Ventilator-Associated Pneumonia: The Role of Ventilator Management Strategies

Neil R MacIntyre MD FAARC

Introduction

Reducing Ventilator-Induced Lung Injury
Lung-Protective Mechanical Ventilatory Strategies Require Tradeoffs
  - Hypercapnic Respiratory Acidosis
  - Sedation
  - Atelectasis
  - Weaning Delays

Summary

Ventilator management strategies can affect the risk for ventilator-associated pneumonia in 3 ways: the development of ventilator-induced lung injury; the need for potentially harmful tradeoffs in providing lung-protective ventilatory strategies; and the prolongation of the duration of mechanical ventilation from iatrogenic factors. Strategies to reduce ventilator-induced lung injury include a smaller tidal volume and careful attention to reducing the maximum pressures in the lung. These lung-protective strategies, however, may require tradeoffs with factors that may in themselves produce risks for ventilator-associated pneumonia. Specifically, hypercapnia, discomfort requiring sedation, and atelectasis may all be potential problems with a lung-protective strategy. However, the weight of evidence suggests that beneficial outcomes from lung-protective strategies outweigh any potential harm from these tradeoffs. Finally, properly performed weaning protocols based on clinical evidence should reduce any iatrogenic delays in ventilator weaning and thereby minimize prolongation of unneeded mechanical ventilatory support.

Key words: mechanical ventilation, ventilator-associated pneumonia, lung-protective ventilation.

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Reducing Ventilator-Induced Lung Injury

It has long been known that the injured lung is at greater risk for superimposed infection.1–7 Lung injury impairs host defenses and creates an environment that is ripe for invasion by microorganisms and the development of pneumonia.7 Indeed, in multivariate analyses of VAP, the presence of underlying lung injury, especially acute lung injury, imposes a several-fold increase in the incidence of VAP.1–6

VILI is now a well recognized form of acute lung injury.7–10 Two mechanisms appear important in producing this injury. The first is a physical stretch injury resulting from lung regions being inflated beyond their physiologic maximum. Interestingly, this stretch injury is due not only to maximal end-inspiratory stretch, but may also involve tidal stretch, rate of stretch, and frequency of stretch.11,12 All of these factors produce a tissue injury characterized by inflammation, edema formation, hyaline membranes, and the release of inflammatory mediators into the circulation.13,14 Lungs with a heterogeneous distribution of disease are at particular risk for this injury, because healthier regions will be preferentially overdistended when a positive-pressure breath is delivered.15 The second mechanism is a shearing injury from repeated opening and closing of atelectatic alveoli in an injured lung. The use of expiratory pressure to prevent alveolar derecruitment can help ameliorate this injury.8,15–18 A smaller tidal volume (VT) may also help reduce repetitive opening and closing of atelectatic units by leaving those units permanently collapsed (fixed atelectasis) (see below).

To minimize this injury potential, mechanical ventilation goals should be 2-fold. The first goal should be to limit both tidal and maximum distention. The tidal breath should thus be 6–8 mL/kg (ideal body weight) and the resulting end-inspiratory plateau pressure should be <30–35 cm H2O, in accordance with the National Institutes of Health (NIH) Acute Respiratory Distress Syndrome (ARDS) Network protocols, which have demonstrated substantial survival benefits to this approach.19,20 The second goal is to provide a level of positive end-expiratory pressure (PEEP) that provides adequate ventilation-perfusion matching but does not contribute to excessive end-inspiratory overdistention. To this end, the PEEP-fraction of inspired oxygen (FIO2) tables used in the aforementioned successful NIH ARDS Network trials3,19,20 might have clinical utility (Table 1).

Potential nonconventional respiratory support strategies and adjuncts that might enhance lung protection include 3 approaches: high-frequency ventilation, airway pressure-release ventilation, and techniques to alter surface active properties. High-frequency ventilation, by providing low maximum pressures and high recruitment pressures, might be the “ultimate” lung-protective strategy for a positive-pressure ventilatory support system.21 Indeed, in infants at risk for overdistention injury, high-frequency ventilation has been shown to offer benefit,22 and a recent randomized trial in adults also suggested an outcome benefit.23 Airway pressure-release ventilation uses a long inspiratory time and short expiratory time strategy to help alveolar recruitment without necessarily having to increase the potentially injurious end-inspiratory pressure with increasing PEEP or Vt. Small studies have shown good gas exchange at lower maximum pressures with airway pressure-release ventilation,24 but outcome data are lacking. Surface active properties can be altered by surfactant administration,25 and the need for high distending pressures should be reduced accordingly. Surfactant replacement in the adult in early trials was unsuccessful, but with newer preparations (that include surfactant proteins) and better delivery strategies it may find utility in the future.

