David C. Warltier, M.D., Ph.D., Editor

Anesthesiology 2007; 106:1226–31

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.§*

CME This article and its accompanying editorial have been selected for the *Anesthesiology* CME Program. After reading both articles, 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 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.

Received from the Department of Intensive Care Medicine, Academic Medical Center, University of Amsterdam, Amsterdam, The Netherlands. Submitted for publication August 31, 2006. Accepted for publication January 11, 2007. Support was provided solely from institutional and/or departmental sources.

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-

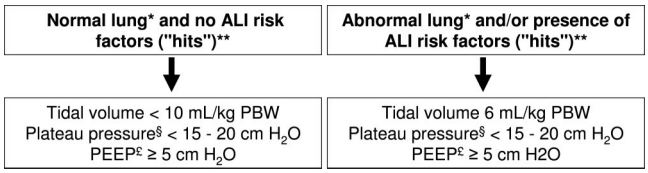

Fig. 1. Initial ventilator settings in patients without acute lung injury (ALI) or acute respiratory distress syndrome. * Interstitial lung disease, lung resection, severe pneumonia, edema. ** Sepsis, aspiration, transfusions. § The patient must be passive without significant spontaneous respiratory 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.

References

1. Suter PM, Fairley B, Isenberg MD: Optimum end-expiratory airway pressure in patients with acute pulmonary failure. N Engl J Med 1975; 292:284–9
2. Jardin F, Farcot JC, Boisante L, Curien N, Margairaz A, Bourdarias JP: Influence of positive end-expiratory pressure on left ventricular performance. N Engl J Med 1981; 304:387–92
3. Esteban A, Anzueto A, Alia I, Gordo F, Apezteguia C, Palizas F, Cide D, Goldwaser R, Soto L, Bugedo G, Rodrigo C, Pimentel J, Raimondi G, Tobin MJ: How is mechanical ventilation employed in the intensive care unit? An international utilization review. Am J Respir Crit Care Med 2000; 161:1450–8
4. Esteban A, Anzueto A, Frutos F, Alia I, Brochard L, Stewart TE, Benito S, Epstein SK, Apezteguia C, Nightingale P, Arroliga AC, Tobin MJ: Characteristics and outcomes in adult patients receiving mechanical ventilation: A 28-day international study. JAMA 2002; 287:345–55
5. Brun-Buisson C, Minelli C, Bertolini G, Brazzi L, Pimentel J, Lewandowski K, Bion J, Romand JA, Villar J, Thorsteinsson A, Damas P, Armaganidis A, Lemaire F: Epidemiology and outcome of acute lung injury in European intensive care units: Results from the ALIVE study. Intensive Care Med 2004; 30:51–61
6. Sakr Y, Vincent JL, Reinhart K, Groeneveld J, Michalopoulos A, Sprung CL, Artigas A, Ranieri VM: High tidal volume and positive fluid balance are associated with worse outcome in acute lung injury. Chest 2005; 128:3098–108
7. Dellinger RP, Carlet JM, Masur H, Gerlach H, Calandra T, Cohen J, Gea-Banacloche J, Keh D, Marshall JC, Parker MM, Ramsay G, Zimmerman JL, Vincent JL, Levy MM: Surviving Sepsis Campaign guidelines for management of severe sepsis and septic shock. Crit Care Med 2004; 32:858–73
8. Villar J: Ventilator or physician-induced lung injury? Minerva Anestesiol 2005; 71:255–8
9. Dreyfuss D, Saumon G: Ventilator-induced lung injury: Lessons from experimental studies. Am J Respir Crit Care Med 1998; 157:294–323
10. Webb HH, Tierney DF: Experimental pulmonary edema due to intermittent positive pressure ventilation with high inflation pressures: Protection by positive end-expiratory pressure. Am Rev Respir Dis 1974; 110:556–65
11. Dreyfuss D, Soler P, Basset G, Saumon G: High inflation pressure pulmonary edema: Respective effects of high airway pressure, high tidal volume, and positive end-expiratory pressure. Am Rev Respir Dis 1988; 137:1159–64
12. Kawano T, Mori S, Cybulsky M, Burger R, Ballin A, Cutz E, Bryan AC: Effect of granulocyte depletion in a ventilated surfactant-depleted lung. J Appl Physiol 1987; 62:27–33
13. Sugiura M, McCulloch PR, Wren S, Dawson RH, Froese AB: Ventilator pattern influences neutrophil influx and activation in atelectasis-prone rabbit lung. J Appl Physiol 1994; 77:1355–65
14. Ricard JD, Dreyfuss D, Saumon G: Production of inflammatory cytokines in ventilator-induced lung injury: A reappraisal. Am J Respir Crit Care Med 2001; 163:1176–80
15. Tremblay L, Valenza F, Ribeiro SP, Li J, Slutsky AS: Injurious ventilatory strategies increase cytokines and c-fos m-RNA expression in an isolated rat lung model. J Clin Invest 1997; 99:944–52
16. Haitsma JJ, Uhlig S, Goggel R, Verbrugge SJ, Lachmann U, Lachmann B: Ventilator-induced lung injury leads to loss of alveolar and systemic compartmentalization of tumor necrosis factor-alpha. Intensive Care Med 2000; 26:1515–22
17. Haitsma JJ, Uhlig S, Lachmann U, Verbrugge SJ, Poelma DL, Lachmann B:

