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What Tidal Volumes Should Be Used in Patients without Acute Lung Injury?

Marcus J. Schultz, M.D., Ph.D., Jack J. Haitsma, M.D., Ph.D.,† Arthur S. Slutsky, M.D.,‡ Ognjen Gajic, M.D.§*

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Mechanical ventilation practice has changed over the past few decades, with tidal volumes (V_T) decreasing significantly, especially in patients with acute lung injury (ALI). Patients without acute lung injury are still ventilated with large—and perhaps too large—V_T. Studies of ventilator-associated lung injury in subjects without ALI demonstrate inconsistent results. Retrospective clinical studies, however, suggest that the use of large V_T favors the development of lung injury in these patients. Side effects associated with the use of lower V_T in patients with ALI seem to be minimal. Assuming that this will be the case in patients without ALI/acute respiratory distress syndrome too, the authors suggest that the use of lower V_T should be considered in all mechanically ventilated patients whether they have ALI or not. Prospective studies should be performed to evaluate optimal ventilator management strategies for patients without ALI.

OVER the past decades, tidal volumes (V_T) used by clinicians have progressively decreased from greater than 12–15 ml/kg to less than 9 ml/kg actual body weight.[1–6] Currently, there are guidelines that strongly support the use of lower V_T (*i.e.*, 6 ml/kg predicted body weight [PBW]) in patients with acute lung injury/acute respiratory distress syndrome (ALI/ARDS).[7] Widely-agreed-upon guidelines for setting V_T in patients who do not meet the ALI/ARDS consensus criteria are lacking, partly because there is a paucity of randomized controlled trial evidence on the best way to ventilate these patients.

We searched the literature for data addressing the size of V_T in patients without ALI/ARDS, including articles on clinical mechanical ventilation practice and preclinical animal experiments. Based on this review, we propose a ventilator strategy for patients without ALI/ARDS.

This article is accompanied by an Editorial View. Putensen C, Wrigge H: Tidal volumes in patients with normal lungs: One for all or the less, the better? Please see: ANESTHESIOLOGY 2007; 106:1085–7.

Ventilator-associated Lung Injury in Patients with ALI/ARDS

Insights into the pathophysiology of ventilation-induced lung injury came from animal studies that showed that mechanical ventilation with larger V_T rapidly results in pulmonary changes that mimic ARDS[8,9]: Injurious ventilatory settings result in development of diffuse alveolar damage with pulmonary edema,[10,11] recruitment and activation of inflammatory cells,[12,13] local production of inflammatory mediators (*e.g.*, cytokines),[14,15] and leakage of such mediators into the systemic circulation.[16,17] Ranieri *et al.*[18,19] confirmed a reduction in bronchoalveolar lavage fluid and systemic concentrations of inflammatory mediators with lung-protective mechanical ventilation as compared with conventional mechanical ventilation in a clinical trial.

The randomized trial of Amato *et al.*[20] found reduced 28-day mortality and faster liberation from mechanical ventilation with a lung-protective strategy, in part aiming at lower V_T, compared with conventional mechanical ventilation. The large, multicenter, prospective ARDS Network trial unambiguously confirmed that mechanical ventilation with lower V_T (6 ml/kg PBW) rather than traditional V_T (12 ml/kg PBW) resulted in a significant increase in the number of ventilator-free days and a reduction of in-hospital mortality.[21] Although initially concerns over increased sedation requirements hampered implementation of the so-called lung-protective mechanical ventilation strategy, two secondary analyses

* Staff Internist-Intensivist, Department of Intensive Care Medicine and Laboratory of Experimental Intensive Care and Anesthesiology, Academic Medical Center, University of Amsterdam. Interdepartmental Division of Critical Care, St. Michael's Hospital, University of Toronto, Toronto, Ontario, Canada. † Senior Investigator, Interdepartmental Division of Critical Care, St. Michael's Hospital, University of Toronto, Toronto, Ontario, Canada. ‡ Professor, Interdepartmental Division of Critical Care and Department of Medicine, St. Michael's Hospital, University of Toronto, Toronto, Ontario, Canada. § Staff Anesthesiologist-Intensivist, Division of Pulmonary and Critical Care, Mayo Clinic, Rochester, Minnesota.

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Address correspondence to Dr. Schultz: c/o Interdepartmental Division of Critical Care, University of Toronto, St. Michael's Hospital, Room 4-042 Queen Wing, M5B 1W8 Toronto, Ontario, Canada. m.j.schultz@amc.uva.nl.

of the ARDS Network trial showed this to be not true.[22,23]

In addition, the commonly held view that plateau pressures of 30–35 cm H_2O are safe was recently challenged.[24] Results from a secondary analysis of the prospective ARDS Network trial suggest that there is a beneficial effect of V_T reduction from 12 ml/kg to 6 ml/kg PBW, regardless of the plateau pressure, and lower V_T are also suggested for patients with plateau pressures less than 30 cm H_2O. Lower V_T are now strongly recommended in patients with ALI/ARDS.[7]

Ventilator-associated Lung Injury in Patients without ALI/ARDS

There are several reasons for not separating patients with ALI from those without ALI. First, diagnosing ALI/ARDS is at times challenging.[25] Although the ALI/ARDS consensus criteria seem relatively simple to apply, use of higher levels of positive end-expiratory pressure (PEEP) can improve both the oxygenation ratio and abnormalities on chest radiographs to the extent that the patients no longer have ALI (by definition).[8,26] Second, patients may not yet fulfill ALI/ARDS criteria at the initiation of mechanical ventilation but may develop lung injury in their disease course. Third, critically ill patients are at a constant threat of other causes of lung injury (*e.g.*, ventilator-associated pneumonia, transfusion-related lung injury). A multiple hit theory can be suggested in which repeated challenges lead to the clinical picture of ALI/ARDS.