Lung-Protective Mechanical Ventilatory Strategies Require Tradeoffs

To provide lung-protective mechanical ventilatory support, several tradeoffs may be required that could have impact on the development of VAP. Three that may have particular relevance are hypercapnic respiratory acidosis, sedation requirements, and atelectasis. Each of these will be reviewed separately.

Hypercapnic Respiratory Acidosis

Lower-Vt strategies may result in a lower minute ventilation, with a resulting respiratory acidosis. Indeed, in almost all reports of lung-protective ventilatory strategies, a mild to moderate respiratory acidosis was noted in the lung-protective group.26 This observation has lead to the term “permissive hypercapnia,” the concept of allowing hypercapnia to develop in an effort to protect the lung. In the NIH ARDS Network trial, the low-Vt protocol allowed for pH as low as 7.15 to develop before a patient was declared a ventilatory failure.19 However, in this study ventilatory failure was very uncommon in patients with severe ARDS receiving 6 mL/kg Vt, and the average pH in the lower-Vt group was less than 0.04 pH units lower than the average pH in the larger-Vt group.

Since a low-Vt lung-protective strategy might produce substantial respiratory acidosis, an important question is whether this level of acidosis is actually harmful to the lung. Clearly, severe acidosis (eg, pH < 7.0) can have profound toxic cellular effects, promote cardiac dysrhythmias, and make a number of medications (including pressors) less effective. The evidence that more modest acidosis (eg, pH 7.15–7.35) causes harm is far less clear, and the positive outcomes associated with smaller Vt suggest that any harm is outweighed by less VILI. Indeed, a grow-
Synchrony has led to strategies that can reduce this asynchrony with patient demand, to avoid discomfort and improve flow synchrony (eg, pressure-targeting breaths and using pressure-flow graphics to adjust inspiratory flow patterns). The recent introduction of dual-control modes that adjust the pressure level automatically to a target Vₜ may conceptually be a very rational way to optimize flow synchrony while giving smaller Vₜ.

Even without pressure-targeting features, the ARDS Network low-Vₜ strategy, using skilled respiratory therapists to optimize flow and timing settings, seems to have not increased the sedation requirement in the small-Vₜ group versus the large-Vₜ group. This was demonstrated both in an analysis of total days of sedation required in all the ARDS Network sites as well as a more careful analysis of sedation usage in one of the ARDS Network sites (Table 2).

Taken together, a better awareness and understanding of patient ventilator flow synchrony plus newer techniques to improve flow synchrony would seem to not require additional sedatives in order to provide low-Vₜ lung-protective ventilatory strategies.

### Atelectasis

Atelectasis describes lung-unit collapse and occurs when surface tension forces fall below transpulmonary pressures. Causes of atelectasis are multiple. In acute lung injury, surfactants break down and inflammatory products destabilize surface tension to produce collapse. Airway secretion clearance difficulties may also block ventilation to lung units, creating absorption atelectasis. Atelectasis can also occur when negative pleural pressure falls, as in pneumothorax.

During positive-pressure ventilation, atelectasis is of 2 types: cyclical and fixed. Cyclical atelectasis occurs with repetitive applications of inspiratory pressure that initially opens (recruits) lung units but then is followed by collapse during expiration (derecruitment). Mechanical modeling studies and numerous animal studies have shown that this cyclical reopening and closing phenomenon produces substantial shear stress forces along alveolar walls, which can also lead to a form of VILI. Indeed, one of the major

<table>
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<th>Table 1. The PEEP/FIO₂ Tables Used During 2 National Institutes of Health ARDS Network Studies*</th>
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<td>FIO₂</td>
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*The clinical target is a PEEP of 55-80 mm Hg or arterial oxygen saturation (measured via pulse oximetry) of 88-95%. If the patient is below these target values, move up the table to the right. If the patient is above these targets, move down the table to the left.
†PEEP (positive end-expiratory pressure) values, in cm H₂O, used in the original ARDS Network tidal-volume trial.
‡PEEP values, in cm H₂O, used in the more recent National Institutes of Health ARDS Network ALVEOLI trial.
ARDS = acute respiratory distress syndrome
FIO₂ = fraction of inspired oxygen

Sedation

Current approaches to mechanical ventilatory support tend to favor assisted forms of ventilation over controlled forms of ventilation. Assisted forms of ventilation allow the patient to trigger the ventilator and thus set the respiratory rate. Assisted forms of ventilation also permit patient muscle activity, which may forestall atrophy that is associated with total machine-controlled ventilation.

