Mechanical ventilation practice has changed over the past few decades, with tidal volumes (VT) decreasing significantly, especially in patients with acute lung injury (ALI). Patients without acute lung injury are still ventilated with large—and perhaps too large—VT. Studies of ventilator-associated lung injury in subjects without ALI demonstrate inconsistent results. Retrospective clinical studies, however, suggest that the use of large VT favors the development of lung injury in these patients. Side effects associated with the use of lower VT 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 VT 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 (VT) 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 VT (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 VT 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 VT 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.

Ventricular-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 VT rapidly results in pulmonary changes that mimic ARDS8,9: 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 VT, compared with conventional mechanical ventilation. The large, multicenter, prospective ARDS Network trial unambiguously confirmed that mechanical ventilation with lower VT (6 ml/kg PBW) rather than traditional VT (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...
of the ARDS Network trial showed this to be not true.\textsuperscript{22,25}

In addition, the commonly held view that plateau pressures of 30–35 cm H\textsubscript{2}O are safe was recently challenged.\textsuperscript{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\textsubscript{2}O. Lower \(V_T\) are now strongly recommended in patients with ALI/ARDS.\textsuperscript{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.\textsuperscript{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).\textsuperscript{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,\textsuperscript{3,4,27} many patients are still exposed to relatively large \(V_T\).\textsuperscript{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 \textit{et al.}\textsuperscript{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\textsubscript{2}O 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 \textit{et al.}\textsuperscript{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\textsuperscript{4} and found development of ARDS to be associated with the initial ventilator settings.\textsuperscript{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\textsubscript{2}O) 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 \textit{et al.}\textsuperscript{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 \textit{et al.}\textsuperscript{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\textsubscript{2}O 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

<table>
<thead>
<tr>
<th>Reference</th>
<th>Type of Patients (Number of Patients)</th>
<th>$V_t$ in Study Groups</th>
<th>Other Differences between Study Groups</th>
<th>Main Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Michelet et al. 32</td>
<td>Patients undergoing esophagectomy (52)</td>
<td>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</td>
<td>None</td>
<td>Lower blood levels of IL-1, IL-6, and IL-8, higher $Pao_2/Fio_2$ ratio during one-lung ventilation and after surgery; reduction of postoperative mechanical ventilation duration</td>
</tr>
<tr>
<td>Lee et al. 33</td>
<td>Postoperative patients (103)</td>
<td>6 vs. 12 ml/kg ABW</td>
<td>None</td>
<td>Incidence of pulmonary infection tended to be lower; duration of intubation tended to be shorter</td>
</tr>
</tbody>
</table>
| 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$_2$O PEEP vs. 10 cm H$_2$O PEEP | After 1 h, no differences in plasma levels of TNF-$
\alpha$, IL-1, IL-6, and IL-10 |
| Koner et al. 35         | Patients undergoing bypass grafting (44) | 6 vs. 10 ml/kg with PEEP vs. 10 ml/kg without PEEP | 0 cm H$_2$O PEEP vs. 5 cm H$_2$O PEEP | No differences in plasma levels of TNF-$
\alpha$ 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$_2$O PEEP with lower $V_t$ vs. 0 cm H$_2$O PEEP with larger $V_t$ | No differences in time course of tracheal aspirate or plasma levels of TNF-$
\alpha$, IL-1, IL-6, IL-8, IL-12, and IL-10 |
| Wrigge et al. 37        | Patients after cardiopulmonary bypass (44) | 6 vs. 12 ml/kg PBW for 6 h | None | BALF levels of TNF-$
\alpha$ 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$_2$O PEEP with lower $V_t$ vs. 2–3 cm H$_2$O 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$_2$O PEEP with lower $V_t$ vs. 5 cm H$_2$O 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 ≥ 5 h (40) | 6 vs. 12 ml/kg PBW | 10 cm H$_2$O PEEP with lower $V_t$ vs. 0 cm H$_2$O 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; $Fio_2$ = fraction of inspired oxygen; IL = interleukin; OLC = open lung concept; $Pao_2$ = arterial oxygen tension; PBW = predicted body weight; PEEP = positive end-expiratory pressure; TNF-$\alpha$ = tumor necrosis factor $\alpha$; $V_t$ = tidal volume.

Effit of protective lung ventilation in patients without ALI/ARDS comes from a randomized clinical trial in postoperative patients.34 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$_2$O. Initiation of mechanical ventilation for 1 h caused no consistent changes in plasma levels of various medi-
Lower Tidal Volumes in Non-ALI Patients

Similar results were found by Zupancich 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 VT of 12 or 15 ml/kg, respectively, and no PEEP, or VT of 6 ml/kg with PEEP of 10 cm H2O. 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 VT in patients with noninjured lungs, other articles have demonstrated the injurious effects of large VT.37–40 Wrigge et al.37 reported on the effect of postoperative mechanical ventilation with lower VT on inflammatory responses induced by cardiopulmonary bypass surgery. In this study, immediately after surgery, mechanical ventilation was applied for 6 h with either VT 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 VT. Similar results were found by Zupancich et al., who randomly assigned elective coronary artery bypass patients to ventilation after surgery with large VT/low PEEP (10–12 ml/kg and 2–3 cm H2O) or low VT/high PEEP (8 ml/kg and 10 cm H2O).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 VT and low PEEP. Reis Miranda et al.39 randomly assigned patients undergoing elective cardiopulmonary bypass to conventional ventilation with VT of 6–8 ml/kg PBW and PEEP of 5 cm H2O, or lung-protective ventilation with VT of 4–6 ml/kg PBW and PEEP of 10 cm H2O. 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 ≥5 h) to mechanical ventilation with either large VT (12 ml/kg) and no PEEP, or lower VT and PEEP of 10 cm H2O. In contrast to lung-protective mechanical ventilation, the use of larger VT promoted procoagulant changes, potentially leading to fibrin deposits within the airways. With the use of lower VT, 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 VT 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,” may cause more injury than shorter periods of mechanical ventilation with no extrapulmonary challenges.34,36

It is important to emphasize that “lower VT” in fact are “normal VT.” Mammals have a normal VT 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 VT.29

Clinical Recommendations and Future Considerations

The inconsistent results of the aforementioned randomized studies do not definitively support the use of lower VT. 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 VT 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 VT falls back on re-
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$_2$O) 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$_2$O), $V_T$ 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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LOWER TIDAL VOLUMES IN NON-ALI PATIENTS


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