Although average V_T in nonselected mechanically ventilated patients have declined to approximately 10 ml/kg PBW,[3,4,27] many patients are still exposed to relatively large V_T.[28,29] In addition to the theoretical arguments advanced above, there are clinical data suggesting that patients without a diagnosis of ALI/ARDS may benefit from lower V_T. In a large international prospective observational study, Esteban *et al.*[4] determined the survival of patients receiving mechanical ventilation and the relative importance of factors influencing survival. Among the conditions independently associated with increased mortality were characteristics present at the start of mechanical ventilation and occurring over the course of mechanical ventilation, but also factors related to patient management. Plateau pressures greater than 35 cm H_2O were associated with an increased risk for death. Although not definitive (the higher plateau pressures may simply have been an indication that the patients were sicker), this study suggested that V_T were too large (per lung size) in these patients, thereby causing an exaggeration of lung injury and eventually death.

In a single-center observational cohort study, Gajic *et al.*[29] reported a significant variability in the initial V_T settings in mechanically ventilated patients without ALI/ARDS. Of patients ventilated for 2 days or longer who did not have ALI/ARDS at the onset of mechanical ventilation, 25% developed ALI/ARDS within 5 days of mechanical ventilation. In a multivariate analysis, the main risk factors associated with the development of lung injury were the use of large V_T, transfusion of blood products, acidemia, and a history of restrictive lung disease. The odds ratio of developing ALI was 1.3 for each milliliter above 6 ml/kg PBW. Interestingly, female patients were ventilated with larger V_T (per predicted body weight) and tended to develop lung injury more often. The investigators explored this association in a large sample of patients prospectively enrolled in the aforementioned multicenter international study on mechanical ventilation[4] and found development of ARDS to be associated with the initial ventilator settings.[30] Large V_T (odds ratio 2.6 for $V_T > 700$ ml) and high peak airway pressure (odds ratio 1.6 for peak airway pressure > 30 cm H_2O) were independently associated with development of ARDS in patients who did not have ARDS at the onset of mechanical ventilation ("late ARDS").

Deleterious effects of large V_T have also been suggested in patients who were ventilated for only several hours (summarized in table 1). Fernandez *et al.*[31] collected intraoperative V_T of pneumonectomy patients. Of these patients, 18% developed postoperative respiratory failure; in half of the cases, these patients developed ALI/ARDS consensus criteria. Patients who developed respiratory failure had been ventilated with larger intraoperative V_T than those who did not (median, 8.3 *vs.* 6.7 ml/kg predicted body weight; $P < 0.001$). In a multivariate logistic regression analysis, larger intraoperative V_T, in addition to larger volumes of intraoperative fluid, was identified as a risk factor of postoperative respiratory failure.

Similar findings were found in a recent study by Michelet *et al.*[32] In this study, 52 patients undergoing planned esophagectomy for cancer were randomly assigned to a conventional ventilation strategy (V_T of 9 ml/kg during two-lung and one-lung ventilation; no PEEP) or a protective ventilation strategy (V_T of 9 ml/kg during two-lung ventilation, reduced to 5 ml/kg during one-lung ventilation; PEEP of 5 cm H_2O throughout the operative time). Patients who received protective strategy had lower blood levels of interleukin (IL)-1, IL-6, and IL-8 at the end of one-lung ventilation and 18 h after surgery. Protective strategy also resulted in higher arterial oxygen tension/fraction of inspired oxygen ratio during one-lung ventilation and 1 h after surgery and in a reduction of postoperative mechanical ventilation duration.

Several other investigators have prospectively tested the hypothesis that mechanical ventilation settings could be deleterious and induce or alter pulmonary inflammation in patients without lung injury at the onset of mechanical ventilation. The strongest evidence for ben-

Table 1. Prospective Studies on Tidal Volumes in Patients without ALI/ARDS

Reference	Type of Patients (Number of Patients)	V_T in Study Groups	Other Differences between Study Groups	Main Outcomes
Michelet *et al.*[32]	Patients undergoing esophagectomy (52)	9 ml/kg during two-lung and one-lung ventilation; no PEEP *vs.* 9 ml/kg reduced to 5 ml/kg during one-lung ventilation; PEEP	None	Lower blood levels of IL-1, IL-6, and IL-8, higher $Pa_{O_2}/F_{I_{O_2}}$ ratio during one-lung ventilation and after surgery; reduction of postoperative mechanical ventilation duration
Lee *et al.*[33]	Postoperative patients (103)	6 *vs.* 12 ml/kg ABW	None	Incidence of pulmonary infection tended to be lower; duration of intubation tended to be shorter
Wrigge *et al.*[34]	Patients during elective surgery (39)	6 *vs.* 15 ml/kg without PEEP *vs.* 6 ml/kg with PEEP	0 cm H_2O PEEP *vs.* 10 cm H_2O PEEP	After 1 h, no differences in plasma levels of TNF-α, IL-1, IL-6, and IL-10
Koner *et al.*[35]	Patients undergoing bypass grafting (44)	6 *vs.* 10 ml/kg with PEEP *vs.* 10 ml/kg without PEEP	0 cm H_2O PEEP *vs.* 5 cm H_2O PEEP	No differences in plasma levels of TNF-α and IL-6
Wrigge *et al.*[36]	Patients during major thoracic and abdominal surgery patients (64)	6 *vs.* 12 or 15 ml/kg	10 cm H_2O PEEP with lower V_T *vs.* 0 cm H_2O PEEP with larger V_T	No differences in time course of tracheal aspirate or plasma levels of TNF-α, IL-1, IL-6, IL-8, IL-12, and IL-10
Wrigge *et al.*[37]	Patients after cardiopulmonary bypass (44)	6 *vs.* 12 ml/kg PBW for 6 h	None	BALF levels of TNF-α were higher in patients ventilated with larger V_T; no differences in the time course of IL-6 and IL-8; no differences in plasma values
Zupancich *et al.*[38]	Patients after elective coronary artery bypass grafting (40)	8 *vs.* 10–12 ml/kg	10 cm H_2O PEEP with lower V_T *vs.* 2–3 cm H_2O PEEP with larger V_T	IL-6 and IL-8 levels in BALF and plasma increased only in patients ventilated with larger V_T
Reis Miranda *et al.*[39]	Patients after elective coronary artery bypass grafting (62)	4–6 *vs.* 6–8 ml/kg PBW	10 cm H_2O PEEP with lower V_T *vs.* 5 cm H_2O PEEP with larger V_T; OLC	IL-8 levels decreased more rapidly in patients ventilated with lower V_T
Choi *et al.*[40]	Patients during surgery for $\geq$ 5 h (40)	6 *vs.* 12 ml/kg PBW	10 cm H_2O PEEP with lower V_T *vs.* 0 cm H_2O PEEP with larger V_T	Ventilation with lower V_T prevented pulmonary coagulopathy as compared with ventilation with larger V_T