Assisted forms of ventilation with patient activity present, however, need to provide inspiratory flow that is synchronous with patient demand, to avoid discomfort and imposed muscle loading.

When using lung-protective strategies, there is theoretical concern that the smaller Vₜ may not be as synchronous with patient effort as a larger Vₜ. A resulting concern would be that this discomfort might require additional sedatives, which as noted above, may delay the ventilator-withdrawal process and thus increase the risk of VAP.

Evidence that a smaller Vₜ is actually less comfortable than a larger Vₜ, however, is sparse. Indeed, much of this concern may stem from older approaches of using fixed-flow volume-assist control breaths, which would often require a slow flow and/or short inspiratory time to keep the Vₜ low. Better clinical understanding of patient-ventilator synchrony has led to strategies that can reduce this asynchrony (eg, pressure-targeting breaths and using pressure-flow graphics to adjust inspiratory flow patterns). The recent introduction of dual-control modes that adjust the pressure level automatically to a target Vₜ may conceptually be a very rational way to optimize flow synchrony while giving smaller Vₜ.

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benefits of reduced-V_{T} ventilation may be a reduction in this opening-and-closing phenomenon.

Another approach to reducing cyclical atelectasis is to maintain alveolar recruitment with PEEP.37 A downside to PEEP, however, is that it raises all intrathoracic pressures, and thus when coupled with a subsequent V_{T}, can lead to over-distention VILI, especially in healthier regions of the lung.15

Acute lung injury being supported with positive-pressure ventilation may also have fixed atelectasis, lung units that remain closed throughout the respiratory cycle. Fixed atelectasis may be a consequence of a severe lung injury or low levels of PEEP, but it may also be a consequence of a lung-protective strategy with a reduced V_{T}. A key question is then whether this fixed atelectasis from a low-V_{T} lung-protective strategy is a risk factor for subsequent VAP (ie, Is fixed atelectasis “incipient pneumonia”?).

There are theoretical reasons to be concerned that fixed atelectasis may predispose to infection. Collapsed lung units may not have appropriate clearance mechanisms and may attract inflammatory cells, which might compromise the normal host defense systems. Clinically, the surgical literature is replete with reports of postoperative atelectasis being associated with subsequent pneumonia.38,39 One must be cautious, however, in interpreting these surgical studies, in that the factors that produce postoperative atelectasis in this environment (ie, reduced cough, chest-wall splinting, airway toilet issues) may not be operative in the fixed atelectasis of acute lung injury. Interestingly, multiple prediction models for VAP have not shown atelectasis to be an independent risk factor, although it must be pointed out that atelectasis is often not selected as one of the risk factors to be included in the model.1–6 Thus, although theoretically a source for infection, clinical evidence that fixed atelectasis in acute lung injury indeed leads to pneumonia is sparse.

Lung-protective ventilator strategies involve atelectasis “tradeoffs.” On one hand, large V_{T} and aggressive PEEP strategies minimize fixed atelectasis. On the other hand, however, overdistention VILI may be a consequence of this approach and, as noted above, a larger V_{T} may increase cyclical atelectasis and resulting opening-closing VILI.

Fortunately, the ARDS Network studies on ventilator management have provided considerable insight into these atelectasis “tradeoffs.” In the original small-versus-large-V_{T} study,19 it was very clear that the small-V_{T} strategy did indeed produce more atelectasis, as evidenced by a lower thoracic compliance and lower PaO_{2}/FIO_{2} ratio over the first several days of the trial (Fig. 1). Importantly,
however, the survival in the small-VT group was significantly better than the large-VT group. The conclusion from this trial is thus that the fixed atelectasis resulting from a small VT seemed worth it, in that healthier regions of the lung were protected from excessive pressures from larger VT. In the second large ARDS Network trial, a more aggressive PEEP strategy was compared to the original less aggressive PEEP strategy (see Table 1). In both groups the small-VT protocol was used. The high-PEEP strategy clearly produced less atelectasis, as evidenced by markedly improved compliance, P\textsubscript{aO}\textsubscript{2}/F\textsubscript{I}\textsubscript{O}\textsubscript{2} ratios, and a reduced need for supplemental oxygen. Despite this fixed atelectasis reduction, the outcomes were exactly the same in terms of mortality and ventilator-free days. Importantly, indirect evidence of infection (e.g., white blood cell count and fever) was also not increased in the low-PEEP group.

