristic in which there was a trend toward a difference between corresponding quartiles. In the final regression model, lower V_T assignment, lower plateau pressure quartile, and lower Acute Physiology and Chronic Health Evaluation III score were all significant predictors of lower mortality. Notably, the interaction between V_T assignment and plateau pressure quartile was not significant. This suggests that patients in the 12 mL/kg PBW V_T group would have benefited from V_T reduction in each of the quartiles, including the two in which plateau pressure was already ≤ 31 cm H₂O (Fig. 1). These data argue against the belief that V_T reduction is without benefit when plateau pressure is already lower than 30–35 cm H₂O.¹⁷

V_T in Patients at Risk for ALI

Once the therapeutic benefits of low-V_T ventilation in patients with established ALI/ARDS became known, researchers began asking whether patients at risk for ALI might benefit from a similar lung-protective ventilation strategy. It has been observed that slightly injured lungs are more susceptible to VILI than are normal lungs.^{18,19} Thus, if mechanical ventilation can potentiate ALI, the incidence of the syndrome might be decreased if low V_T were used in patients at risk. Two recent observational studies provided preliminary data on this topic. Gajic and associates reported the results of a retrospective cohort study in which 332 patients without ALI were examined for the development of ALI.²⁰ They found that women were ventilated with higher V_T than men and trended toward greater development of ALI (29% versus 20%, p = 0.068). The percentage of patients who developed ALI increased as V_T increased (Fig. 2). After multivariate analyses to control for confounding variables, each mL/kg of V_T received greater than 6 mL/kg was associated with a 30% increase in the odds of developing ALI (p < 0.001). In a subsequent cohort study of 3,261 patients who received mechanical ventilation, both a V_T greater than 700 mL and a peak airway pressure greater than 30 cm H₂O were independently associated with the development of ALI.²¹ These studies provide preliminary evidence that low-V_T lung-protective ventilation may benefit patients at risk for ALI. This remains unproven, however, and a large randomized controlled trial would be needed to confirm this hypothesis.

V_T in Patients With Non-ALI ARF

Patients without ALI may also be at risk for adverse effects of normal-V_T mechanical ventilation. Patients with

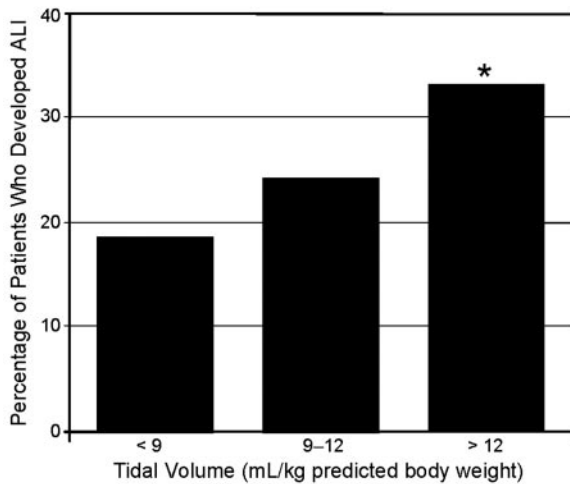


Fig. 2. Tidal volume versus percentage of patients who developed acute lung injury (ALI). Patients at risk for ALI were significantly less likely to develop ALI if they were managed with a lower V_T during the risk period. * $p < 0.001$, compared to the group that received < 9 mL/kg predicted body weight. (Data from Reference 20.)

obstructive lung disease, such as acute asthma or chronic obstructive pulmonary disease, are at high risk for developing dynamic hyperinflation (intrinsic PEEP) during mechanical ventilation. This hyperinflation results from the characteristics of obstructive lung disease: loss of elastic recoil of the lung, bronchospasm, mucus hypersecretion and plugging, and airway inflammation. End-inspiratory lung volume is closely correlated with intrathoracic pressure, and if end-inspiratory lung volume is reduced, intrathoracic pressure will decrease, independent of the mechanical properties of the lung.²² An elevated intrathoracic pressure can decrease cardiac output and blood pressure by impeding venous return and right-ventricular filling, increasing pulmonary vascular resistance, and increasing pericardial pressure. Barotrauma, manifested by extra-alveolar air (pneumothorax and pneumomediastinum), is also related to elevated end-inspiratory lung volume in patients with obstructive lung disease. Decreasing dynamic hyperinflation can improve gas exchange by reducing physiologic dead-space ventilation, improving oxygen delivery to the tissues by improving cardiac function, decreasing the risk of barotrauma, decreasing the work of breathing, and maybe also decreasing dyspnea. Thus, the very first description in the literature of limiting airway pressure and permissive hypercapnia was in patients with severe acute asthma (status asthmaticus).²³ Darioli and Perret studied 34 cases of status asthmaticus that required mechanical ventilation. They maintained the peak airway pressure at less than 50 cm H₂O and allowed the P_{aCO_2} to rise if necessary. All the patients survived, which represented a marked decrease in mortality from that reported in previous studies.²³

Patients with congestive heart failure and cardiogenic pulmonary edema may also benefit from a reduction in V_T . Like the noncardiogenic pulmonary edema seen in ALI/ARDS, cardiogenic pulmonary edema causes alveolar flooding, interstitial thickening, and reduced lung compliance. Normal V_T in a less compliant lung will lead to an increase in plateau pressure. Thus, while there are no outcome data on the effect of V_T reduction in patients with cardiogenic pulmonary edema, avoiding alveolar overdistension by limiting the transalveolar pressure could be beneficial.