ABW = actual body weight; ALI = acute lung injury; ARDS = acute respiratory distress syndrome; BALF = bronchoalveolar lavage fluid; $F_{I_{O_2}}$ = fraction of inspired oxygen; IL = interleukin; OLC = open lung concept; Pa_{O_2} = arterial oxygen tension; PBW = predicted body weight; PEEP = positive end-expiratory pressure; TNF-α = tumor necrosis factor α; V_T = tidal volume.

efit of protective lung ventilation in patients without ALI/ARDS comes from a randomized clinical trial in postoperative patients.[33] Intubated mechanically ventilated patients in the surgical intensive care unit were randomly assigned to mechanical ventilation with V_T of 12 ml/kg actual body weight or lower V_T of 6 ml/kg. The incidence of pulmonary infection tended to be lower, and duration of intubation and duration of stay tended to be shorter for nonneurosurgical and noncardiac surgical patients randomly assigned to the lower V_T strategy, suggesting that morbidity may be decreased. Importantly, use of lower V_T seemed to be safe. Indeed, although use of lower V_T was associated with a statistically significant decrease in oxygenation, this was clinically irrelevant.

Wrigge *et al.*[34] randomly assigned patients without previous lung injury scheduled for elective surgery with general anesthesia to receive mechanical ventilation with either large V_T (15 ml/kg) or lower V_T (6 ml/kg) without the use of PEEP, or lower V_T with PEEP of 10 cm H_2O. Initiation of mechanical ventilation for 1 h caused no consistent changes in plasma levels of various medi-

ators, and no differences were found among the three study groups. Similar results came form a study by Koner *et al.*[35] Wrigge *et al.*[36] also studied the effects of mechanical ventilation on inflammatory responses during major thoracic or abdominal surgery. Patients undergoing elective thoracotomy or laparotomy were randomly assigned to receive either mechanical ventilation with V_T of 12 or 15 ml/kg, respectively, and no PEEP, or V_T of 6 ml/kg with PEEP of 10 cm H_2O. In this study, neither time course nor concentrations of pulmonary or systemic mediators differed between the two ventilatory settings within 3 h.

In contrast to the reports that did not show any deleterious effects of larger V_T in patients with noninjured lungs, other articles have demonstrated the injurious effects of large V_T.[37–40] Wrigge *et al.*[37] reported on the effect of postoperative mechanical ventilation with lower V_T on inflammatory responses induced by cardiopulmonary bypass surgery. In this study, immediately after surgery, mechanical ventilation was applied for 6 h with either V_T of 6 or 12 ml/kg PBW. The time course of inflammatory mediators did not differ significantly between the ventilatory strategies, although in bronchoalveolar lavage fluid sampled after 6 h of initiation of mechanical ventilation, tumor necrosis factor α levels were significantly higher in patients ventilated with large V_T. Similar results were found by Zupancich *et al.*, who randomly assigned elective coronary artery bypass patients to ventilation after surgery with large V_T/low PEEP (10–12 ml/kg and 2–3 cm H_2O) or low V_T/high PEEP (8 ml/kg and 10 cm H_2O).[38] Bronchoalveolar lavage fluid and plasma was obtained before sternotomy, immediately after cardiopulmonary bypass separation, and after 6 h of mechanical ventilation. IL-6 and IL-8 levels in the bronchoalveolar lavage fluid and plasma significantly increased before sternotomy in both groups but further increased only in patients ventilated with large V_T and low PEEP. Reis Miranda *et al.*[39] randomly assigned patients undergoing elective cardiopulmonary bypass to conventional ventilation with V_T of 6–8 ml/kg PBW and PEEP of 5 cm H_2O, or lung-protective ventilation with V_T of 4–6 ml/kg PBW and PEEP of 10 cm H_2O. IL-8 levels decreased more rapidly in the lung-protective group in the 3 days after the operation.

Choi *et al.*[40] randomly assigned patients scheduled for an elective surgical procedure (lasting $\geq$ 5 h) to mechanical ventilation with either large V_T (12 ml/kg) and no PEEP, or lower V_T and PEEP of 10 cm H_2O. In contrast to lung-protective mechanical ventilation, the use of larger V_T promoted procoagulant changes, potentially leading to fibrin depositions within the airways. With the use of lower V_T, these procoagulant changes were largely prevented.

Many mechanically ventilated critically ill patients are at risk of developing ALI/ARDS. Such patients may have lung injury but do not yet fulfill the ALI/ARDS consensus criteria at the start of mechanical ventilation. Patients with pneumonia or restrictive lung disease and those undergoing lung resection are among those at particular risk of ALI and ventilator-induced lung injury. Furthermore, in subjects without ALI but who have a predisposing condition, one or more "subsequent hits" can result in full-blown lung injury. Because nonprotective forms of mechanical ventilation may initiate or exacerbate pulmonary inflammation, use of large V_T may induce the "primary hit" or form a "second or third hit." Consequently, differences in results from the several pathophysiologic studies on ventilator-associated lung injury in healthy lungs may be explained. Longer periods of mechanical ventilation,[38,40] with or without extrapulmonary "hits,"[37,38] may cause more injury than shorter periods of mechanical ventilation with no extrapulmonary challenges.[34,36]

It is important to emphasize that "lower V_T" in fact are "normal V_T." Mammals have a normal V_T of 6.3 ml/kg.[41] Normal lung volumes can be predicted on the basis of sex and height.[42,43] In the ARDS Network trial, the predicted body weight of male patients was calculated as 50 + 0.91 (centimeters of height − 152.4); that of female patients was calculated as 45.5 + 0.91 (centimeters of height − 152.4).[21] Unfortunately, many textbooks of medicine state 10 ml/kg actual body weight as initial ventilator settings, exposing women and shorter patients to higher and potentially injurious V_T.[29]

Clinical Recommendations and Future Considerations

The inconsistent results of the aforementioned randomized studies do not definitively support the use of lower V_T. Most of the studies favoring a protective ventilation regimen in non-ALI patients measured surrogate markers such as inflammatory mediators instead of clinical outcome measures. Only three retrospective studies identified large V_T as a risk factor of respiratory failure. Therefore, although likely, clinical relevance of these results is not proven, and prospective studies ought to be performed.

