Ventilator-Associated Pneumonia: The Role of Ventilator Management Strategies

Neil R MacIntyre MD FAARC

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.* [Respir Care 2005;50(6):766–772. © 2005 Daedalus Enterprises]

Introduction

Risk factors for ventilator-associated pneumonia (VAP) include several issues that may be affected by ventilator management strategies. These include lung injury induced or worsened by ventilator settings (ventilator-induced lung injury [VILI]), consequences of using lung-protective ventilator strategies to reduce VILI (eg, respiratory acidosis, sedation requirements that suppress cough or spontaneous breathing capabilities, atelectasis), and iatrogenic delays in the weaning process that unduly prolong invasive ventilatory support.[1–6] This paper will review these issues in 3 sections: (1) the importance of ventilator management strategies in the prevention of VILI, (2) the various tradeoffs required to provide lung-protective strategies, and (3) approaches to facilitate the weaning process so as to avoid unnecessary delays in withdrawing mechanical ventilatory support.

Neil R MacIntyre MD FAARC is affiliated with Respiratory Care Services, Duke University Medical Center, Durham, North Carolina.

Neil R MacIntyre MD FAARC presented a version of this article at the 35th RESPIRATORY CARE Journal Conference, Ventilator-Associated Pneumonia, held February 25–27, 2005, in Cancún, Mexico.

Correspondence: Neil R MacIntyre MD FAARC, Respiratory Care Services, PO Box 3911, Duke University Medical Center, Durham NC 27710. E-mail: neil.macintyre@duke.edu.

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 (V_T) 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 H_2O, 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 (F_{IO_2}) tables used in the aforementioned successful NIH ARDS Network trials[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 V_T. 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-V_T 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-V_T 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 V_T, and the average pH in the lower-V_T group was less than 0.04 pH units lower than the average pH in the larger-V_T group.

Since a low-V_T 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 V_T suggest that any harm is outweighed by less VILI. Indeed, a grow-

Table 1. The PEEP/F_{IO_2} Tables Used During 2 National Institutes of Health ARDS Network Studies*

F_{IO_2}	0.30	0.30	0.40	0.40	0.50	0.50	0.60	0.70	0.70	0.70	0.80	0.80	0.90	0.90	0.90	1.0	1.0	1.0	1.0
PEEP†	5	5	5	8	8	10	10	10	10	12	14	14	14	16	18	18	20	22	24
PEEP‡	12	14	14	16	16	18	20	20	20	20	20	22	22	22	22	22	24	24	24

*The clinical target is a P_{aO_2} 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 H_2O, used in the original ARDS Network tidal-volume trial.[19]
‡PEEP values, in cm H_2O, used in the more recent National Institutes of Health ARDS Network ALVEOLI trial.[20]
ARDS = acute respiratory distress syndrome
F_{IO_2} = fraction of inspired oxygen

ing body of literature from a number of animal studies (not all of which are consistent) has actually suggested that this level of acidosis may in some ways ameliorate acute lung injury from a variety of etiologies, including VILI.[27,28]

Taken together, the available data, especially the positive clinical trials showing the benefit to low-V_T ventilation, suggest that the degree of respiratory acidosis seen with protocols such as the NIH ARDS Network is worth the tradeoff of a mild respiratory acidosis. Of note is that a new technique, tracheal gas insufflation, flushes the endotracheal tube free of CO_2 during expiration, which thereby reduces dead space and may thus reduce the respiratory acidosis. There are a number of technical problems remaining with this technique, however, and its role in respiratory failure is yet to be determined.[29]

Sedation

Current approaches to mechanical ventilatory support tend to favor assisted forms of ventilation over controlled forms of ventilation.[30,31] 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.[30,31] 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.[30,31]

When using lung-protective strategies, there is theoretical concern that the smaller V_T may not be as synchronous with patient effort as a larger V_T. 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 V_T is actually less comfortable than a larger V_T, 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 V_T 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).[30,31] The recent introduction of dual-control modes that adjust the pressure level automatically to a target V_T may conceptually be a very rational way to optimize flow synchrony while giving smaller V_T.[32]

