# Critical Care Perspective

# Tidal Volume Reduction in Patients with Acute Lung Injury When Plateau Pressures Are Not High

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Use of a volume- and pressure-limited mechanical ventilation strategy improves clinical outcomes of patients with acute lung injury and acute respiratory distress syndrome (ALI/ARDS). However, the extent to which tidal volumes and inspiratory airway pressures should be reduced to optimize clinical outcomes is a controversial topic. This article addresses the question, "Is there a safe upper limit to inspiratory plateau pressure in patients with ALI/ARDS?" We reviewed data from animal models with and without preexisting lung injury, studies of normal human respiratory system mechanics, and the results of five clinical trials of lung-protective mechanical ventilation strategies. We also present an original analysis of data from the largest of the five clinical trials. The available data from each of these assessments do not support the commonly held view that inspiratory plateau pressures of 30 to 35 cm $H_2O$ are safe. We could not identify a safe upper limit for plateau pressures in patients with ALI/ARDS.

**Keywords:** acute respiratory distress syndrome; acute lung injury; plateau; mechanical ventilation

Ventilator-induced lung injury (VILI) is reduced and clinical outcomes of patients with acute lung injury and the acute respiratory distress syndrome (ALI/ARDS) are improved if the mechanical ventilation (MV) approach uses smaller tidal volumes ($V_T$) and lower inspiratory pressures than were used in the past (1–7). However, there is controversy regarding the extent to which $V_T$ and inspiratory airway pressures should be reduced to achieve these objectives (8–18). Some investigators have recommended that $V_T$ in patients with ALI/ARDS should be reduced to maintain inspiratory plateau pressures ($P_{plat}$) of less than 30 to 35 cm $H_2O$ (or that MV with pressure-controlled modes should limit inspiratory pressures to no more than 30–35 cm $H_2O$) (1, 11–13). This suggests that $P_{plat}$ lower than 30 to 35 cm $H_2O$ may be considered safe, and that further reductions in $V_T$ and $P_{plat}$ are without benefit. Several lines of evidence have been interpreted to support this suggestion, including the results of animal models of VILI (19, 20), considerations of normal human physiology (21), and comparisons of clinical trials of lung-protective MV strategies

(3, 4, 22–24). The purpose of this article is to review these lines of evidence and present an original analysis of the data from a large clinical trial to determine if there is a sound scientific basis to consider $V_T$ reduction unnecessary when $P_{plat}$ levels are lower than 30 to 35 cm $H_2O$. Some of the results of the original analysis contained in this review were previously reported in an abstract (25).

## ANIMAL MODELS OF VILI

In a consensus statement regarding the use of MV, the investigators said, "Based primarily on animal data, a plateau pressure $\geq$ 35 cm $H_2O$ is of concern. We, therefore, recommend that when plateau pressure equals or exceeds this pressure, that tidal volume can be decreased" (1). Abundant data support this statement (6, 7, 19, 20, 26–33). However, many animal studies suggest that, under some circumstances, $P_{plat}$ lower than 35 cm $H_2O$ should also be of concern.

In intact rats without other causes of ALI, perivascular edema occurred in all animals ventilated for 60 min with peak inspiratory pressures (PIP) of 30 cm $H_2O$ (26, 28) and in three of six animals ventilated with PIP of 14 cm $H_2O$ (28). In isolated rat lungs, edema occurred at PIP as low as 13 cm $H_2O$ (29). In animal models with other causes of ALI, VILI has been observed at relatively low airway pressures and $V_T$ (6, 7). In intact rats with hydrochloric acid–induced lung injury, extravascular lung water was 55% lower after 4 h of MV with $P_{plat}$ of 21 cm $H_2O$ ($V_T$, 6 ml/kg) than with $P_{plat}$ of 30 cm $H_2O$ ($V_T$, 12 ml/kg). Lung water was reduced further when $P_{plat}$ levels of 16 cm $H_2O$ were used ($V_T$, 3 ml/kg; Figure E1 in the online supplement) (6). Histologic examination of lung tissue and indices of endothelial and epithelial injury also showed less injury at lower $V_T$ and airway pressures. A similar study compared alveolar protein permeability in a rabbit model of *Pseudomonas* pneumonia. After 8 h, the PIP of animals ventilated with $V_T$ of 6 and 15 ml/kg increased from 17 to 21 cm $H_2O$ and from 22 to 35 cm $H_2O$, respectively. Alveolar protein permeability was 30% lower in animals that received the lower $V_T$ and PIP (7).