It may be important to distinguish between mechanical ventilation in the operating room and the intensive care unit. Patients in the operating room are mechanically ventilated for a much shorter time than those in the intensive care unit. Furthermore, as stated above, a multiple hit theory can be suggested in which repeated challenges (including mechanical ventilation) lead to the clinical picture of ALI/ARDS. Both surgical patients and critically ill patients are at risk for several causes of lung injury. However, these may not be the same for both patient groups, and each challenge may have different effects in both groups. Finally, much of our knowledge on the importance of using lower V_T falls back on re-

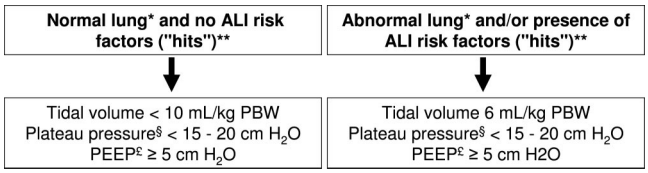

Fig. 1. Initial ventilator settings in patients without acute lung injury (ALI) or acute respiratory distress syndrome. * Interstitial lung disease, lung resection, severe pneumonia, edema. ** Sepsis, aspiration, transfusions. § The patient must be passive without significant spontaneous respiratory efforts or plateau pressure underestimates the propensity for pulmonary overdistention; if the patient has a stiff chest wall (*e.g.*, ascites), plateau pressure overestimates the propensity for overdistention. & To prevent atelectasis and maintain oxygenation. PBW = predicted body weight; PEEP = positive end-expiratory pressure.

search in the field of ALI/ARDS; the cellular response to injury, however, is different depending on the priming of pulmonary cells by ischemia or inflammation. Both processes can occur in the perioperative period. Therefore, it remains to be determined whether we need to ventilate patients in the operating room and in the intensive care unit equally (*i.e.*, with lower V_T).

Nevertheless, while awaiting the results of further prospective studies, we recommend avoidance of high plateau pressures and high V_T in patients who do not have ALI/ARDS at the onset of mechanical ventilation (fig. 1). These recommendations are based on expert opinion, as well as currently available evidence cited in this review.[24,29–32] Future studies are mandatory to confirm our recommendations. These recommendations do not take into account specific ventilator management of patients with obstructive lung diseases; problems encountered in these patients (dynamic hyperinflation) are not discussed in this review.

The main objective of lung-protective mechanical ventilation strategies is to minimize regional end-inspiratory stretch, thereby decreasing alveolar damage as well as alveolar inflammation/decompartmentalization.[18,19] In many patients with normal lungs (*e.g.*, patients undergoing short-term ventilation during low-risk surgical procedures, those with muscle weakness) the end-inspiratory stretch may be relatively low even with a V_T of 10 ml/kg PBW. In these patients, if the plateau pressure is low (*e.g.*, $<$ 15 cm H_2O) and they are not breathing spontaneously, lower V_T are probably not indicated—in fact, it may lead to atelectasis, especially if PEEP is low or not used at all. If plateau pressures increase (*e.g.*, $>$ 15–20 cm H_2O), V_T should be decreased to approximately 6 ml/kg PBW (fig. 1). Sufficient PEEP must be used to minimize atelectasis and maintain oxygenation. It is important to realize that plateau pressures may be misleading in some occasions: In patients with significant spontaneous breathing efforts, plateau pressures may be low, but the transalveolar pressures and lung overdistension may still be high because of large negative pleural pressures. Conversely, in patients who have decreased chest wall compliance (increased intraabdominal pressure, obesity), plateau pressures may be high without there being pulmonary overdistension.

Finally, the use of lower V_T could improve the hemodynamic tolerance of mechanical ventilation and in this way may improve outcome. Moreover, by decreasing the need for fluids, this beneficial hemodynamic effect could contribute to the decreased incidence of secondary ALI/ARDS. So far, no studies have been performed addressing this issue.

In conclusion, patients without ALI/ARDS may also be at risk for ventilator-associated lung injury. The association with the potentially injurious initial ventilator settings, in particular large V_T, suggests that ARDS in mechanically ventilated patients is in part a preventable complication. Prospective studies are required to further evaluate optimal ventilator management strategies for patients without ALI/ARDS at the onset of mechanical ventilation.

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much more variable. Therefore, the findings of both Solus-Biguenet *et al.*[11] and Cannesson *et al.*[12] must be validated in the setting of other pulse oximeter devices and different patient groups. Furthermore, the manufacturers of the various pulse oximeters must reintroduce the graphic display of POV as part of their usual output both onto the screen and into recoverable data logs.

Second, pulse oximeter plethysmographic density will be a function of tissue (nonchanging signal) and blood (changing signal) inputs, and its pulsatility will be primarily a function of changing blood density. Therefore, one must ask: What determines the blood density change over the sensing region? Clearly this will be a function of both perfusion pressure and vasomotor tone. As upstream vasomotor tone increases, for example, pulse oximeter plethysmographic changes would decrease for the same pulse pressure, and *vice versa* with vasodilation. Accordingly, it would be interesting to see the relation between PPV and POV as cardiovascular conditions are varied by pharmacologic intervention and disease. Clearly, this new use of pulse oximetry is exciting and potentially very important. Let us define its value carefully and, if it is proven to be useful, apply this new use of an established monitor broadly to help both monitor and guide resuscitation.

Michael R. Pinsky, M.D., Department of Critical Care Medicine, University of Pittsburgh, Pittsburgh, Pennsylvania.
pinskymr@ccm.upmc. edu

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Anesthesiology 2007; 106:1085–7

Tidal Volumes in Patients with Normal Lungs

One for All or the Less, the Better?