Even without pressure-targeting features, the ARDS Network low-V_T strategy, using skilled respiratory therapists to optimize flow and timing settings, seems to have not increased the sedation requirement in the small-V_T group versus the large-V_T group. This was demonstrated both in an analysis of total days of sedation required in all the ARDS Network sites[19] as well as a more careful analysis of sedation usage in one of the ARDS Network sites (Table 2).[33]

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-V_T 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.[34] 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.[35,36] Indeed, one of the major

Table 2. Sedation Needs for Patients in the Small-Tidal-Volume (6 mL/kg) and Large-Tidal-Volume (12 mL/kg) Groups in One Center in the National Institutes of Health ARDS Network Tidal-Volume Trial*

Variable	Day 1	p	Day 2	p
Fentanyl (μg)				
6 mL/kg	1,760 (800–3,630) $n = 53$	1.0	2,763 (1,331–4,975) $n = 48$	0.32
12 mL/kg	1,560 (869–3,090) $n = 47$		2,260 (925–3,900) $n = 45$	
Midazolam (mg)				
6 mL/kg	16 (4–41) $n = 34$	0.29	38 (6–72) $n = 28$	1.0
12 mL/kg	22 (6–49) $n = 27$		24 (7–73) $n = 24$	
Lorazepam (mg)				
6 mL/kg	3 (2–4) $n = 21$	0.71	6 (2–9) $n = 18$	0.60
12 mL/kg	2 (1–19) $n = 13$		7 (3–25) $n = 14$	
Propofol (mg/kg)				
6 mL/kg	46 (23–61) $n = 9$	0.52	51 (35–72) $n = 5$	1.0
12 mL/kg	29 (8–49) $n = 5$		50 (40–52) $n = 5$	

*Total includes bolus doses and continuous infusions. Data include only patients who receive each medication.
Values expressed as median (interquartile range). p values by Mann-Whitney test.
Data from Reference 33.

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 P_{aO_2}/F_{IO_2} ratio over the first several days of the trial (Fig. 1). Importantly,

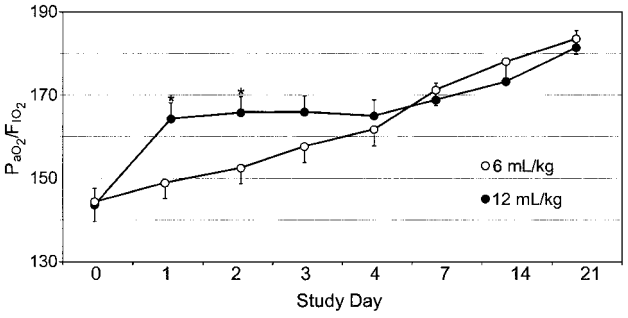

Fig. 1. The ratio of P_{aO_2} to fraction of inspired oxygen (P_{aO_2}/F_{IO_2} or P/F) in the patients in the small-tidal-volume (6 mL/kg) and large-tidal-volume (12 mL/kg) groups over the duration of the ARDS Network V_T trial.[19] Note that the large V_T strategy produced a better ratio (presumably from less fixed atelectasis) over the first few days of the trial (* = $p < 0.05$), even though the ultimate outcome was worse. (Data from Reference 19.)

however, the survival in the small-V_T group was significantly better than the large-V_T group. The conclusion from this trial is thus that the fixed atelectasis resulting from a small V_T seemed worth it, in that healthier regions of the lung were protected from excessive pressures from larger V_T. In the second large ARDS Network trial,[20] a more aggressive PEEP strategy was compared to the original less aggressive PEEP strategy (see Table 1). In both groups the small-V_T protocol was used. The high-PEEP strategy clearly produced less atelectasis, as evidenced by markedly improved compliance, P_{aO_2}/F_{IO_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 (eg, white blood cell count and fever) was also not increased in the low-PEEP group. As with a reduced V_T, a low-PEEP strategy, with resulting increase in fixed atelectasis, does not appear to impact outcome or increase infection.