Although data from animal models of VILI vary considerably, depending on species, preparation (open or closed chest), duration of MV, and presence or absence of other causes of lung injury (19), these studies suggest that the $P_{plat}$ or PIP threshold for VILI in rats and rabbits is considerably lower than 30 to 35 cm $H_2O$. However, rodent chest wall compliance is high relative to lung compliance, and VILI from overdistention probably occurs at lower airway pressures than in larger animals or humans. Therefore, direct application of the results of these small animal studies to the management of clinical ALI/ARDS is difficult. Studies in large animal models may be more informative.

In isolated dog lobes ventilated for 20 to 30 min, there was little indication of VILI (increased microvascular permeability)

unless PIP exceeded 42 cm $H_2O$ (32). In open-chest dogs, VILI (increased lung lymph flow and decreased lymph-to-plasma protein ratio) occurred after 30 min of MV with PIP of 64 cm $H_2O$ but not with PIP of 22 cm $H_2O$ (33). In intact lambs, lung lymph flow and protein concentration did not change significantly after 4 h of MV with PIP of 33 and then 43 cm $H_2O$. However, lymph flow and protein concentration increased after an additional 4 h of MV with PIP of 61 cm $H_2O$, indicating that pulmonary vascular permeability had increased (34). These studies in dogs and lambs suggest that VILI may not occur until PIP levels are as high as 40 to 60 cm $H_2O$. However, these experiments were relatively short in duration. Longer periods of MV could lead to VILI at lower pressures. In the studies in intact lambs (34), the 4-h period of MV at the highest PIP occurred after sequential 4-h periods of MV at PIP of 33 and 43 cm $H_2O$ in the same animals. The indications of vascular injury late in the experiments may represent the cumulative effect of MV at the lower PIP in addition to VILI caused by the final period of MV at the highest PIP. Unfortunately, few studies have considered the effects of prolonged periods (many hours to days) of MV at moderate airway pressures and lung injury. However, in one notable study in intact sheep, VILI (increased lung water and decreased surfactant function) was observed after 48 h of MV with PIP of 30 cm $H_2O$ (31). In many of these animals, $V_T$ was reduced over time to limit PIP to 30 cm $H_2O$. This suggests that a strategy of reducing $V_T$ only when PIP levels exceed 30 cm $H_2O$ may not be sufficiently protective.

In summary, abundant evidence from animal models supports the concern for $P_{plat}$ greater than 35 cm $H_2O$. Some studies suggest that VILI does not occur after relatively brief periods of MV with PIP as high as 40 to 60 cm $H_2O$. However, there is little evidence to support the safety of prolonged MV with $P_{plat}$ as high as 30 to 35 cm $H_2O$.

## CONSIDERATIONS OF NORMAL HUMAN PHYSIOLOGY

The distending pressure of the normal relaxed human respiratory system (equivalent to $P_{plat}$) at total lung capacity is approximately 37 cm $H_2O$ (21, 35). Normal humans can inspire voluntarily to their total lung capacities without apparent adverse effects, suggesting that the mechanical forces associated with these distending pressures are safe (36). However, we were unable to find any evidence that these forces and pressures at total lung capacity are safe when applied thousands of times over periods of hours or days, with or without preexisting injury. On the other hand, experimental evidence suggests that spontaneous breathing with large $V_T$ may be injurious. Sodium salicylate injected into the cisterna magna of intact sheep caused spontaneous ventilation with large $V_T$ and rapid respiratory rates (30). In a control group, sheep received sodium salicylate injections, neuromuscular blockade, and MV with physiologic $V_T$ and respiratory rates. After approximately 12 h, the alveolar-arterial $P_{O_2}$ gradients were significantly higher in the animals that hyperventilated spontaneously, as were the lung-to-bodyweight ratios. These findings could represent a hydrostatic effect of spontaneous breathing with pleural pressures that are lower than those that occur during MV (37). However, there were histologic changes consistent with ALI in the lungs of the animals that breathed spontaneously. These results suggest that the mechanical forces in the lungs during spontaneous breathing with supraphysiologic $V_T$ may not be safe over periods of hours to days.

