Prevention of ventilator-associated lung injury in patients without acute lung injury using lower tidal volumes

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Abstract. Mechanical ventilation practice has changed over time; as new insights are provided by scientific research, so traditional modes of ventilation are being revised. In patients with acute lung injury (ALI) mechanical ventilation with lower tidal volumes contributes to patient survival, most likely by preventing ventilator-associated lung injury. In contrast, patients without ALI are still subjected to traditional ventilation modes using higher tidal volumes. Studies on ventilator-associated lung injury in subjects without ALI demonstrate inconsistent results. However, retrospective clinical studies suggest that higher tidal volumes increase the risk of developing lung injury. Moreover, even short-term mechanical ventilation seems to induce a pro-inflammatory response locally in the lungs, which can be limited by the use of lower tidal volumes. Conversely, the use of lower tidal volumes in patients has been associated with minimal adverse events. We propose that regardless of pre-existent lung injury, all patients in need of respiratory support should be ventilated with lower tidal volumes (i.e. 6 mL/kg ideal body weight), thereby preventing ventilator-associated lung injury. Prospective studies in both the operating rooms and intensive care units should be performed to evaluate optimal ventilator management strategies for patients without ALI.

Introduction
For years, mechanical ventilation has been one of the cornerstones of care for critically ill patients. Over past decades, the tidal volumes used by clinicians have progressively decreased from more than 12–15 mL/kg to less than 9 mL/kg actual body weight (1-6). The reduction in tidal volumes in ventilation practices is related to the awareness that mechanical ventilation may aggravate or even initiate processes injurious to lungs thus inducing ventilator-associated lung injury (Figure 1) (7, 8). Presently there are guidelines strongly supporting the use of lower tidal volumes (i.e. 6 mL/kg predicted body weight) in patients with acute lung injury and acute respiratory distress syndrome (ALI/ARDS) (9). In patients without lung injury (i.e. who do not meet the ALI/ARDS-consensus criteria (10)), guidelines for the most appropriate ventilation strategy are lacking.

In this review, we briefly describe the concept of ventilator-associated lung injury. We searched the literature for data addressing the management of tidal volumes in patients without ALI/ARDS. Finally, a protective ventilation strategy is proposed for patients without lung injury.

Search Results
Ventilator-associated lung injury in patients with ALI/ARDS. Detailed aspects of the pathophysiology of ventilator-associated lung injury have been described in previous reviews (7, 8). Briefly, ventilator-associated lung injury consists of several components, including volutrauma (damage caused by mechanical overdistention) and biotrauma (generation of inflammatory mediators causing pulmonary and systemic inflammation). Experimental studies using healthy animals confirm that mechanical ventilation with higher tidal volumes rapidly results in lung injury and hyperinflammatory response within the lungs, as seen in patients with ARDS (11). Mere ventilation with higher tidal volumes was shown to cause diffuse alveolar damage with pulmonary oedema (12), both a cellular (13, 14) and humoral (15, 16) inflammatory response in the lungs, and leakage of inflammatory mediators into the systemic circulation (a process referred to as “decompartmentalization”) (17, 18). In a clinical trial of ARDS patients, Ranieri et al demonstrated that a lung-protective ventilation strategy, in part aiming at lower tidal volumes, limited both pulmonary and systemic inflammation (19, 20). At least two randomized controlled trials confirm that limitation of ventilator-induced inflammatory alterations contributes to