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) V_T 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.[40–42] Specifically, withdrawal potential is often not appreciated by the patient's clinical team, the ventilator reduction "rules" may be unnecessarily slow (ie, synchronized intermittent mandatory ventilation rate reductions), and sedation may be excessive.[41,42] 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[40] 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_{IO_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_2O 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.[43] 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.[44]

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 V_T 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 V_T 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 unneeded mechanical ventilatory support.

REFERENCES

1. Cook DJ, Walter SD, Cook RJ, Griffith LE, Guyatt GH, Leasa D, et al. Incidence of and risk factors for ventilator-associated pneumonia in critically ill patients. Ann Intern Med 1998;129(6):433–440.
2. Kollef MH. Ventilator-associated pneumonia: a multivariate analysis. JAMA 1993;270(16):1965–1970.
3. Markowicz P, Wolff M, Djedaini K, Cohen Y, Chastre J, Delclaux C, et al. Multicenter prospective study of ventilator-associated pneumonia during acute respiratory distress syndrome: incidence, prognosis, and risk factor. ARDS Study Group. Am J Respir Crit Care Med 2000;161(6):1942–1948.
4. Pawar M, Mehta Y, Khurana P, Chaudhary A, Kulkarni V, Trehan N. Ventilator-associated pneumonia: incidence, risk factors, outcome, and microbiology. J Cardiothorac Vasc Anesth 2003;17(1):22–28.
5. Joshi N, Localio AR, Hamory BH. A predictive risk index for nosocomial pneumonia in the intensive care unit. Am J Med 1992;93(2): 135–142.
6. Sofianou DC, Constandinidis TC, Yannacou M, Anastasiou H, Sofianos E. Analysis of risk factors for ventilator-associated pneumonia in a multidisciplinary intensive care unit. Eur J Clin Microbiol Infect Dis 2000;19(6):460–463.
7. Kollef M. Ventilator-associated pneumonia and ventilator-induced lung injury: two peas in a pod. Crit Care Med 2002;30(10):2391–2392.
8. Tsuno K, Miura K, Takeya M, Kolobow T, Morioka T. Histopathologic pulmonary changes from mechanical ventilation at high peak airway pressures. Am Rev Respir Dis 1991;143(5 Pt 1):1115–1120.
9. Parker JC, Hernandez LA, Peevy KJ. Mechanisms of ventilator-induced lung injury. Crit Care Med 1993;21(1):131–143.
10. 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(5):1159–1164.
11. Rich PB, Reickert CA, Sawada S, Awad SS, Lynch WR, Johnson KJ, Hirschl RB. Effect of rate and inspiratory flow on ventilator-induced lung injury. J Trauma 2000;49(5):903–911.
12. Simonson DA, Adams AB, Wright LA, Dries DJ, Hotchkiss JR, Marini JJ. Effects of ventilatory pattern on experimental lung injury caused by high airway pressure. Crit Care Med 2004;32(3):781–786.
13. Murphy DB, Cregg N, Tremblay L, Engelberts D, Laffey JG, Slutsky AS, et al. Adverse ventilatory strategy causes pulmonary-to-systemic translocation of endotoxin. Am J Respir Crit Care Med 2000;162(1): 27–33. *Erratum in Am J Respir Crit Care Med 2002;166(11):1517.*
14. Ranieri VM, Suter PM, Tortorella C, De Tullio R, Dayer JM, Brienza A, et al. Effect of mechanical ventilation on inflammatory mediators in patients with acute respiratory distress syndrome: a randomized controlled trial. JAMA 1999;282(1):54–61.