CME This editorial accompanies the article selected for this month's *Anesthesiology* CME Program. After reading the article and editorial, go to http://www.asahq.org/journal-cme to take the test and apply for Category 1 credit. Complete instructions may be found in the CME section at the back of this issue.

MECHANICAL ventilation (MV) using tidal volumes (V_T) of not more than 6 ml/kg predicted body weight (PBW) has been shown to result in reduction of systemic inflammatory markers, increased ventilator-free days, and reduction in mortality when compared with V_T of 12 ml/kg PBW in patients with acute lung injury (ALI) and acute respiratory distress syndrome (ARDS) (table 1).[1,2] In the low V_T group, V_T was reduced further to 5 or 4 ml/kg PBW if necessary to maintain plateau pressure (P_{plat}) at less than 30 cm H_2O.[1] However, decreasing V_T did not improve outcome in three other controlled trials investing V_T in ALI and ARDS patients, which was explained by differences in study design (table 1).[3–5] Using V_T of not more than 6 ml/kg PBW comparing a high positive end-expiratory pressure (PEEP)–low inspiratory oxygen fraction (F_{IO_2}) with a low PEEP–high F_{IO_2} strategy to prevent hypoxemia did not demonstrate advantageous of higher PEEP levels in ALI and ARDS patients.[6] The lack of effect of higher PEEP levels was partially explained by the resulting higher P_{plat}. A secondary analysis of the ARDS Network database showed a beneficial effect of V_T reduction from 12 ml/kg to 6 ml/kg PBW even in patients with low P_{plat} ranging between 16 and

This Editorial View accompanies the following article: Schultz MJ, Haitsma JJ, Slutsky AS, Gajic O: What tidal volumes should be used in patients without acute lung injury? ANESTHESIOLOGY 2007; 106:1226–31.

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Table 1. Randomized and Controlled Trials Comparing High *versus* Low Tidal Volume Ventilation in Patients with Acute Lung Injury and Acute Respiratory Distress Syndrome

	V_T, ml/kg		RR, breaths/min		PEEP, cm H_2O		$Paco_2$, mmHg		Mortality, %	
Trial	Low	High	Low	High	Low	High	Low	High	Low	High
Brochard *et al.*,[4] 1998 (n = 116)	7.1	10.5	NA	NA	10.6	10.8	60	41	46.6	37.9
Stewart *et al.*,[3] 1998 (n = 120)	7.2	10.8	23	17	8.7	8.4	54	46	50.0	47.0
Brower *et al.*,[5] 1999 (n = 52)	7.3	10.2	NA	NA	8.0	8.0	50	40	50.0	46.0
Amato *et al.*,[2] 1998 (n = 53)	6.0	12.0	20	17	16.4	8.7	55	33	38.0	71.0
ARDSnet,[1] 1998 (n = 861)	6.0	12.0	30	17	9.2	8.6	43	36	31.0	39.8

ARDSnet = Acute Respiratory Distress Syndrome Network; High = high tidal volume group; Low = low tidal volume group; NA = not applicable; $Paco_2$ = arterial carbon dioxide tension; PEEP = positive end-expiratory pressure; RR = respiratory rate; V_T = tidal volume.

26 cm H_2O before V_T reduction.[7] In this issue of ANESTHESIOLOGY, Schultz *et al.*[8] suggest the use of low V_T ventilation with PEEP levels above 5 cm H_2O in patients without ALI or ARDS in absence of large-scale prospective randomized trials.

Schultz *et al.* argue that in critically ill patients requiring MV for pulmonary edema, chronic obstructive pulmonary disease, congestive heart failure, aspiration, pneumonia, and trauma and after surgery not fulfilling ARDS criteria, mortality is associated with application of high V_T and P_{plat}.[8,9] Two retrospective analyses identified high airway pressures and V_T as independent risk factors for development of ALI and ARDS in patients requiring MV for acute respiratory failure.[10,11] It is of importance that these analyses included patients who were critically ill and had obviously either cardiopulmonary disease or ventilatory dysfunction and had thus *per se* a certain risk to develop ALI or ARDS. In an international cohort of unselected ARDS patients, neither P_{plat} nor V_T but use of low or no PEEP was associated with adjusted mortality.[12] Recent surveys demonstrated that V_T in critically ill patients is on average approximately 7–8 ml/kg BW but that still V_T between 12 and 18 ml/kg BW are used with low or nil PEEP.[13] Based on these data, it seems justified to request protective ventilator strategies in risk patients routinely and not to wait until the ALI or ARDS criteria are fulfilled. Although we do not have evidence that the ventilator settings suggested by Schultz *et al.*, which are essentially based on the ARDS Network protocol, are the best way to ventilate patients at risk for ALI or ARDS, they may prevent harm from the use of too-high V_T and low or nil PEEP levels.

Potential adverse effects of protective MV should be considered in all critically ill patients. Hypercapnia may cause increased intracranial pressure, pulmonary hypertension, decreased myocardial contractility, decreased renal blood flow, and release of endogenous catecholamines. Moreover, MV with low V_T and P_{plat} may promote atelectasis formation and increase requirements for higher FIO_2 and PEEP. To counteract cardiovascular depression caused by higher PEEP levels, fluid loading frequently associated with a positive fluid balance and/or catecholamines may be required. Therefore, all of these variables must be carefully considered and balanced when reducing V_T in individual patients.