Lack of Harm With Low V_T

Perhaps the 2 biggest concerns about low- V_T ventilation are the risks of atelectasis and hypoxemia. It seems intuitive that decreasing the V_T might lead to more atelectasis, which might lead to the repetitive closing and re-opening of some lung units, which can lead to VILI.¹ However, the appropriate use of PEEP may prevent this cyclic closure and re-opening of alveolar units, thus counteracting the effect of loss of V_T . Though repetitive alveolar closure and expansion can be injurious, it must be pointed out that the development of atelectasis itself, or the failure to recruit areas of atelectatic lung, has never been shown to adversely affect patient outcomes. It may be that the necessary maneuvers to recruit or prevent atelectasis, such as high V_T or high PEEP, may be more injurious than the atelectasis itself: the “cost” of lung injury may exceed the benefit of regional recruitment. Thus, in addition to the concept of permissive hypercapnia, perhaps we should begin to consider the benefit of “permissive atelectasis.”

Reducing V_T often leads to a reduction in arterial oxygenation, and, in fact, the low- V_T group in the ARDS Network study did have a lower average P_{aO_2}/F_{IO_2} than the normal- V_T group.¹⁶ Yet the low- V_T group’s survival was better. Thus it is unclear that a small reduction in arterial oxygenation is harmful in most patients, given the marked benefit of V_T reduction.

Other potential adverse effects of low V_T include hypercarbia and respiratory acidosis, but this is generally not detrimental to the patient unless there is a co-existing severe metabolic acidosis. In those cases the resulting pH may be unacceptably and dangerously low. But respiratory acidosis, in and of itself, is generally safe and well tolerated.²⁴ Some experimental evidence even suggests that hypercapnic acidosis may have a lung-protective effect. Brocard and associates demonstrated that respiratory acidosis attenuated the severity of VILI in isolated, perfused rabbit lungs.²⁵ Sinclair and colleagues then found that hypercapnic acidosis protected against VILI in intact rabbits ventilated at high V_T .²⁶ Based on these animal data, Kregnow and colleagues performed a secondary analysis of the patients who participated in the ARDS Network V_T

trial, and defined hypercapnic acidosis as a day-1 $\text{pH} < 7.35$ with a $\text{P}_{\text{aCO}_2} > 45$ mm Hg.²⁷ After multivariable analysis, they found a significantly lower odds of death at 28 days among the patients with hypercapnic acidosis in the 12-mL/kg V_T group (odds ratio 0.14, 95% confidence interval 0.03–0.70%, $p = 0.016$). Acidosis was not associated with lower mortality in the 6-mL/kg V_T group, which suggests that hypercapnia might be protective only when used with injuriously high V_T .

Finally, dyspnea can result from reducing V_T , and there is a concern that this dyspnea may lead to significant patient discomfort. However, in the ARDS Network trial there was no evidence of higher doses of sedatives used by the 6 mL/kg PBW study group. Respiratory rate does increase when V_T is reduced, but that does not necessarily mean that the patient is more dyspneic, especially if work of breathing is reasonably well-supported by the mode of mechanical ventilation. Work by Hough and colleagues, in an analysis of ventilator data in a subset of patients enrolled in the ARDS Network trial, suggests that intrinsic PEEP was not clinically importantly increased in the low- V_T group, despite an increase in respiratory rate.²⁸ In a single-institution study, Kahn and colleagues found that low- V_T ventilation was not associated with higher dose or duration of sedatives in patients with ALI, which suggests that concern about oversedation should not be a barrier to implementing a lung-protective ventilation strategy.²⁹

Clinical Application of Low- V_T Ventilation

Much has been written about the implementation of the ARDS Network protocol, and that clinicians might not use lung-protective ventilation as often as indicated. Rubenfeld and colleagues published results from a survey of intensive care unit nurses and respiratory therapists, in which they examined barriers to providing lung-protective ventilation.² Identified barriers included: physician willingness to relinquish control of the ventilator; physician recognition of ALI/ARDS; physician perceptions of patient contraindications to low V_T ; concern about patient discomfort; and concern about hypercapnia, acidosis, and hypoxemia. Despite these barriers, it has been shown that the protocol can be successfully implemented with ease. A concise description of the protocol is available in a review by Brower.³⁰ Kallet and associates have discussed the implementation of this protocol and provided specific suggestions for setting up and troubleshooting the protocol.³¹

Summary of Pro Position

There is very good evidence from randomized controlled trials that the approach to mechanical ventilation affects mortality in ALI/ARDS. The single variable in these studies that was associated with better outcomes was a V_T of

6 mL/kg PBW, even in patients with plateau pressure below 30 cm H₂O. Lung-protective ventilation is safe and has few adverse effects. These data, along with the retrospective analysis of patients who started without ALI but developed it after initiation of mechanical ventilation, indicate that a V_T of 6 mL/kg PBW should be the standard for all patients who acutely require ventilatory support, either for ALI/ARDS or a condition that places the patient at risk of ALI/ARDS. This may well be true in patients at high risk of dynamic hyperinflation and in patients with other causes of reduced pulmonary compliance. Once the patient is established on a V_T of 6 mL/kg PBW, the V_T can be adjusted up or down, based on the patient's lung mechanics, gas exchange, tolerance, and lung disease.