Exogenous surfactant reduces ventilator-induced decompartmentalization of tumor necrosis factor alpha in absence of positive end-expiratory pressure. Intensive Care Med 2002; 28:1131–7

18. Ranieri VM, Suter PM, Tortorella C, De Tullio R, Dayer JM, Brienza A, Bruno F, Slutsky AS: Effect of mechanical ventilation on inflammatory mediators in patients with acute respiratory distress syndrome: A randomized controlled trial. JAMA 1999; 282:54–61

19. Ranieri VM, Giunta F, Suter PM, Slutsky AS: Mechanical ventilation as a mediator of multisystem organ failure in acute respiratory distress syndrome. JAMA 2000; 284:43–4

20. Amato MB, Barbas CS, Medeiros DM, Magaldi RB, Schettino GP, Lorenzi-Filho G, Kairalla RA, Deheinzelin D, Munoz C, Oliveira R, Takagaki TY, Carvalho CR: Effect of a protective-ventilation strategy on mortality in the acute respiratory distress syndrome. N Engl J Med 1998; 338:347–54

21. The Acute Respiratory Distress Syndrome Network: Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. N Engl J Med 2000; 342:1301–8

22. Cheng IW, Eisner MD, Thompson BT, Ware LB, Matthay MA: Acute effects of tidal volume strategy on hemodynamics, fluid balance, and sedation in acute lung injury. Crit Care Med 2005; 33:3–70

23. Kahn JM, Andersson L, Karir V, Polissar NL, Neff MJ, Rubenfeld GD: Low tidal volume ventilation does not increase sedation use in patients with acute lung injury. Crit Care Med 2005; 33:766–71

24. Hager DN, Krishnan JA, Hayden DL, Brower RG: Tidal volume reduction in patients with acute lung injury when plateau pressures are not high. Am J Respir Crit Care Med 2005; 172:1241–5

25. Rubenfeld GD, Cooper C, Carter G, Thompson BT, Hudson LD: Barriers to providing lung-protective ventilation to patients with acute lung injury. Crit Care Med 2004; 32:1289–93

26. Villar J, Perez-Mendez L, Kacmarek RM: Current definitions of acute lung injury and the acute respiratory distress syndrome do not reflect their true severity and outcome. Intensive Care Med 1999; 25:930–5

27. Wongsurakiat P, Pierson DJ, Rubenfeld GD: Changing pattern of ventilator settings in patients without acute lung injury: Changes over 11 years in a single institution. Chest 2004; 126:1281–91