outcome in ARDS patients. Amato et al demonstrated reduced 28-day mortality and more rapid resolution of respiratory failure with a lung-protective strategy, avoiding higher tidal volumes, compared with conventional mechanical ventilation (21). The large multicentre prospective ARDS Network trial unambiguously confirmed that mechanical ventilation with lower tidal volumes rather than traditional tidal volumes (6 versus 12 mL/kg predicted body weight) results in a significant increase in the number of ventilator-free days and a reduction of in-hospital mortality (22). Concerns over increased sedation requirements and higher plateau pressures initially hampered implementation of the newly proposed ventilation strategy with lower tidal volumes. However, these concerns were disproved by secondary analyses of
may benefit from mechanical ventilation lower tidal volumes. Supporting the view that patients without pre-existent lung injury initiating or exacerbating pulmonary injury. There are clinical studies of higher tidal volumes should be considered a significant second hit or more subsequent hits can result in full blown lung injury. The use of these patients may well have lung injury at the start of mechanical ventilation initiated. Patients with pneumonia, restrictive lung disease, or those undergoing pulmonary surgery are among those at particular risk. ALI/ARDS, even before mechanical ventilation (“second hit”) is associated. Because ventilator-associated lung injury primarily concerns critically ill patients, a “multiple hit” theory has been proposed. Accordingly, a primary injurious process (”first hit”; e.g. infection, trauma) is able to prime critically ill patients for the development of ALI/ARDS, even before mechanical ventilation (“second hit”). ALI/ARDS, even before mechanical ventilation (“second hit”) is associated with increased mortality were patient characteristics at initiation of mechanical ventilation, complications during mechanical ventilation, and factors related to patient management. Plateau pressures of more than 35 cmH2O were associated with an increased risk of death. Although higher plateau pressures may simply reflect the more severe clinical status of patients, this study suggested that resulting higher tidal volumes were considerably contributing to exaggeration of lung injury and eventually death. In a single centre observational cohort study, Gajic et al reported a significant variability in tidal volumes settings in patients without ALI/ARDS at initiation of mechanical ventilatory support [25]. Twenty-four percent of patients ventilated for at least two days who did not meet ALI/ARDS criteria at the onset of mechanical ventilation, developed ALI/ARDS within five days of mechanical ventilation. In a large international prospective observational study, Esteban et al investigated risk factors for negative outcome of mechanically ventilated patients [4]. Among the conditions independently associated with increased mortality were patient characteristics at initiation of mechanical ventilation, complications during mechanical ventilation, and factors related to patient management. Plateau pressures of more than 35 cmH2O were associated with an increased risk of death. Although higher plateau pressures may simply reflect the more severe clinical status of patients, this study suggested that resulting higher tidal volumes were considerably contributing to exaggeration of lung injury and eventually death. In a single centre observational cohort study, Gajic et al reported a significant variability in tidal volumes settings in patients without ALI/ARDS at initiation of mechanical ventilatory support [25]. Twenty-four percent of patients ventilated for at least two days who did not meet ALI/ARDS criteria at the onset of mechanical ventilation, developed ALI/ARDS within five days of mechanical ventilation. In a multivariate analysis, the ARDS Network trial [23, 24] and lower tidal volumes are now strongly recommended in patients with ALI/ARDS [9].