Con: V_T Should Not Be 6 mL/kg PBW in Virtually All Patients With ARF

The development of VILI is associated with overdistension of lung parenchyma and repetitive opening and closing of unstable lung units. Small (6 mL/kg PBW) V_T is used in the management of ARF to avoid overdistension. However, in the context of this discussion, the question is this: is V_T the bedside variable most reflective of overdistension? From my (RMK) perspective the answer is no! A standard V_T of 6 mL/kg PBW should not be used in all cases of ARF because: (1) plateau pressure, not V_T , is the most accurate bedside indicator of overdistension; (2) there is a plateau pressure where VILI is unlikely to be induced, provided that minimal PEEP is maintained; and (3) forcing a V_T of 6 mL/kg PBW in all patients who require mechanical ventilation may require large amounts of sedation, which may induce other complications and prolong the course of mechanical ventilation. V_T should be individualized based on the patient's lung mechanics, specifically, plateau pressure!

Why Is 6 mL/kg the Target?

Two randomized control trials,^{12,16} have demonstrated that V_T of 6 mL/kg PBW results in better outcome than V_T of 12 mL/kg PBW. However, in these 2 trials no other V_T were evaluated. Whereas, most recently, Villar et al³² conducted a randomized controlled trial of lung-protective ventilation and demonstrated that a group ventilated with V_T of 7.3 ± 0.9 mL/kg PBW and PEEP set at 2 cm H₂O above the inflection point had better outcome than patients managed with a V_T of 10.2 ± 1.2 mL/kg PBW and PEEP set relative to oxygenation response. In a negative trial of partial liquid ventilation, Kacmarek et al³³ reported a mortality of 15.0% in the control group using conventional volume ventilation managed with a V_T of 9.0 ± 2.0 mL/kg PBW. In addition, it can be argued that the patients studied in the Villar et al³² and Kacmarek et al³³ trials were much

sicker, from a pulmonary perspective, than those enrolled in the ARDS Network trial. Villar et al³² required that patients meet ARDS criteria ($P_{aO_2}/F_{IO_2} < 200$ mm Hg) to be enrolled, but only randomized those who 24 hours later still had a $P_{aO_2}/F_{IO_2} < 200$ mm Hg on standard ventilator settings (PEEP ≥ 5 cm H₂O and $F_{IO_2} \geq 0.5$). Kacmarek et al³³ also required that patients meet ARDS criteria to be enrolled, and only randomized those with $P_{aO_2}/F_{IO_2} < 300$ mm Hg on standard ventilator settings (PEEP ≥ 13 cm H₂O and $F_{IO_2} \geq 0.5$). The ARDS Network enrolled and randomized patients with a $P_{aO_2}/F_{IO_2} < 300$ mm Hg, without any PEEP and F_{IO_2} requirement. The ARDS Network study proved the concept that small V_T results in better outcomes than large V_T but did not determine that 6 mL/kg PBW V_T was the volume that must be used on all patients. It is not known what specific V_T causes VILI in an individual patient.

Plateau Pressure Is the Best Indicator of Overdistension

Overdistension is present when the pressure change across the alveoli (intra-alveolar minus intrathoracic pressure) is excessive.¹ In healthy adults, a transalveolar pressure of 15 cm H₂O does not induce injury but may result in a V_T of 1,500 mL, or well over 12 mL/kg PBW. However, in severely lung-injured patients with ARDS a transalveolar pressure of 40 cm H₂O may only establish a V_T of 5 mL/kg but will induce lung injury because of the high transalveolar pressure.

Animal data that have defined the development of VILI in otherwise healthy lungs have all used excessive V_T to establish a high transalveolar pressure and induce lung injury.^{4–8,34} Webb and Tierney⁴ required a V_T of > 30 mL/kg to induce lung injury when zero PEEP was applied (peak inspiratory pressure 45 cm H₂O). Similarly, Parker et al⁵ required a peak inspiratory pressure of 64 cm H₂O and a V_T of > 30 mL/kg to induce injury in open-chest dogs. Dreyfuss et al⁶ used peak inspiratory pressure of 45 cm H₂O and $V_T > 30$ mL/kg to induce lung injury in rats. All of these laboratory models of lung injury used high transalveolar pressure, with very low or no PEEP.