The weight of evidence thus suggests that the benefits of lung-protective strategies that might increase fixed atelectasis outweigh any VAP risk. The clinical goal should thus be, in all forms of respiratory failure, to use a 6–8 mL/kg (ideal body weight) VT and to set a PEEP level adequate for an acceptable level of oxygenation, and not pushed to extremes in order to minimize or eliminate fixed atelectasis.

**Weaning Delays**

As respiratory failure stabilizes and begins to reverse, clinical attention shifts to the ventilator-withdrawal process. Unfortunately, a number of large clinical trials have clearly demonstrated that current assessment/management strategies are not optimal. Specifically, withdrawal potential is often not appreciated by the patient’s clinical team, the ventilator reduction “rules” may be unnecessarily slow (i.e., synchronized intermittent mandatory ventilation rate reductions), and sedation may be excessive.

As a consequence, considerable delay in ventilator withdrawal occurs. Increased length of stay, costs, and exposure to positive pressure and infection result. Attempts to increase withdrawal aggressiveness, however, must be balanced against the risk of premature withdrawal, with consequent airway loss, aspiration, and ventilatory muscle fatigue.

A recent evidence-based task force has recommended a 2-step assessment and management process:

1. Consider a patient a candidate for withdrawal if (A) the lung injury is stable/resolving, (B) the gas exchange is adequate with low PEEP/F\textsubscript{I}\textsubscript{O}\textsubscript{2} requirements, (C) hemodynamics are stable without a need for vasopressors, and (D) the patient can initiate spontaneous breaths. In patients meeting all 4 of these requirements, proceed to Step 2 below. In those not meeting all 4 requirements, leave on current ventilator settings and reassess 24 hours later.

2. In patients meeting all 4 of the requirements in Step 1 above, perform a spontaneous breathing trial, using T-piece, continuous positive airway pressure, or 5 cm H\textsubscript{2}O pressure support for 30–120 min. Assessments should include the ventilatory pattern, gas exchange, hemodynamics, and comfort. Patients “passing” this trial should be considered for immediate ventilator withdrawal. Patients “failing” this trial need to return to a comfortable, stable level of mechanical ventilatory support for the next 24 hours and then be reassessed again.

Incorporating these concepts into protocols has been shown to significantly reduce the need for mechanical ventilatory support. In addition, small studies have also suggested that deliberately extubating selected chronic obstructive pulmonary disease patients who have failed a spontaneous breathing trial assessment for ventilator discontinuation and applying noninvasive mask ventilatory support might also shorten the need for invasive ventilatory support and reduce the development of VAP.

**Summary**

Ventilator management strategies can clearly impact the development of VILI and the duration of mechanical ventilation, both risk factors for VAP. Strategies to reduce VILI include a smaller VT and careful attention to reducing the maximum pressures in the lung. These lung-protective strategies, however, may require tradeoffs with factors that may in themselves produce risks for VAP. Specifically, hypercapnia, discomfort requiring sedation, and atelectasis may all be potential problems with a lung-protective strategy. Clinical data supporting the concept that modest respiratory acidosis is harmful are lacking, and indeed some animal work suggests that this level of hypercapnia may even be protective. Careful attention to ventilator settings to optimize patient-ventilator synchrony may reduce or even eliminate any need for additional sedation with a lung-protective strategy. Finally, atelectasis, while conceptually a risk factor for subsequent infection, may not be as important a risk in the patient with acute lung injury as it is in the postoperative arena. More importantly, clinical trials strongly suggest that a certain degree of fixed atelectasis is well worth the tradeoff if the lung can be protected from excessive VT and PEEP levels.

In terms of weaning patients who are recovering from respiratory failure, frequent assessments with spontaneous breathing trials should serve as a backbone for weaning protocols and should shorten any iatrogenic delays in ventilator weaning and thus unnecessary prolongations of unnecessary mechanical ventilatory support.
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ventilated patients. We may be seeing a lot more of this in the future. Staphylococcus aureus tine-leukocidin-producing strains of Staphylococcus aureus are more likely to contribute to lung injury when they cause VAP. I’ve started to think more about that since we’ve started seeing Panton-Valentine leukocidin. There is at least one study that suggests that if you have pneumonia in the setting of acute lung injury it might not add to mortality but might increase stay. There are specific reasons to do other-than-ARDS Network protocol or some similar low-tidal-volume strategy, unless those are all very circumstantial reflections of what was going on in these 1,400 patients. In the patient population that had a lower mortality—as you might expect—there were lower temperatures and white-blood-cell counts, and things looked better. But I don’t know how that ties into the role of pneumonia in these patients; it’s all inferential.