Another question is whether protective ventilation is beneficial in patients with healthy lungs requiring short-term MV during anesthesia. Besides airway closure and reduced lung volumes in the supine position, distortion of rib cage (and lung), cephalad shift of the diaphragm, surfactant alteration, blood shift from abdomen to thorax, or a combination of these contribute to atelectasis formation in 90% of the patients during anesthesia.[14] In the 1960s, use of large V_T of approximately 15 ml/kg BW was advocated to reopen collapsed lung tissue and prevent impaired oxygenation during anesthesia.[15] Cyclic opening and closing caused by recruitment and derecruitment of small airways or lung units may lead to increased local shear stress (atelectrauma), which has been suggested to contribute to lung damage even in the absence of high P_{plat}.[16] However, for identical V_T and PEEP, reducing respiratory frequency attenuates or delays damage, provided that tidal ventilatory stress is sufficiently high.[17] This indicates that the doses of stress will matter. Whereas a ventilator cycle is repeated 20,000–40,000 times per day for a longer period in critically ill patients, probably not more than 900 cycles are commonly applied per 1 h of anesthesia. PEEP levels up to 10 cm H_2O are necessary in healthy patients during anesthesia to keep open those units that are most likely to close. However, any lung-protective benefit of PEEP is expected to be unimpressive when P_{plat} is modest or when the lung contains few recruitable units. Atelectatic area on computed tomography slice near the diaphragm is generally approximately 5–6% of the total lung area but can exceed 15–20% during uneventful anesthesia.[14] This may explain why in patients with healthy lungs undergoing elective major thoracic or abdominal surgery, MV with V_T of 12–15 ml/kg PBW and nil PEEP did not result in different pulmonary or systemic levels of inflammatory markers when compared with V_T of 6 ml/kg PBW and PEEP of 10 cm H_2O.[18]

Individual factors such as obesity, pneumoperitoneum, preexisting disease, and some surgical interventions may aggravate atelectasis formation. In addition, a variety of cofactors apart from ventilator settings such as position-

ing; systemic inflammatory response depending, for example, on the amount of surgical trauma; and higher precapillary[19] and lower postcapillary[20] pulmonary vascular pressures are important for generation or prevention of ventilator-induced lung injury. As highlighted by Schultz *et al.*, smaller randomized controlled trials of perioperative ventilatory strategies during major surgery revealed nonuniform results.[8] The impression is that ventilatory strategy is more relevant during surgery that triggers a higher inflammatory response, such as esophagectomy or cardiac surgery. However, these studies where not designed or powered to draw clinically relevant conclusions on clinical outcome measures, but studied inflammatory markers that are likely to but not proven to be surrogate markers of clinical outcome. To avoid high plateau pressures during one-lung ventilation, it has been suggested to use V_T of 5–6 ml/kg BW with PEEP in the absence of auto PEEP and to limit P_{plat} to less than 25 cm H_2O during one-lung ventilation.[21] However, application of PEEP in the dependent ventilated lung may increase pulmonary vascular resistance in this lung, diverting blood flow to the nonventilated lung, and thereby increasing intrapulmonary shunt and hypoxemia.

Although V_T of more that 10 ml/kg PBW are probably seldom used during anesthesia, there is no sound scientific basis to consider further V_T reduction necessary when P_{plat} is not higher than 16 cm H_2O to prevent lung injury.[8] Hypercapnia and its side effects can be generally prevented by moderate increased respiratory rates due to reduced carbon dioxide production during anesthesia. To counteract atelectasis formation during MV with low V_T and P_{plat}, higher F_{IO_2} and PEEP may be required. Especially in the presence of hypovolemia or shock, already moderate PEEP levels require fluid loading resulting in a positive fluid balance, which is a significant risk factor for major and minor morbidity and gastrointestinal paralysis after colorectal and major surgery.[22] To what extent postoperative complications are caused by respiratory dysfunction and ventilator settings during anesthesia is not yet clear.

Therefore, it is essential to tailor ventilator settings during anesthesia to the specific physiologic changes caused by surgery and preexisting disease of the patient, while treating the lungs gently. It may be concluded so far that the more ill the patient is, the more relevant the ventilatory strategy may be.

Christian Putensen, M.D., Hermann Wrigge, M.D. Department of Anesthesiology and Intensive Care Medicine, University of Bonn, Bonn, Germany. putensen@uni-bonn.de

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In Reply:—We are grateful to Dr. Tobinick for his clinical work evaluating etanercept for spinal pain, and his astute and prescient comments regarding our past and future endeavors.[1] First, we would like to point out that intradiscal tumor necrosis factor-α administration to relieve radicular pain is not quite analogous to the intradiscal injection of corticosteroid, which has been shown in previous studies to be no more effective than placebo for this condition.[2,3] Although inflammatory cytokines released from a degenerative disc might be the source of a painful, chemically irritated nerve root,[4–6] the disc itself is not the primary site of inflammation. Therefore, it is not surprising that intradiscal steroids are ineffective for lumbosacral radiculopathy. For predominantly axial low back pain presumed secondary to internal disc disruption, there is no scientific basis to suppose that the epidural injection of tumor necrosis factor-α inhibitors might be effective.

In contrast, the "mechanistic-based treatment of pain" paradigm advocates identifying the principal pain generator (*i.e.*, high concentrations of tumor necrosis factor α expelled from a degenerated disc) and treating it with target-specific medications (*i.e.*, tumor necrosis factor-α inhibitors).[7] In this context, injecting etanercept intradiscally can be viewed as a logical extension of this theory.

Second and perhaps more importantly, Dr. Tobinick seems to have overlooked the possibility that our intradiscal study was never intended to be the decisive word on the subject. Rather, our main objectives in undertaking this endeavor were to establish safety (hence our low, logarithmically increasing doses) in this setting and to determine dose ranges for the more definitive and auspicious epidural study he alluded to. The risk:benefit ratio is considerably higher for the epidural administration of etanercept in radiculopathy, a condition for which effective treatments are available, than it is for refractory low back pain patients already scheduled to undergo discography in a last-ditch effort to determine eligibility for either experimental intradiscal procedures or spine surgery. In addition, we have previously demonstrated that a significant portion of intradiscal injectate extravasates into the epidural space in patients with degenerative disc disease.[8] This suggests that the poor response of our patients may better reflect their long duration of pain (inflammatory cytokines play a more prominent role in acute pain than chronic pain) and multiple previous treatment failures, rather than the intradiscal route of administration.

Steven P. Cohen, M.D.,* Daniel Wenzell, M.D., Thomas M. Larkin, M.D. *Johns Hopkins School of Medicine, Baltimore, Maryland, and Walter Reed Army Medical Center, Washington, D.C. scohen40@jhmi.edu

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Perioperative Protective Ventilatory Strategies in Patients without Acute Lung Injuries

To the Editor:—We enjoyed reading the recent editorial and review article about optimal tidal volume (V_T) in patients without acute lung injury.[1,2] Overstretching healthy lungs with "traditional" V_T in the range of 10–15 ml/kg predicted body weight has been shown to trigger inflammatory and procoagulant alveolar responses. Furthermore, synergism rather than additivity between ventilator-induced alveolar stress and other injurious pulmonary factors (sepsis, ischemia–reperfusion, hypoxia–reoxygenation, major trauma and surgery) has been incriminated in damaging the alveolocapillary barrier. Ultimately, a multiple hit concept has emerged to explain the pathophysiologic mechanisms of acute lung injury.