At the bedside, the best indicator of transalveolar pressure is plateau pressure. A high plateau pressure—not necessarily a large V_T —indicates overdistension. In fact, in a recent review, Dreyfuss et al⁶ stated that “very high distending pressure, typically > 30 cm H₂O, depending on the species, results in pulmonary edema.” In general, a distending pressure of > 30 cm H₂O translates into a plateau pressure > 30 cm H₂O. In fact, there are no data from any animal species that indicate that VILI occurs when plateau pressure is < 25 cm H₂O, provided PEEP is > 5 cm H₂O.

As a result, plateau pressure, not V_T , should be used at the bedside to determine the presence of overdistension. Ideally, in all patients, as recommended by Dreyfuss and Saumon,⁹ plateau pressure should be < 30 cm H₂O. However, as illustrated by data from the ARDS Network, the lower the plateau pressure, the better the patient outcome, for patients in both the 6 mL/kg and 12 mL/kg groups.^{16,17} This is clearly true across all V_T , but once plateau pressure is < 25 cm H₂O, no significant mortality benefit exists, even if plateau pressure is further decreased.¹⁷

The concept of plateau pressure being more important than V_T is clearly evident if one compares the V_T , plateau pressure, and PEEP relationships in the data from the original ARDS Network trial¹⁶ and the recent partial liquid ventilation trial.³³ In the control group of the partial liquid ventilation trial, V_T was 9 mL/kg PBW with a PEEP of 14 cm H₂O, whereas in the ARDS Network trial V_T was 6 mL/kg PBW with a PEEP of 9 mL/kg. In both of these groups mortality was low (ARDS Network 31%, Kacmarek et al 15%). The single factor that was similar across these 2 studies was the plateau pressure: about 28 cm H₂O in both studies.^{16,33} In addition, as discussed earlier, the level of lung injury at study entry was greater in the partial liquid ventilation study than in the ARDS Network study.

These data are consistent with the meta-analysis performed by the Cochrane group.³⁵ They analyzed the effect of V_T on mortality in the original 5 randomized controlled trials that focused on lung-protective ventilation in ARDS/ALI,^{12–16} and found that a small V_T was associated with better mortality if the plateau pressure was > 31 cm H₂O. However, if the plateau pressure was < 31 cm H₂O, V_T had no impact on mortality.³⁵

Deans et al,³⁶ in a recent point-of-view article in *Critical Care Medicine*, also questioned the benefit of a 6 mL/kg PBW V_T in all patients with ARF. Their perspective on the results of the ARDS Network original trial¹⁶ was that 12 mL/kg PBW V_T increased mortality, but 6 mL/kg PBW V_T did not decrease mortality. They argued this perspective by performing a retrospective analysis of 2,587 patients who were screened by the ARDS Network and met enrollment criteria but were not enrolled because they were enrolled in other trials, the patient refused participation, the investigators were unable to get consent, the attending physician refused to allow the patient to participate, or > 36 hours had passed after meeting inclusion criteria. Essentially, these patients were the same as those randomized to receive 6 mL/kg PBW or 12 mL/kg PBW V_T . Deans et al³⁶ determined that the mortality of these non-studied patients was 31.7%, which is essentially the same as the 31% mortality in the 6 mL/kg V_T group. Although the precise V_T delivered to these patients were not available, they hypothesized that these patients received a V_T of about 10 mL/kg PBW, because that was the stan-

standard V_T used at the time of the study, as reported in recent epidemiologic studies.^{37,38} One would conclude, if Deans's assumptions about V_T are correct, that all of those patients—those studied and those not studied—would have had, on average, similar mortality, provided their V_T was 6–10 mL/kg PBW and their plateau pressure was low.

V_T and the Development of Lung Injury in Patients Without Lung Injury

There have been 3 retrospective analyses of patients who were intubated without any indication of ARF but developed ALI after > 48 hours of mechanical ventilation.^{20,21,39} In each of these analyses, the patients who received low V_T were least likely to develop lung injury. Gajic et al²⁰ evaluated data from all patients ventilated at the Mayo Clinic between January and December 2001. A total of 4,546 patients received mechanical ventilation. Of that group, 332 patients did not have ALI/ARDS at the time of initiation of mechanical ventilation and were ventilated for > 48 hours. Of these 332 patients, 80 developed ALI ($P_{aO_2}/F_{IO_2} < 300$ mm Hg, diffuse infiltrates, pulmonary artery occlusion pressure < 18 mm Hg, or no clinical evidence of left atrial hypertension). The primary risk factors associated with the development of ALI were transfusion of blood products (odds ratio 3.0, $p < 0.001$), pH < 7.35 (odds ratio 2.0, $p = 0.032$), a history of restrictive lung disease (odds ratio 3.6, $p = 0.044$), and V_T (odds ratio 1.3 for each mL/kg above 6 mL/kg PBW, $p < 0.001$). The percentage of patients who developed ALI decreased as V_T decreased (< 9 mL/kg PBW approximately 18%, 9–12 mL/kg PBW approximately 25%, and > 12 mL/kg PBW approximately 36%) (see Fig. 2).