**Pierson:*** Most of what you’ve presented to us with respect to VILI and the way the ventilator is set has to do with managing acute lung injury and ARDS. Just to clarify, are you recommending that all patients on ventilators be managed according to the ARDS Network protocol or some similar low-tidal-volume strategy, unless there are specific reasons to do otherwise?

**MacIntyre:** Yes. So the clinical risk of increased atelectasis (as shown in a recent study) or other potential adverse effect from ventilating normal lungs with smaller-than-usual tidal volumes is outweighed by the importance of using small tidal volume to prevent VILI?

**REFERENCE**


**MacIntyre:** At the moment I think the risk of atelectasis is outweighed by the benefit you get from a lung-protective strategy. I think the jury is still out, however. There may be subpopulations in which that statement is wrong, but I think the weight of evidence right now is the way I’ve just indicated. I don’t think atelectasis is good; if I could get rid of it, I probably would, because a squashed-up lung just doesn’t sound healthy to me. But we have to deal with tradeoffs, and the tradeoff for reducing atelectasis may be injury in the uninvolved, healthy lung regions. What I’ve tried to present here is my take on the current risk/benefit ratio of atelectasis versus lung protection.

**Kallet:** That you are recommending the ARDS Network protocol, essentially carte blanche, for patients, as another member of the ARDS Network—much lower down on the feeding scale—I disagree with, and—

**REFERENCES**


**MacIntyre:** Those were insightful comments, which I can’t add a whole lot to. There are a lot of questions out there about the relationship of infection and underlying acute lung injury—be it from VILI or any other form of lung injury.

**Solomkin:** What was the observed infection rate in the ARDS Network trials?

**Kolley:** We have a lot of difficulty in diagnosing VAP and ARDS, and some of the more invasive techniques might be helpful. Maybe some newer diagnostic techniques might be helpful as well, such as soluble TREM-1. There’s this issue of whether VAP adds to the morbidity of lung injury in ARDS. A while ago I wrote an editorial on this because it’s not clear to me how that all comes into play here. There is at least one study that suggests that if you have pneumonia in the setting of acute lung injury it might not add to mortality but might increase stay.

I don’t know if there’s any data on this, and maybe other people can comment on whether or not certain bugs are more likely to contribute to lung injury when they cause VAP. I’ve started to think more about that since we’ve started seeing Panton-Valentine-leukocidin-producing strains of Staphylococcus aureus, because if they make their way into the hospital, we may be seeing a lot more of this in ventilated patients.
ARDS Network trial2 the tidal volume in the clouds the issue of the need for sedation and not treat it. So I think that would tolerate rather severe asynchrony, whereas other physicians would tolerate rather severe asynchrony and not treat it. So I think that clouds the issue of the need for sedation in patients with lung injury.

Also—and I think this is more important—is that people forget that in the high-tidal-volume protocol in the ARDS Network trial2 the tidal volume could be turned down to 4 mL/kg to keep the plateau under 50 cm H₂O. I can tell you—because Ivan Cheng's paper is based on data from our 1-center, 2-hospital ARDS Network site in California—that some of my patients at San Francisco General Hospital had sepsis and decreased chest wall compliance. They were on tidal volume of 12 mL/kg, and within a few hours were down to 4 or 5 mL/kg, and I think that probably those patients were sedated the same way as someone at 6 mL/kg would be. So I think the issue of sedation and low-tidal-volume ventilation is not settled in terms of the ARDS Network data. Just from my experience of 9 years of doing this at the bedside, I do think it is an issue.

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MacIntyre: You ignorant slut!

Kallet: Yes: proven many times over. You raised the issue of sedation in relation to Ivan Cheng's paper,1 I think it is very important for everyone to realize that sedation was not controlled in the ARDS Network trial, so there was a wide variation in practice, particularly between Moffitt Hospital at University of California San Francisco and San Francisco General Hospital. Some clinicians would sedate for any degree of patient-ventilator asynchrony, whereas other physicians would tolerate rather severe asynchrony and not treat it. So I think that clouds the issue of the need for sedation in patients with lung injury.

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