We fully agree that protective ventilatory strategies (V_T of 6 ml/kg predicted body weight, inspiratory plateau pressure <20 cm H_2O, positive end-expiratory pressure [PEEP] levels >5 cm H_2O) currently applied in the intensive care unit should also be adopted to manage surgical patients with "vulnerable" lungs (*e.g.*, ongoing inflammatory/infectious disease, lung resection, major trauma and surgery). Unfortunately, in the majority of surgical patients with "healthy" lungs and no acute lung injury risk factors, the proposed ventilatory guidelines (V_T <10 ml/kg predicted body weight, inspiratory plateau pressure <20 cm H_2O, PEEP ≥ 5 cm H_2O) will little influence the incidence and severity of postoperative respiratory complications. Indeed, in this large population group, postoperative atelectasis is the commonest problem and the major cause of hypoxemia and nosocomial pneumonia. Accordingly, preventing atelectasis should be considered as an important objective in perioperative management.[3]

After anesthesia induction in the supine position, functional residual capacity is markedly reduced (approximately 0.7–1.3 l), and atelectasis develops in the dependent part of the lungs as a result of the loss of inspiratory muscle tone, cephalad diaphragm displacement, intrathoracic shift of blood volume, and oxygen resorption.[4] Starting from a lower functional residual capacity, the inspiratory–expiratory cycles are completed on a lesser compliant part of the pressure–volume curve, and the repetitive opening–closing of small airways and unstable alveoli initiate proinflammatory responses. Accordingly, the mechanical breath (V_T) is delivered to a nonhomogenous lung with a continuum ranging from variable degree of alveolar collapse (dependent areas) to a variable degree of overdistension (nondependent areas) that translates into ventilation–perfusion mismatch with impaired oxygenation.

After numerous failed attempts to acquire a Reply from the Editorial authors to this Letter, it is being published without the benefit of their response.—James C. Eisenach, M.D., Editor-in-Chief.

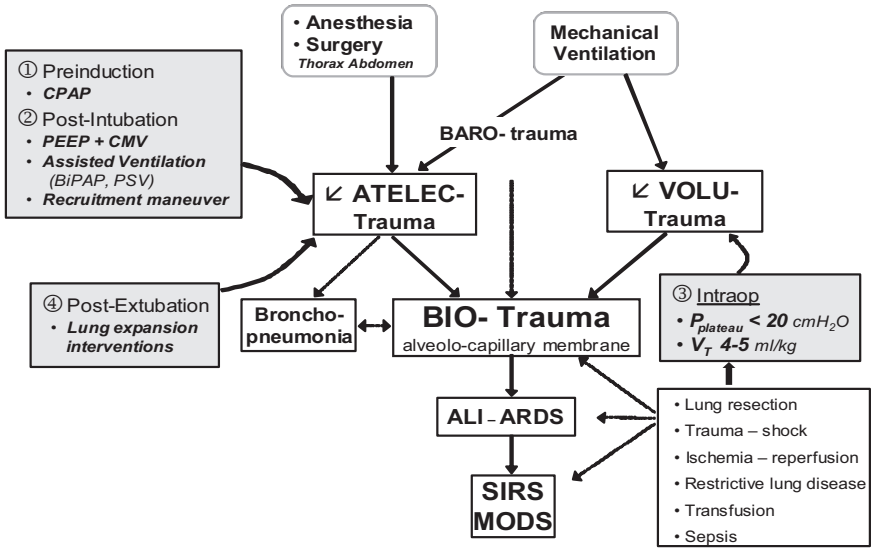

Fig. 1. Perioperative multimodal lung-protective approach. ALI = acute lung injury; ARDS = adult respiratory distress syndrome; BiPAP = bilevel positive airway pressure; CMV = controlled mechanical ventilation; CPAP = continuous positive airway pressure; Intraop = intraoperative; MODS = multiple organ dysfunction syndrome; PEEP = positive end-expiratory pressure; PSV = pressure-support ventilation; SIRS = systemic inflammatory response syndrome; V_T = tidal volume.

Besides limiting alveolar trauma with low V_T, attenuating the loss of functional residual capacity and preventing the formation of atelectasis should be attempted by a stepwise approach (fig. 1): (1) application of continuous positive airway pressure and PEEP during the induction of anesthesia[5,6]; (2) titration of low to moderate PEEP levels according to physiologic indices (lower inflection point of the pressure–volume curve, oxygenation indices, hemodynamics) and/or lung imaging techniques (*e.g.*, electrical thoracic impedance)[7]; (3) intraoperative lung recruitment maneuvers (manual inflation up to the vital capacity, "ramp" PEEP elevation up to 20 cm H_2O)[8]; (4) use of inspiratory oxygen concentration less than 80%; and (5) postoperative lung expansion strategies, including postural changes, early mobilization, and deep breathing exercises, as well as noninvasive ventilatory support.

Whenever possible, partial ventilatory modes (assist-controlled, pressure-support, bilevel positive airway pressure) through facial or laryngeal masks should be considered to avoid tracheal (re)intubation, to reduce the duration of mechanical ventilation, and to promote active displacement of the dependent part of the diaphragm. Intraoperatively, bilevel positive airway pressure ventilation has been shown to improve oxygenation indices by decreasing ventilation–perfusion mismatch.[9] Likewise, reversal of atelectasis and hypoxemia after major thoracic and abdominal surgery has been successfully achieved with noninvasive ventilatory techniques that resulted in a reduced need for reintubation and a lower incidence of pneumonia and sepsis.[10]

To date, further randomized controlled trials are needed to question whether a multimodal lung approach effectively prevents the formation of lung atelectasis and reduces the incidence of other pulmonary complications (pneumonia, respiratory failure, hypoxemia necessitating oxygen therapy) after various types of surgical procedures.