Gajic et al²¹ also did a retrospective analysis of the epidemiologic data gathered by Esteban et al³⁷ on ventilated intensive care unit patients. In that database they identified 205 patients who at the onset of mechanical ventilation did not have ALI/ARDS but developed it after 48 hours of mechanical ventilation. They found that large V_T (odds ratio 2.6 for $V_T > 700$ mL) and high peak airway pressure (odds ratio 1.6 for peak pressure > 30 cm H₂O) were associated with the development of ALI. Similarly, Fernandez-Perez et al³⁹ noted that in pneumonectomy patients, those who developed postoperative respiratory failure had a larger intra-operative V_T (8.3 mL/kg PBW vs 6.7 mL/kg PBW) and that there was an interaction between V_T and fluid administration intra-operatively (odds ratio 1.36). That is, the larger the V_T , the greater the fluid administration. However, in that analysis, no airway pressures whatsoever were reported.

A number of factors regarding these 3 papers must be considered when evaluating their conclusions. First, all are retrospective analyses, so it is impossible to establish a

direct cause-and-effect relationship. In addition, no plateau pressure data were provided for the vast majority of patients in the subgroups analyzed. A breakdown of ventilation modes is not provided in two of the 3 studies. The one study in which pressure and volume ventilation were used gives no indication of the pressures used during pressure or volume ventilation.²⁰ As a result, it is impossible to evaluate the level of overdistension associated with those V_T or to determine if the patients with lower V_T had plateau pressure above or below 25 cm H₂O. In addition, since these data are retrospective, it is impossible to know if other not-easily-identified factors contributed to the development of lung injury. Although these data are interesting, a prospective trial is needed to clarify these findings.

What Is an Appropriate V_T ?

V_T set or considered acceptable should be based on the patient's lung mechanics: specifically, plateau pressure. However, it is quite clear in the literature that $V_T \geq 12$ mL/kg PBW in acutely ill patients is unacceptable and associated with high mortality.^{12–17,32} It is also true that mammals, regardless of species, under resting steady-state conditions all breathe with a V_T of about 6.3 mL/kg PBW.^{40–42} The critical question is, if a patient demands a V_T larger than 6 mL/kg PBW but has a low plateau pressure, is it in the patient's best interest to prevent them from receiving greater than 6 mL/kg? This can be accomplished by ventilation in volume assist/control mode with a set V_T of 6 mL/kg and by sedating the patient to whatever level is required to force them to accept a low V_T . Or should a larger V_T be allowed, provided the plateau pressure stays below 25 cm H₂O? Based on my discussion, I believe the data support the use of V_T up to 10 mL/kg PBW, provided the plateau pressure is < 25 cm H₂O, regardless of the patient's diagnosis, provided PEEP is ≥ 5 cm H₂O. However, if the plateau pressure is > 25 cm H₂O but < 30 cm H₂O, I would recommend a V_T of 6–8 mL/kg PBW. And if the plateau pressure is > 30 cm H₂O, re-

Table 1. Con Perspective on the Relationship Between Tidal Volume and Plateau Pressure*

Plateau Pressure (cm H ₂ O)	Tidal Volume (mL/kg PBW)
< 25	≤ 10
25–30	6–8
> 30	≤ 6

*If the plateau pressure is within the defined ranges, the tidal volume listed may be delivered, assuming appropriate positive end-expiratory pressure (≥ 5 cm H₂O) is applied.

regardless of the etiology of the respiratory failure, the V_T should be < 6 mL/kg (Table 1).⁴³

Forcing a V_T of 6 mL/kg PBW on every patient can result in marked cardiovascular instability, as a result of the patient fighting the ventilator for a larger V_T . This increases the patient's effort, discomfort, oxygen consumption, and carbon dioxide production, increasing the complexity of managing the patient. Sedation to force a V_T of 6 mL/kg PBW increases the probability of aspiration, gastric immobility, and prolongation of mechanical ventilation. It is important to remember that all the published randomized controlled trials demonstrate is that 6 mL/kg is better than 12 mL/kg; none of the other V_T in between those values have been studied^{12,16} in a systematic manner. In addition, low mortality was associated with V_T of 7 mL/kg³² and 9 mL/kg³³ in patients with ARDS. The critical factor is localized overdistension, which is best determined at the bedside with the plateau pressure, so V_T used should be individualized to the patient, based on the plateau pressure established.

Summary of Con Position

There is very good evidence from randomized controlled trials that the approach to mechanical ventilation affects mortality in ALI/ARDS. These data, along with the retrospective analysis of patients who were ventilated without respiratory failure but developed it after initiation of mechanical ventilation, indicate that a V_T of 6 mL/kg should be the standard for all patients who acutely require ventilatory support, regardless of etiology. However, on the con side of this controversy, plateau pressure—not V_T —appears to be the best indicator of local overdistension. In addition, based on the available data, if plateau pressure is maintained at < 25 cm H₂O, provided appropriate PEEP is applied, the likelihood of inducing lung injury is minimal. Thus, the actual V_T used should be based on the individual patient's lung mechanics, specifically plateau pressure, and in patients with a low plateau pressure a $V_T \leq 10$ mL/kg may be more appropriate than forcing a V_T of 6 mL/kg PBW, with or without the use of sedation.