### Table 1. Prospective studies on ventilator-associated lung injury in patients without ALI/ARDS

<table>
<thead>
<tr>
<th>Primary author</th>
<th>Patients</th>
<th>Ventilator settings</th>
<th>Clinical outcome</th>
<th>Biochemical parameters</th>
</tr>
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<tbody>
<tr>
<td>Michelet [29]</td>
<td>Elective esophagectomy</td>
<td>Peri- and postoperative: I: VT 9 ml/kg PBW and ZEEP (n=26) II: VT 5 ml/kg PBW and 5 cmH2O PEEP (n=26)</td>
<td>Higher PaO2/FiO2 ratios Reduction of postoperative MV duration.</td>
<td>Lower plasma levels of IL-1, IL-6, and IL-8</td>
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<tr>
<td>Lee [30]</td>
<td>Surgical intensive care</td>
<td>At admission: I: VT 12 ml/kg ABW (n=56) II: VT 6 ml/kg ABW (n=47)</td>
<td>Lower incidence of pulmonary infection Shorter duration of intubation Shorter length of stay</td>
<td>n/a</td>
</tr>
<tr>
<td>Wrigge [31]</td>
<td>Elective surgery</td>
<td>Perioperative: I: VT 6 ml/kg + ZEEP (n=13) II: VT 15 ml/kg + ZEEP (n=13) III: VT 6 ml/kg + 10 cmH2O PEEP (n=13)</td>
<td>No differences in plasma TNF, IL-6, and IL-1 receptor antagonist after 1 h of MV.</td>
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<tr>
<td>Koner [32]</td>
<td>Cardiopulmonary bypass surgery</td>
<td>Perioperative: I: VT 6 ml/kg + 5 cmH2O PEEP (n=15) II: VT 10 ml/kg + 5 cmH2O PEEP (n=14) III: VT 10 ml/kg + ZEEP (n=15)</td>
<td>Lower shunt fraction in I. Both PEEP groups: better oxygenation.</td>
<td>No differences in plasma TNF and IL-6 levels.</td>
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<tr>
<td>Wrigge [33]</td>
<td>Major thoracic or abdominal surgery</td>
<td>Perioperative: I: VT 12-15 ml/kg + ZEEP (n=32) II: VT 6 ml/kg + 10 cmH2O PEEP (n=30)</td>
<td>No differences in pulmonary or systemic inflammatory mediators after 3 h of MV.</td>
<td></td>
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<tr>
<td>Wrigge [34]</td>
<td>Cardiopulmonary bypass surgery</td>
<td>Postoperative: I: VT 6 ml/kg (n=22) II: VT 12 ml/kg (n=22)</td>
<td>No differences in inotropics requirement, postoperative pulmonary complications, postoperative MV duration, or duration of ICU treatment. Lower TNF levels in BALF after 6 h of MV.</td>
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<tr>
<td>Zupancich [35]</td>
<td>Coronary artery bypass</td>
<td>Perioperative: I: VT 10-12 ml/kg, 2-3 cmH2O PEEP (n=20) II: VT 8 ml/kg, 10 cmH2O (n=20)</td>
<td>No major complications or postoperative mortality in both groups.</td>
<td>No sustained increase of IL-6 and IL-8 in plasma and BALF.</td>
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<tr>
<td>Reis Miranda [37]</td>
<td>Cardiopulmonary bypass surgery</td>
<td>Perioperative: I: VT 6-8 ml/kg, 5 cmH2O PEEP (n=22) II: VT 4-6 ml/kg, 10 cmH2O (n=18)</td>
<td>No difference in incidence of pneumonia, pneumothorax, or myocardial infarction.</td>
<td>More rapid decrease of plasma IL-8 after surgery.</td>
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<tr>
<td>Choi [36]</td>
<td>Major abdominal surgery</td>
<td>Perioperative: I: VT 12 ml/kg PBW and ZEEP (n=9) II: VT 6 ml/kg PBW and 10 cmH2O PEEP (n=2)</td>
<td>No differences in postoperative pulmonary complications or hospital mortality. After 5 h of MV: lower BALF levels of markers of coagulation, preservation of protein C pathway and fibrinolytic activity in BALF.</td>
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<tr>
<td>Wolthuis [38]</td>
<td>Major abdominal surgery</td>
<td>Perioperative: I: VT 12 ml/kg PBW and ZEEP (n=19) II: VT 6 ml/kg PBW and 10 cmH2O PEEP (n=2)</td>
<td>No differences in postoperative pulmonary complications or hospital mortality. After 5 h of MV: lower BALF levels of IL-8, MPO, elastase.</td>
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Abbreviations: BALF, bronchoalveolar lavage fluid; IL, interleukin; MPO, myeloperoxidase; MV, mechanical ventilation; n/a, not available; PEEP, positive end-expiratory pressure; TNF, tumor necrosis factor α; VT, tidal volumes; ZEEP, 0 cmH2O PEEP.

*According to acute lung injury / acute respiratory distress syndrome criteria [10].
were the use of higher tidal volumes, transfusion of blood products, acidaemia, and a history of restrictive lung disease. The odds ratio of developing ALI was 1.3 for tidal volumes of every ml/kg above 6 ml/kg predicted body weight (Figure 2). Interestingly, female patients were ventilated with larger tidal volumes and were more prone to develop lung injury. The investigators found a similar association between the development of ARDS and initial ventilator settings in a larger patient cohort using the above mentioned multicentre international study on mechanical ventilation [4, 26]. Higher tidal volumes (odds ratio 2.6 for tidal volumes > 700 ml) and high peak airway pressure (odds ratio 1.6 for peak airway pressure > 30 cmH₂O) were independently associated with development of “late” ARDS, i.e. in patients who did not have ARDS at the onset of mechanical ventilation. Most recently, Mascia et al confirmed the association between higher tidal volumes ventilation with pulmonary complications in patients with severe brain injury; i.e. mechanical ventilation with higher tidal volumes was independently associated with development of acute lung injury after severe brain injury [27].