28. Wolthuis EK, Korevaar JC, Spronk P, Kuiper MA, Dzoljic M, Vroom MB, Schultz MJ: Feedback and education improve physician compliance in use of lung-protective mechanical ventilation. Intensive Care Med 2005; 31:540–6

29. Gajic O, Dara SI, Mendez JL, Adesanya AO, Festic E, Caples SM, Rana R, St Sauver JL, Lymp JF, Afessa B, Hubmayr RD: Ventilator-associated lung injury in patients without acute lung injury at the onset of mechanical ventilation. Crit Care Med 2004; 32:1817–24

30. 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; 31:922–6

31. Fernandez-Perez ER, Keegan MT, Brown DR, Hubmayr RD, Gajic O: Intraoperative tidal volume as a risk factor for respiratory failure after pneumonectomy. ANESTHESIOLOGY 2006; 105:14–8

32. Michelet P, D'Journo XB, Roch A, Doddoli C, Marin V, Papazian L, Decamps I, Bregeon F, Thomas P, Auffray JP: Protective ventilation influences systemic inflammation after esophagectomy: A randomized controlled study. ANESTHESIOLOGY 2006; 105:911–9

33. Lee PC, Helsmoortel CM, Cohn SM, Fink MP: Are low tidal volumes safe? Chest 1990; 97:430–4

34. Wrigge H, Zinserling J, Stuber F, von Spiegel T, Hering R, Wetegrove S, Hoeft A, Putensen C: Effects of mechanical ventilation on release of cytokines into systemic circulation in patients with normal pulmonary function. ANESTHESIOLOGY 2000; 93:1413–7

35. Koner O, Celebi S, Balci H, Cetin G, Karaoglu K, Cakar N: Effects of protective and conventional mechanical ventilation on pulmonary function and systemic cytokine release after cardiopulmonary bypass. Intensive Care Med 2004; 30:620–6

36. Wrigge H, Uhlig U, Zinserling J, Behrends-Callsen E, Ottersbach G, Fischer M, Uhlig S, Putensen C: The effects of different ventilatory settings on pulmonary and systemic inflammatory responses during major surgery. Anesth Analg 2004; 98:775–81

37. Wrigge H, Uhlig U, Baumgarten G, Menzenbach J, Zinserling J, Ernst M, Dromann D, Welz A, Uhlig S, Putensen C: Mechanical ventilation strategies and inflammatory responses to cardiac surgery: A prospective randomized clinical trial. Intensive Care Med 2005; 31:1379–87

38. Zupancich E, Paparella D, Turani F, Munch C, Rossi A, Massaccesi S, Ranieri VM: Mechanical ventilation affects inflammatory mediators in patients undergoing cardiopulmonary bypass for cardiac surgery: A randomized clinical trial. J Thorac Cardiovasc Surg 2005; 130:378–83

39. Reis Miranda D, Gommers D, Struijs A, Dekker R, Mekel J, Feelders R, Lachmann B, Bogers AJ: Ventilation according to the open lung concept attenuates pulmonary inflammatory response in cardiac surgery. Eur J Cardiothorac Surg 2005; 28:889–95

40. Choi G, Wolthuis EK, Bresser P, Levi M, van der Poll T, Dzoljic M, Vroom B Schultz MJ: Mechanical ventilation with lower tidal volumes and positive end-expiratory pressure prevents alveolar coagulation in patients without lung injury. ANESTHESIOLOGY 2006; 105:689–95

41. Tenney SM, Remmers JE: Comparative quantitative morphology of the mammalian lung: Diffusing area. Nature 1963; 197:54–6

42. Crapo RO, Morris AH, Gardner RM: Reference spirometric values using techniques and equipment that meet ATS recommendations. Am Rev Respir Dis 1981; 123:659–64

43. Crapo RO, Morris AH, Clayton PD, Nixon CR: Lung volumes in healthy nonsmoking adults. Bull Eur Physiopathol Respir 1982; 18:419–25