Conclusion

We agree that there is ample evidence in the literature that alveolar overdistension injures the lung, that the approach to mechanical ventilation affects survival, and that the best-studied variable to date in lung-protective ventilation for patients with ALI/ARDS is a V_T of 6 mL/kg PBW. However, the question debated in this paper is highly controversial and the state of the literature prevents consensus at this time. One of us (RMK) believes firmly that plateau pressure is a more physiologic, and therefore better, target for lung-protective ventilatory strategies and

that, as long as plateau pressure is maintained at < 25 cm H₂O with an appropriate amount of PEEP, the likelihood of VILI is minimal. The strategy supported by this argument is a patient-specific, targeted approach to V_T based on the individual patient's lung mechanics. The other author (KPS) believes that at this time the strongest evidence-based approach to clinical mechanical ventilation is for V_T reduction regardless of plateau pressure. This approach incorporates patients with ALI/ARDS and patients at-risk for ALI/ARDS, as well as patients with cardiogenic pulmonary edema and obstructive lung disease. The strategy supported by this argument is a disease-specific approach that can be widely and easily adopted, even by clinicians who are not experts in mechanical ventilation.

However, we agree that each approach has the potential to improve outcomes across intensive care units, since far too many clinicians still fail to practice lung-protective ventilation by either strategy. We also agree that the ideal approach to mechanical ventilation in most forms of ARF has yet to be determined. We hope that ongoing research will get us closer to solving this important controversy.

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Discussion

MacIntyre: The ARDS Network protocol starts at 6 mL/kg, but if there are issues of gas exchange or patient comfort, it allows you to go to 8 mL/kg, as long as the plateau pressure remains below 30 cm H₂O. So it's not true that the ARDS Network protocol forces you to stay at 6 mL/kg. In fact, 8 mL/kg is allowed. Similarly, if the plateau pressure is above 30 cm H₂O at a V_T of 6 mL/kg, you are supposed to drop the V_T to 5 or even 4 mL/kg to keep the plateau pressure below 30 cm H₂O. So the ARDS Network didn't ignore the plateau pressure. In fact, wouldn't both of you agree that it's probably a little bit of both? I think lung stretch and tidal stretch both play a role in VILI. My philosophy is to start at 6 mL/kg, and if the patient tolerates that, and the gas exchange and plateau pressure are fine, I just leave the V_T there. I start at 6 mL/kg as the default condition, and then adjust accordingly.

Kacmarek: The issue here is the perspective that many have in the community, which is that you *must* use a V_T of 6 mL/kg and that V_T is the primary factor that induces lung injury. But I don't think there's any data to support that. If you look at the original data you are referring to, the V_T were huge; they were way out of the range we'd consider clinically. A particular V_T is not necessarily going to cause overdistension. You have to have an increase in transpulmonary pressure. I could put a V_T of 2 L into a normal adult's lungs and his peak alveolar or plateau pressure might be 10–12 cm H₂O, but I doubt it would cause any overdistension lung injury, because of the lack of any existing lung injury.

Rubin: Speaking as a pediatrician, I want to point out a couple of important caveats about this. Although it's true that physiologic V_T is about 7 mL/kg throughout life, there are a

lot of things that prevent us from using that strategy in children. No pediatric data I am aware of are consistent with the ARDS Network data. We rarely use cuffed endotracheal tubes in children, because they can lead to tracheal damage, so we avoid cuffed tubes until adolescence.

I run a home ventilator program, and I've found that it's extraordinarily difficult to measure the V_T at the trachea—with most home ventilators—at the tube, so there is substantial variability in the volume delivered to children because of the tubing compliance. And the lower the ideal body weight, the more you worry about that variability. Also, although permissive hypercarbia may be quite safe for the developed brain of an adult, there are important concerns, raised by studies of children with congenital central hypoventilation syndrome, that elevated CO₂ can cause slow neural development and may induce long-term neurologic disability in children who have a growing brain. So we need to be careful when we interpret these. We can't brush everything with the same stroke.

Cheifetz: I agree. In pediatrics, one of the controversies is where to measure the delivered V_T. Since we do not have pediatric data to compare 6 mL/kg and 12 mL/kg, or any other V_T, we generally do accept the ARDS Network recommendation,¹ though, again, we lack pediatric data. As Bruce indicated, in our smaller patients we lose much of the V_T in the compliance of the ventilator circuit. There is a growing body of literature^{2–4} that supports measuring the V_T at the endotracheal tube in infants and younger children. With them we can't measure it at the ventilator's expiratory valve, because those values may be off by as much as 50%.

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Steinberg: I agree, Neil, that it's probably a combination of total stretch and tidal stretch that's important. I also agree that transpulmonary pressure is probably the more important measurement, if we can get it, because transpulmonary pressure is a much more accurate determinant of lung volume than is plateau pressure. In many ICU patients the plateau pressure may not represent the transpulmonary pressure because of obesity, or massive volume resuscitation, or abdominal compartment syndrome, or pleural disease, or chest wall compliance. It may not be plateau pressure that determines injury. And perhaps in a normal adult's lungs we can't cause VILI very easily.