The potentially deleterious effects of higher tidal volumes have also been investigated in patients that were ventilated for only a few hours, during or after surgery (prospective studies summarized in Table 1). Fernandez et al collected intra-operative tidal volumes of pneumonectomy patients [28]. Of these patients, 18% developed post-operative respiratory failure; in half of these cases the patients developed ALI/ARDS. Patients who developed respiratory failure had been ventilated with higher intra-operative tidal volumes than those who did not (median, 8.3 vs. 6.7 ml/kg predicted body weight). In a multivariate logistic regression analysis, higher intra-operative tidal volumes were identified as a risk factor of postoperative respiratory failure. Similar findings were reported by Michelet et al [29]. In this study 52 patients undergoing elective oesophagectomy for cancer were randomly assigned to a conventional ventilation strategy (tidal volumes of 9 ml/kg during two-lung and one-lung ventilation; no PEEP) or a protective ventilation strategy (tidal volumes of 9 ml/kg during two-lung ventilation, reduced to 5 ml/kg during one-lung ventilation; PEEP of 5 cm H₂O throughout the surgical procedure). The protective strategy resulted in higher Pao₂/Fio₂ ratio during one-lung ventilation and one hour after surgery, and in a reduction of the duration of postoperative mechanical ventilation. Also, patients assigned to protective strategy had lower plasma levels of pro-inflammatory mediators (e.g. IL-1, IL-6, and IL-8) at the end of one-lung ventilation and 18 hours after surgery. The strongest evidence for the beneficial effects of protective lung ventilation in patients without ALI/ARDS comes from a randomized clinical trial in postoperative patients [30]. Intubated mechanically ventilated patients in the surgical intensive care unit were randomly assigned to mechanical ventilation with tidal volumes of 12 ml/kg actual body weight or lower tidal volumes of 6 ml/kg. With the exception of neurosurgical and cardiac surgical patients, patients randomized to the lower tidal volumes strategy had a lower incidence of pulmonary infection, shorter duration of intubation and length of stay, suggesting fewer ventilator-associated complications. Importantly, although use of lower tidal volumes was associated with a statistically significant decrease in oxygenation, this was not clinically relevant. The authors concluded that ventilation with lower tidal volumes is both safe and beneficial to patient outcome.

Several investigators have prospectively tested the hypothesis that mechanical ventilation could induce biotrauma by pro-inflammatory changes in lungs of patients without evident lung injury at the onset of mechanical ventilation. Wrigge et al randomized patients without previous lung injury scheduled for elective surgery with general anaesthesia to receive mechanical ventilation with tidal volumes of either 15 or 6 ml/kg without the use of PEEP, or tidal volumes of 6 ml/kg with 10 cmH₂O PEEP [31]. Mechanical ventilation for one hour caused no consistent changes in plasma levels of various inflammatory mediators, and no differences were found among the three study groups. Similar results came from a study by Koner et al [32]. Wrigge et al also studied the effects of mechanical ventilation on inflammatory responses during major thoracic or abdominal surgery [33]. Patients undergoing elective thoracotomy or laparotomy were randomized to mechanical ventilation with tidal volumes of either 12 or 15 ml/kg, and no PEEP, or tidal volumes of 6 ml/kg with PEEP of 10 cmH₂O. After three hours of mechanical ventilation, there were no differences between the various groups with regard to either time course or concentrations of pulmonary or systemic inflammatory mediators.
In contrast to these reports that did not show any deleterious effects of higher tidal volumes in patients with non-injured lungs, other articles have reported injurious effects of higher tidal volumes [34-37]. Wrigge et al reported on the effect of postoperative mechanical ventilation with lower tidal volumes on inflammatory responses induced by cardiopulmonary bypass surgery [34]. In this study, immediately after surgery, mechanical ventilation was applied for six hours with tidal volumes of either 6 or 12 ml/kg. The time course of inflammatory mediators did not differ significantly between these ventilatory strategies, although in bronchoalveolar lavage fluid sampled six hours after initiation of mechanical ventilation, tumour necrosis factor alpha levels were significantly higher in patients ventilated with higher tidal volumes. Similar results were found by Zapancich et al who randomized elective coronary artery bypass patients to be ventilated after surgery with high tidal volumes and low PEEP (10-12 ml/kg and 2-3 cm H2O) or low tidal volumes and high PEEP (8 ml/kg and 10 cm H2O) [35]. Bronchoalveolar lavage fluid and plasma were obtained before sternotomy, immediately after cardiopulmonary bypass separation, and after six hours of mechanical ventilation. IL-6 and IL-8 levels in the bronchoalveolar lavage fluid and plasma were significantly increased before sternotomy in both groups, but a continued increase was demonstrated only in those patients ventilated with high tidal volumes and low PEEP. Reis Miranda et al randomized patients undergoing elective cardiopulmonary bypass to conventional ventilation with tidal volumes 6-8 ml/kg and PEEP of 5 cmH2O, or lung protective ventilation with tidal volumes 4-6 ml/kg and PEEP of 10 cmH2O [37]. Plasma levels of IL-8 decreased more rapidly in the lung protective group in the three days after surgery. In a report from our group we randomized patients scheduled for an elective surgical procedure (lasting ≥ 5 hours) to mechanical ventilation with tidal volumes of either 12 ml/kg and no PEEP, or lower tidal volumes of 6 ml/kg and PEEP of 10 cm H2O [36]. The use of larger tidal volumes and no PEEP promoted procoagulant changes in the bronchoalveolar compartment (see Figure 3), potentially facilitating fibrin depositions within the airways. With the use of lower tidal volumes and PEEP these procoagulant changes were largely prevented. In the same group of patients, we recently identified an association between higher tidal volumes and increased pulmonary levels of IL-8 and neutrophilic activity (e.g., myeloperoxidase, see Figure 3) [38].