## REVIEW OF CLINICAL TRIALS OF LUNG-PROTECTIVE VENTILATION STRATEGIES

Five clinical trials compared outcomes of patients with ALI/ARDS randomized to either a MV strategy with higher $V_T$ and relatively high inspiratory airway pressures or a volume- and pressure-limited MV strategy (Table 1) (3, 4, 22–24). In the two studies in which volume- and pressure-limited strategies were associated with lower mortality, mean $P_{plat}$ in the higher $V_T$ study groups exceeded 32 cm $H_2O$ (3, 4). In the three studies in which volume- and pressure-limited strategies were not associated with lower mortality (nonbeneficial studies), mean $P_{plat}$ levels in the higher $V_T$ groups were lower than 32 cm $H_2O$ (22–24). This suggested to some that 32 cm $H_2O$ may be a safe $P_{plat}$ threshold (11–13, 38). There were modest differences in the mean $V_T$ and resulting $P_{plat}$ in the different study groups between the beneficial and nonbeneficial studies, and these differences may have contributed to the variable outcomes (39). However, in each of the nonbeneficial studies (22–24), the numbers of patients in the higher $V_T$ groups whose $P_{plat}$ exceeded 32 cm $H_2O$ were considerably greater than in the volume- and pressure-limited groups (Figure E2) (24). If 32 cm $H_2O$ is the critical value that separates safe from unsafe $P_{plat}$, then mortality should have trended lower in the volume- and pressure-limited study groups of these trials. The absence of such trends in these studies suggests that there may have been imbalances in the randomization groups at baseline that favored patients in the higher $V_T$ study groups (40).

## $V_T$ REDUCTION AND $P_{plat}$ IN PATIENTS WITH ALI/ARDS

The ARDS Network trial of MV with higher versus lower $V_T$ enrolled 861 patients with ALI/ARDS (4). Of these, $P_{plat}$ levels (obtained with a 0.5-s inspiratory hold) were available on the

**TABLE 1. SUMMARY OF RANDOMIZED CONTROLLED TRIALS OF VOLUME- AND PRESSURE-LIMITED MECHANICAL VENTILATION**

| Study | $V_T$ (ml/kg) | | Mean $P_{plat}$ (cm $H_2O$) | | Mortality (%) | |
|---|---|---|---|---|---|---|
| | Low | High | Low | High | Low | High |
| Amato and colleagues (3) (n = 53)*† | 6 | 12 | 31.8 | 34.4 | 38 | 71 |
| ARDSnet (4) (n = 861)*‡ | 6.2 | 11.8 | 25 | 33 | 31 | 40 |
| Stewart and colleagues (22) (n = 120)§ | 7.2 | 10.8 | 22.3 | 26.8 | 50 | 47 |
| Brower and colleagues (23) (n = 52)‡ | 7.1 | 10.3 | 24.9 | 30.6 | 50 | 46 |
| Brochard and colleagues (24) (n = 116)‖ | 7.1 | 10.3 | 25.7 | 31.7 | 47 | 38 |

*Definition of abbreviations*: ARDSnet = Acute Respiratory Distress Syndrome Network; $P_{plat}$ = plateau pressure.
* Significant mortality benefit associated with $V_T$ reduction.
† $V_T$ set according to measured bodyweight.
‡ $V_T$ set according to predicted bodyweight.
§ $V_T$ set according to ideal bodyweight.
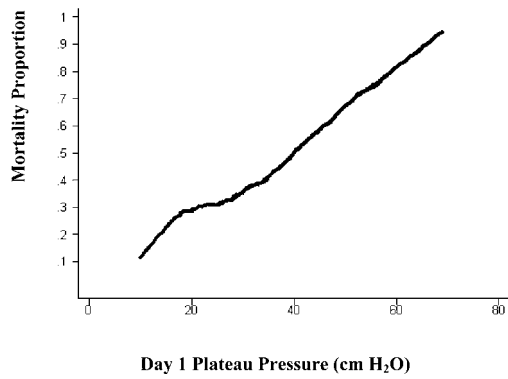‖ $V_T$ set according to dry bodyweight.

**Figure 1.** Robust locally weighted regression and smoothing (Lowess) plot (bandwidth, 0.4) of mortality and Day 1 plateau pressure ($P_{plat}$; cm $H_2O$) among patients enrolled in the ARDS Network study (n = 787) (4, 47). The Lowess method is a nonparametric smoother that uses overlapping neighborhoods of data to estimate a local effect. A bandwidth of 0.4 means 20% of the data on either side of a given $P_{plat}$ will contribute to a local estimate of mortality at that $P_{plat}$. Data at the high and low ends of the curve therefore represent fewer observations. Data are smoothed using a tricubic weight function so that points furthest from the $P_{plat}$ of interest are assigned the least weight (and approach zero).