Marc Licker, M.D.,* John Diaper, R.A., Christoph Ellenberger, M.D. *University Hospital of Geneva, Geneva, Switzerland. marc-joseph.licker@hcuge.ch

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In Reply:—We thank Dr. Licker *et al.* for their comments on our article about optimal ventilator strategies in patients without acute lung injury.[1] Indeed, overstretching lungs with conventional and abnormally high tidal volumes during surgery has been shown to trigger procoagulant and proinflammatory alveolar responses in patients with healthy lungs, while not being particularly useful to prevent intraoperative atelectasis.[2,3] When we consider the concept of "multiple hits" to explain the pathophysiologic mechanisms of acute lung injury, a protective ventilatory strategy (using "normally sized" tidal volume to prevent lung stretch) is certainly indicated in the management of surgical patients with lungs at risk for lung injury (*e.g.*, with systemic inflammatory response syndrome, major trauma, major surgery). In this context, we would like to stress that the terminology chosen for a strategy aiming at prevention of overstretching the lungs (conventional *vs.* low tidal volumes) is wrong and maybe even misleading. Instead of "lower" tidal volumes, we should use the term "normal" or "normally sized" tidal volumes. It is like traffic speeding: traffic speeding during rush hours is very dangerous—but traffic

speeding is always dangerous, even when there are not so many other cars on the road; therefore, regulations mandate that we never drive faster than the speed limit. The size of a normal tidal volume is approximately 6 ml/kg for all mammals[4]—we should always consider use of normally sized tidal volumes rather than (very) high tidal volumes.

We agree that ventilation with normal tidal volumes as proposed in our review may not prevent the development of postoperative atelectasis. Although limited evidence supports the use of higher positive end-expiratory pressure, intraoperative recruitment maneuvers, lower oxygen fraction, and postoperative noninvasive ventilation,[5] a multimodal lung-protective approach has not been tested.

Although postoperative pulmonary complications are common and associated with significant morbidity, few studies investigated the influence of intraoperative ventilator and nonventilator management (*e.g.*, fluid balance, transfusions). Indeed, randomized controlled trials are needed to answer whether a multimodal lung-protective approach effectively prevents the formation of atelectasis and reduces the incidence of acute lung injury and other pulmonary complications after various types of surgical procedures.

Marcus J. Schultz, M.D., Ph.D., F.C.C.P.,* **Ognjen Gajic, M.D., F.C.C.P.** *Academic Medical Center, Amsterdam, The Netherlands. m.j.schultz@amc.uva.nl

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Endotracheal Tube with End-tidal Carbon Dioxide Port

To the Editor:—I read with interest the brief report by Dr. Al-Nabhani *et al.*[1] on problems of monitoring end-tidal carbon dioxide in extremely low-birth-weight infants during perioperative period. For the monitoring of end-tidal carbon dioxide in neonates, I agree that it is necessary to sample alveolar gases to avoid the dilution of carbon dioxide by dead space created by ventilating devices such as the endotracheal tube adaptor, the Y-piece of the breathing circuit, and even the T-piece for carbon dioxide sampling, and it is necessary to insert a catheter into the endotracheal tube for sampling of alveolar gases.

For sampling of alveolar gases without using an endotracheal catheter, an endotracheal tube with end-tidal carbon dioxide monitoring port (Mallinckrodt Inc., St. Louis, MO) is available. As shown in figure 1, the lumen for end-tidal carbon dioxide sampling extends to near the distal end of endotracheal tube. The outside diameter of the 3.0-mm uncuffed tube with monitoring port is 4.5 mm, compared with 4.3 mm for a standard uncuffed tube. Although the endotracheal tube with monitoring port is slightly larger in size by 0.2 mm, the difference is negligible. I have never had any problems with endotracheal intubation. With use of this tube, one can avoid the insertion of the catheter into the endotracheal tube, and hence avoid related complications.

Charles Her, M.D., F.C.C.P., New York Medical College, Valhalla, New York. charles6133@msn.com

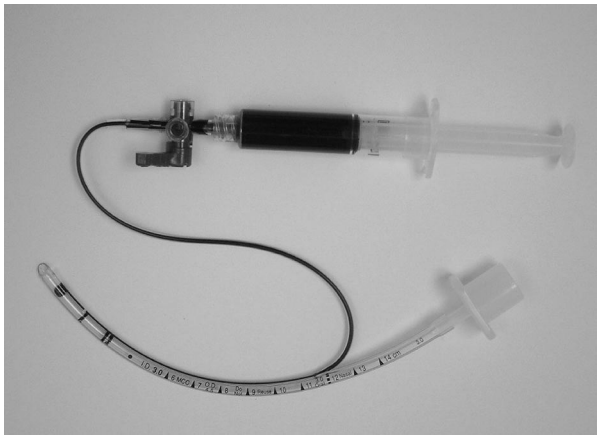

Fig. 1. A 3.0-mm uncuffed endotracheal tube with end-tidal carbon dioxide monitoring port. Methylene blue dye was injected into the end-tidal carbon dioxide monitoring port to visualize the separate lumen. The dye entered the main lumen of the endotracheal tube at the near distal end of tube.

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In Reply:—We are delighted that our report has stimulated some interesting discussion on the challenges of end-tidal carbon dioxide monitoring.[1] Dr. Her describes his experience with a new type of endotracheal tube, which has a built-in end-tidal carbon dioxide monitoring port (Mallinckrodt Inc., St. Louis, MO). We agree that the complication seen in our patient could have been avoided with this form of tube because dislodgement and distal migration are less likely. There are some other advantages that should be noted. Because the monitoring line does not occupy the inner lumen, airway resistance is not increased. This is particularly relevant for very low-birth-weight infants, where 2.0- to 2.5-mm uncuffed endotracheal tubes are commonly used and airway resistance is most likely to be affected. This type of tube can be easily used with an appropriate end-tidal measuring system, provided the sample volume aspirated does not compromise the delivered tidal volume.

There are some limitations that need to be pointed out. The additional tubing may become entangled with other tubes (*e.g.*, nasogastric