To explain the differences in outcome and endpoints from several pathophysiological studies on ventilator-associated lung injury, we once again turn to the multiple-hit theory. Longer periods of mechanical ventilation [35, 36], as well as additional pulmonary “hits” (i.e. cardiopulmonary bypass surgery [34, 35]) seem to cause more lung injury, compared with mechanical ventilation for a shorter time or in patients with extrapulmonary predisposing conditions [31, 33]. Although the clinical relevance of pro-inflammatory or procoagulant changes in both lungs and blood remain uncertain, we propose that limiting these alterations will benefit all mechanically ventilated patients.

Clinical recommendations and future considerations

Although average tidal volumes in non-selected mechanically ventilated patients have declined to ~10 ml/kg PBW [3, 4, 39], many patients are still exposed to relatively large tidal volumes [25, 40]. It is important to emphasize that “lower tidal volumes” in fact are “normal tidal volumes”. Mammals have a normal tidal volume of 6-3 ml/kg [41]. Normal lung volumes can be estimated using gender and height [42, 43]. In the ARDS Network trial, the predicted body weight of male patients was calculated as: 50 + 0.9* (centimetres of height - 152.4); that of female patients: 45.5 + 0.9* (centimetres of height - 152.4) [22]. Unfortunately, many medical textbooks state 10 ml/kg actual body weight as initial ventilator settings, exposing female and shorter patients to higher and potentially injurious tidal volumes [25]. Considering the studies described in this review, and despite the lack of a definitive major clinical trial, we recommend the use of lower tidal volumes in patients without evident lung injury and those who do not meet ALI/ARDS consensus criteria. The practice of medicine should not only be guided by the evidence-based paradigm but also the old – but still very significant – principle of _primum non nocere_. As sceptics may consider the above mentioned studies as “circumstantial evidence” for the use of lower tidal volumes in patients without lung injury, it is clear that ventilator-associated alterations can be limited. While awaiting the results of future prospective studies, we recommend avoidance of high plateau pressures and high tidal volumes in patients who do not have ALI/ARDS at the onset of mechanical ventilation. These recommendations are based on the best currently available evidence cited in this review. Of note, our recommendations do not take into account specific ventilator management of patients with obstructive lung diseases, or other special medical conditions.

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 and decompartmentalization of inflammatory mediators [39, 20]. In many patients with normal lungs (e.g. patients undergoing short term ventilation during low risk surgical procedures, those with muscle weakness, etc.) the end-inspiratory stretch may be relatively low even with a tidal volumes of 10 ml/kg PBW. In these patients, if the plateau pressure is low (e.g. < 15 cm H2O), and they are not breathing spontaneously, lower tidal volumes are probably not indicated - in fact, it may lead to atelectasis, especially if PEEP is low or not used at all. If plateau pressures rise (e.g. > ~15 – 20 cm H2O) then tidal volumes should be lowered to ~ 6 ml/kg PBW (Figure 1). Sufficient PEEP has to be used to minimize atelectasis and maintain oxygenation. It is important to realize that plateau pressures may be misleading on 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. On the other hand, in patients who have decreased chest wall compliance (increased intrathoracic pressure, obesity) plateau pressures may be high without there being pulmonary overdistension.

It may be important to distinguish between mechanical ventilation in the operating room and in the intensive care unit. Indeed, 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 ALI/ARDS. Both surgical patients and critically ill patients are at risk for multiple lung injurious processes. These may, however, not be the same in both patient groups, and each challenge may have different effects in both groups. Finally, much of our knowledge of the importance of using lower tidal volumes falls back on research in the field of ALI/ARDS – the cellular response to injury, however, is different depending on the priming of pulmonary cells by ischaemia or inflammation. Both processes can occur in the peri-operative period. Thus, it remains to be determined whether we need to ventilate the operating room and in the intensive care unit equally (i.e. with lower tidal volumes).

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

Conclusion

Critically ill patients without evident lung injury are at risk for ventilator associated lung injury. Certain initial ventilator settings, in particular higher tidal volumes, have been associated with changes in biological markers and adverse outcome, suggesting that ventilator-associated lung injury can and should be prevented. Prospective studies are required to further evaluate optimal ventilator management strategies for patients at the onset of mechanical ventilation, both in the intensive care unit and in the operating room.

References