first day after randomization (Day 1 $P_{plat}$) for 93% of patients in the higher $V_T$ group (n = 399) and 90% of patients in the lower $V_T$ group (n = 388). We used data from these patients to address the following question: "Is there a safe $P_{plat}$ below which there is no beneficial effect of $V_T$ reduction?" To demonstrate the relationship of mortality versus $P_{plat}$ for all patients, we constructed a plot of mortality against Day 1 $P_{plat}$ (Figure 1). The relationship shows decreasing mortality as Day 1 $P_{plat}$ declines from high to low levels. It does not reveal a safe $P_{plat}$ threshold within the range of Day 1 $P_{plat}$ levels measured in patients with ALI/ARDS. On the other hand, this relationship should not be interpreted to mean that $V_T$ of patients with ALI/ARDS should be decreased below 6 ml/kg to achieve very low $P_{plat}$. Most of the data represented at the very low $P_{plat}$ levels were obtained in patients with relatively high respiratory system compliances while they received $V_T$ of 6 ml/kg predicted bodyweight. $V_T$ was not decreased below 6 ml/kg in these patients. Effects on mortality of reducing $V_T$ below 6 ml/kg in patients whose $P_{plat}$ levels are 30 cm $H_2O$ or lower are unknown.

To assess for independent effects of $V_T$ reduction and $P_{plat}$ on mortality, we constructed a multivariable logistic regression model. For this purpose, each study group was stratified by quartile of Day 1 $P_{plat}$. With this approach, we identified groups of patients who would have had similar $P_{plat}$ had they been randomized to the same $V_T$ strategy. Corresponding quartiles in each randomization group have different $P_{plat}$ ranges because $V_T$ is one of the determinants of $P_{plat}$ (41). For example, Day 1 $P_{plat}$ levels in the lowest $P_{plat}$ quartile (Quartile 1) of the higher $V_T$ group (range, 16–26 cm $H_2O$) are higher than the Day 1 $P_{plat}$ levels of Quartile 1 in the lower $V_T$ group (range, 10–20 cm $H_2O$). Stratifying patients with similar $P_{plat}$ but different $V_T$ into corresponding subsets would have been inappropriate for this purpose because it would have classified patients with more severe lung injury receiving lower $V_T$ (i.e., those with the lower respiratory system compliances) into a subset that corresponded to patients with less severe injury receiving higher $V_T$.

In a bivariate (simple) logistic regression, the lower $V_T$ strategy was associated with a lower mortality than the higher $V_T$ strategy (p = 0.02). Bivariate analysis also demonstrated that lower $P_{plat}$ quartiles were associated with reduced mortality when compared with higher $P_{plat}$ quartiles (p ⩽ 0.039; Table 2).

In addition to $V_T$ assignment and $P_{plat}$ quartile, we included in our multivariable logistic regression model any baseline characteristic in which there was a trend toward a difference (p ⩽ 0.10) between corresponding quartiles. The only such variable was Acute Physiology, Age, and Chronic Health Evaluation (APACHE) III score (42), which was higher in Quartile 1 of the higher $V_T$ group (84.5 ± 24.3 vs. 78.1 ± 24.3 [mean ± SD], p = 0.07; Table E1). In the final regression model, lower $V_T$ assignment, lower $P_{plat}$ quartile, and lower APACHE score were all significant predictors of lower mortality (Table 2). Importantly, the interaction between $V_T$ assignment and $P_{plat}$ quartiles was not significant (p ⩾ 0.23 for all quartiles). This suggests that patients in the higher $V_T$ group would have benefited from $V_T$ reduction in each of the quartiles, including the two in which $P_{plat}$ levels were already 31 cm $H_2O$ or lower (Figure 2).

There were 399 patients in the two lower $P_{plat}$ quartiles of this analysis, including 205 patients with higher $V_T$ whose Day 1 $P_{plat}$ levels were 31 cm $H_2O$ or lower. The reduction in mortality associated with the volume- and pressure-limited strategy in these patients was 6.9%. This difference was not statistically significant (p = 0.13). However, the original clinical trial required enrollment of as many as 1,000 subjects to detect a difference in mortality between study groups of 10% (50 and 40%). A trial designed to demonstrate a difference of 6.9% would require enrollment of up to 1,900 subjects (two-sided test, α = 0.05, power = 0.90).