But we're not talking about a patient who's on the ventilator for only 24 or 48 hours. Sick people probably have some degree of lung inflammation, which might not meet the criteria of ALI, but even normal lung distension—just stretching the lung to normal size—may be detrimental in patients with some injury. I think the data from the Mayo Clinic,¹ though it was not a prospective randomized study, are very compelling. In that study, patients who got a lower V_T—who might have more atelectasis and a little worse hypoxemia, and in whom it might be easier to diagnose ALI because of the bilateral atelectasis and the lower P_{aO₂}/F_{I_{O₂}—had a much lower incidence of ALI.}

Bob, you focused primarily on mechanisms and ALI, but there are a lot of other patients who don't meet those criteria, and stretching their lungs might be detrimental—maybe not full-blown VILI, but cardiac abnormalities, decreased oxygen delivery, intrinsic PEEP, and other things that may also be detrimental.

And I agree with Neil about starting at a lower V_T ; my default starting V_T is approximately 8 mL/kg of predicted body weight, and then I assess the patient, and if they're uncomfortable and their lungs are very compliant, then I may let them take bigger breaths, but if they develop ALI, then I will reduce it to 6 mL/kg. If the normal physiologic V_T is 6–8 mL/kg throughout life, why do we have to push it to 10 or 12 mL/kg when a patient is sick?

1. Gajic O, Dara SI, Mendez JL, Adesanya AO, Festic E, Caples SM, et al. Ventilator-associated lung injury in patients without ALI at the onset of mechanical ventilation. *Crit Care Med* 2004;32(9):1817–1824.

MacIntyre: I think that Mayo Clinic study is important. Their data on lung mechanics on day 1 show that the group that got the biggest V_T actually had the healthiest lungs. Two thirds of them were postoperative patients and their lung compliance was almost twice as good as the group that got the smaller V_T . So they started off with healthier lungs. I think what they're seeing is clinicians who say, "This patient has pretty good looking lungs, the plateau pressure is not too bad, so he can tolerate a bigger V_T , and I'll give it to him." And then the patient gets ALI.

Kacmarek: The problem with the Mayo data is that they did not indicate the plateau pressure: only the peak pressure. The same is true of most of the data in their second review, in which they looked at Esteban's data.¹ Without the plateau pressure it's very difficult to interpret the level of stretch.

I have a difficult time accepting that a V_T of 10 mL/kg with a very low plateau pressure would cause cardiovascular embarrassment. You have to have a high intrathoracic pressure to cause cardiovascular embarrassment. Without high intrathoracic pressure it doesn't matter what volume of gas you deliver, because if you don't stretch the lung and you don't increase pleural pressure with that volume delivery, you can't increase the intrathoracic pressure. Unless you increase alveolar pressure, which increases pleural pressure, you won't impede venous return.

1. Gajic O, Frutos-Vivar F, Esteban A, Hubmayr RD, Anzueto A. Ventilator settings as a risk factor for acute respiratory distress syndrome in mechanically ventilated patients. *Intensive Care Med* 2005;31(7):922–926.

Hurford: Speaking as an anesthesiologist, in the operating room we often use comparatively high V_T , but we don't create the lung injury that you're talking about. Wrigge and co-workers¹ looked at indices of lung injury, including P_{aO_2} and release of inflammatory mediators, in relatively normal surgery patients who received relatively high V_T , but, because the transpulmonary pressure was low, and the plateau pressure was well below 30 cm H₂O, they found no evidence of lung injury. That suggests that if plateau pressure is low, it won't cause lung injury.

Similarly, if you ventilate a small portion of the lung at a very low V_T , as in one-lung or one-lobe ventilation, that can also cause lung injury in normal lungs. The situation I've encountered is that when I conduct one-lung ventilation, or one-lobe ventilation, in which I might be only ventilating a small section of the lung, or one lung, even a 6 mL/kg V_T may occasionally produce plateau pressure well above 30 cm H₂O. Those are the patients I worry about.

1. Wrigge H, Zinserling J, Stuber F, von Spiegel T, Hering R, Wetegrove S, et al. Effects

of mechanical ventilation on release of cytokines into systemic circulation in patients with normal pulmonary function. *Anesthesiology* 2000;93(6):1413–1417.

Pierson:* I want to hark back to Ken's rhetorical question of where did that 15 mL/kg V_T come from in the first place? It came out of the operating room, with studies 40 years ago from Massachusetts General Hospital,^{1–3} with healthy people undergoing anesthesia. Those patients rapidly developed increasing alveolar-arterial oxygen difference and, presumably, micro-atelctasis with physiologic V_T of 5–7 mL/kg, but those changes were prevented—at least during the short-term of those observations—by using 15 mL/kg. And it was because of that, and the habit of using large V_T in the operating room, that everyone began using large V_T when ventilating patients with ARF.

There has definitely been a trend in the last 15 years toward progressively lower V_T that ordinary clinicians use in setting patients up on ventilators. This was documented in a recent study from Harborview Medical Center,⁴ which showed that among patients resuscitated from ventricular fibrillation arrest out of the hospital, and who had no problems with their lungs, the starting V_T progressively decreased over the period of that study, which was about 12 years. In concert with that was an increase in the diagnosis of atelctasis during those periods. So atelctasis probably occurs more often and is more widespread when we use smaller V_T , in people with and without ALI.

The issue we have to contend with is whether this is an important problem from a clinical perspective. Bendixen and associates¹ thought it was, because they recommended large V_T , because it didn't happen when you used large V_T .

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But now, based on what we know about ALI and the potential hazards of larger V_T , should we be unconcerned about a little atelectasis, either radiographically or in terms of a larger alveolar-arterial oxygen difference?

1. Bendixen HH, Hedley-Whyte J, Laver MB. Impaired oxygenation in surgical patients during general anesthesia with controlled ventilation: a concept of atelectasis. *N Engl J Med* 1963;269:991-996.
2. Bendixen HH, Bullwinkel B, Hedley-Whyte J, Laver MB. Atelectasis and shunting during spontaneous ventilation in anesthetized patients. *Anesthesiology* 1964;25:297-301.
3. Pierson DJ, Lakshminarayan S. Postoperative ventilatory management. *Respir Care* 1984;29(6):603-610; discussion 611-613.
4. Wongsurakiat P, Pierson DJ, Rubenfeld GD. Changing pattern of ventilator settings in patients without ALI: changes over 11 years in a single institution. *Chest* 2004;126(4):1281-1291.

MacIntyre: The smaller- V_T group clearly had more atelectasis, because their P_{O_2} was worse and their lung compliance was worse, and yet their survival was better. So if there is a risk from atelectasis, it's overwhelmed by the benefits of lower V_T . But why not start at 6 mL/kg as a default condition, and then adjust accordingly? Why not start at a V_T that at least has been shown to be effective, and then adjust upward if necessary?

Kacmarek: I counter that question by asking, why not start at a reasonable plateau pressure that the ARDS Network data indicates is safe? I would say start at a plateau pressure around 25 cm H_2O and then change that as necessary to maintain appropriate gas exchange.

MacIntyre: So you completely dismiss the idea of a tidal stretch injury?

Kacmarek: As I said before, it is localized overdistension. I can't tell

whether a V_T of 6 mL/kg will cause overdistension unless I know the patient's lung mechanics.

MacIntyre: Let me clarify the question. I agree that overdistension causes injury. The question that Ken and I are wrestling with is whether there is a *second* type of injury caused by cycling above the normal V_T , even if the plateau pressure is low? We don't have the data to answer that question. We're coming at it very indirectly. In a study a long time ago, Mascheroni¹ infused acid into the fourth ventricle of sheep, and hyperventilation caused lung injury. And they were using tidal volumes within the normal range and below the maximal stretch of the lungs.

1. Mascheroni D, Kolobow T, Fumagalli R, Moretti MP, Chen V, Buckhold D. Acute respiratory failure following pharmacologically induced hyperventilation: an experimental animal study. *Intensive Care Med* 1988;15(1):8-14.

Kacmarek: Yes, but they also injected salicylate, and is not clear what impact that had on lung permeability. Even a mediocre marathon runner doesn't suffer lung injury from 6-8 hours of running, and their tidal volumes are enormous. A seasoned athlete can run a marathon much faster, but there are folks who take 8 hours to run a marathon.

MacIntyre: I think that comparison is a little unfair. They're only running for 6 or 8 hours. We're ventilating people for 6 days.

Kacmarek: And I'm not talking about those kinds of volumes. I don't think we're off the mark with the volumes we're talking about. The question is, What is the more appropriate variable to monitor: plateau pressure

or V_T ? I believe the data clearly point to plateau pressure.

MacIntyre: Why do you polarize it so? I'm arguing that of course you should monitor plateau pressure, but why not reduce the V_T at the same time? Why do you make it so black-and-white?

Kacmarek: But I'm not recommending large V_T .

MacIntyre: You said if the plateau pressure was less than 25 cm H_2O , you'd use 8-10 mL/kg.

Kacmarek: Yes, I said *up to* 10 mL/kg if the plateau pressure is < 25 cm H_2O . If the plateau pressure is low, I think it's not in the patient's best interest to force a V_T of 6 mL/kg, which may require substantial sedation, which increases the duration of mechanical ventilation and has its own complications.

MacIntyre: But it doesn't require more sedation.

Kacmarek: I'm going to remember that the next time you're on the ventilator, and I force a 6 mL/kg V_T on you.

MacIntyre: My advance directive reads: "Please keep Kacmarek away from me."

Kacmarek: Recall the figure that shows the ARDS Network data on plateau pressure versus mortality [Fig. 1]. It was the plateau pressure, not the V_T , that determined the mortality in both the lower and higher V_T groups. Higher plateau pressure was associated with higher mortality, and vice versa. It didn't matter what the V_T was.