In a previous report, we analyzed the effects of $V_T$ reduction on mortality after dividing both study groups into quartiles

## TABLE 2. SUMMARY OF LOGISTIC REGRESSION ANALYSIS

| Variable | Unadjusted | | | Adjusted | | |
|---|---|---|---|---|---|---|
| | OR | p Value | 95% CI | OR | p Value | 95% CI |
| Low $V_T$ | 0.71 | 0.022 | 0.53–0.95 | 0.73 | 0.049 | 0.54–1.0 |
| Traditional $V_T$ | 1.00 | NA | NA | 1.00 | NA | NA |
| Quartile 1 | 0.44 | 0.000 | 0.29–0.67 | 0.48 | 0.001 | 0.31–0.74 |
| Quartile 2 | 0.47 | 0.000 | 0.31–0.72 | 0.53 | 0.004 | 0.34–0.82 |
| Quartile 3 | 0.65 | 0.039 | 0.43–0.98 | 0.73 | 0.156 | 0.48–1.12 |
| Quartile 4 | 1.00 | NA | NA | 1.00 | NA | NA |
| APACHE III* | 1.02 | 0.000 | 1.02–1.03 | 1.02 | 0.000 | 1.02–1.03 |

*Definition of abbreviations*: APACHE III = Acute Physiology, Age, and Chronic Health Evaluation; CI = confidence interval; NA = not applicable; OR = odds ratio for mortality before hospital discharge.
* APACHE III score was treated as a continuous variable and was not available for five patients. All others are categoric variables. APACHE scores can range from 0 to 299, with higher scores indicating more severe illness (42).
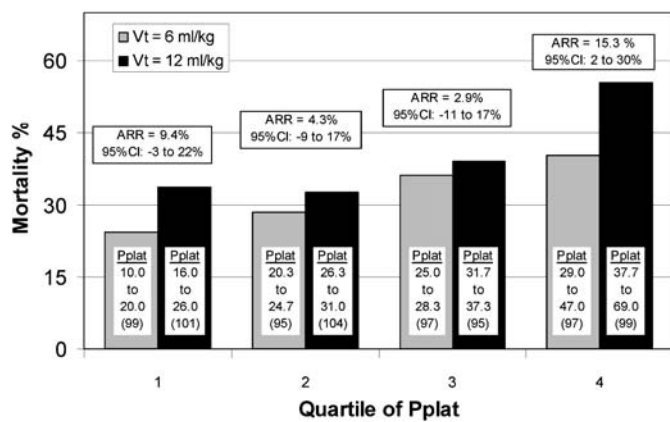
**Figure 2.** Mortality difference by quartile of Day 1 $P_{plat}$. The range of $P_{plat}$ levels in cm $H_2O$ and the number of patients (n) is detailed in each bar of the graph. ARR = absolute risk reduction; CI = confidence interval.

according to baseline respiratory system compliance (4). Mortality rates in the highest compliance quartiles (analogous to lowest $P_{plat}$ quartiles) did not favor the volume- and pressure-limited group. We have more confidence in our $P_{plat}$ quartile analysis because the required data were available for a greater number of patients (787 compared with 517). Moreover, VT can affect compliance when compliance is measured during tidal ventilation (higher VT was associated with higher measured compliance [4]), and the range of baseline VT was broad (17). In contrast, the Day 1 $P_{plat}$ levels were obtained when VT was tightly controlled in each study group. Therefore, the $P_{plat}$ quartiles better represent disease severity than the compliance quartiles. Importantly, in both the compliance and $P_{plat}$ quartile analyses, the interaction between quartiles and VT study group was not significant, suggesting that VT reduction was beneficial regardless of baseline compliance or Day 1 $P_{plat}$.

## CONCLUSIONS

The ARDS Network volume- and pressure-limited strategy used a VT goal of 6 ml/kg predicted bodyweight (4). With this approach, mean $P_{plat}$ was approximately 25 cm $H_2O$. Most patients would have had $P_{plat}$ below 31 cm $H_2O$ on VT that was greater than 6 ml/kg and less than or equal to 12 ml/kg. Some investigators have questioned the value of VT reduction in patients with ALI/ARDS whose $P_{plat}$ levels are already below 30 to 35 cm $H_2O$. We have been unable to find justification for this position after reviewing the results of animal models and comparing the results of clinical trials of lung-protective ventilation strategies. Our secondary analysis of the ARDS Network database suggests that there was a beneficial effect of VT reduction from 12 to 6 ml/kg predicted bodyweight, regardless of the $P_{plat}$ before VT reduction. We do not advocate using VT of less than 6 ml/kg predicted bodyweight to achieve very low $P_{plat}$. Potential adverse effects of volume- and pressure-limited MV should be considered in all patients. Hypercapnia may cause elevated intracranial pressure, pulmonary hypertension, decreased myocardial contractility, decreased renal blood flow, and the release of endogenous catecholamines (43, 44). Moreover, MV with low VT and $P_{plat}$ may cause more atelectasis and increase requirements for higher $F_{IO_2}$ and positive end-expiratory pressure (4, 45). All of these variables should be considered when titrating VT (46). However, we could not substantiate the widespread belief that VT reduction is without benefit when $P_{plat}$ is already lower than 30 to 35 cm $H_2O$.

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