15. Gattinoni L, Pelosi P, Crotti S, Valenza F. Effects of positive end expiratory pressure on regional distribution of tidal volume and recruitment in adult respiratory distress syndrome. Am J Respir Crit Care Med 1995;151(6):1807–1814.
16. Webb HH, Tierney DF. Experimental pulmonary edema due to intermittent positive pressure ventilation with high inflation pressure: protection by positive end expiratory pressure. Am Rev Respir Dis 1974;110(5):556–565.
17. Amato MB, Barbas CS, Medeiros DM, Magaldi RB, Schettino GP, Lorenzi-Filho G, et al. Effect of a protective ventilation strategy on mortality in ARDS. N Engl J Med 1998;338(6):347–354.
18. Gattinoni L, Caironi P, Carlesso E. How to ventilate patients with acute lung injury and acute respiratory distress syndrome. Curr Opin Crit Care 2005;11(1):69–76.
19. 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(18):1301–1308.
20. Brower RG, Lanken PN, MacIntyre N, Matthay MA, Morris A, Ancukiewicz M, et al. Higher versus lower positive end-expiratory pressures in patients with the acute respiratory distress syndrome. N Engl J Med 2004;351(4):327–336.
21. Gerstmann DR, Minton SD, Stoddard RA, Meredith KS, Monaco F, Bertrand JM, et al. The Provo multicenter early high-frequency oscillatory ventilation trial: improved pulmonary and clinical outcome in respiratory distress syndrome. Pediatrics 1996;98(6 Pt 1):1044–1057.
22. Rotta AT, Gunnarsson B, Fuhrman BP, Hernan LJ, Steinhorn DM. Comparison of lung protective ventilation strategies in a rabbit model of acute lung injury. Crit Care Med 2001;29(11):2176–2184.
23. Derdak S, Mehta S, Stewart TE, Smith T, Rogers M, Buchman TG, et al. High-frequency oscillatory ventilation for acute respiratory distress syndrome in adults: a randomized, controlled trial. Am J Respir Crit Care Med 2002;166(6):801–808.
24. Habashi NM. Other approaches to open-lung ventilation: airway pressure release ventilation. Crit Care Med 2005;33(3 Suppl):S228–240.
25. Jobe AH. Pulmonary surfactant therapy. N Engl J Med 1993;328(12): 861–868.
26. Hickling KG. Permissive hypercapnia. Respir Care Clin N Am 2002; 8(2):155–169.
27. Laffey JG, Honan D, Hopkins N, Hyvelin JM, Boylan JF, McLoughlin P. Hypercapnic acidosis attenuates endotoxin-induced acute lung injury. Am J Respir Crit Care Med 2004;169(1):46–56.
28. Broccard AF, Hotchkiss JR, Vannay C, Markert M, Sauty A, Feihl F, Schaller MD. Protective effects of hypercapnic acidosis on ventilator-induced lung injury. Am J Respir Crit Care Med 2001;164(5): 802–806.
29. Hess DR, MacIntyre NR. Tracheal gas insufflation: overcoming obstacles to clinical implementation. Respir Care 2001;46(2):198–199.
30. Tobin MJ, Jubran A, Laghi F. Patient-ventilator interaction. Am J Respir Crit Care Med 2001;163(5):1059–1063.
31. Dick CW, Sassoon CS. Patient-ventilator interactions. Clin Chest Med 1996;17(3):423–438.
32. Branson RD, MacIntyre NR. Dual-control modes of mechanical ventilation. Respir Care 1996;41(4):294–305.
33. Cheng IW, Eisner MD, Thompson BT, Ware LB, Matthay MA; Acute Respiratory Distress Syndrome Network. Acute effects of tidal volume strategy on hemodynamics, fluid balance, and sedation in acute lung injury. Crit Care Med 2005;33(1):63–70; discussion 239–240.
34. Gibb KA, Carden DL. Atelectasis. Emerg Med Clin N Am 1983; 1(2):371–378.
35. Dreyfuss D, Saumon G. Role of tidal volume, FRC, and end-inspiratory volume in the development of pulmonary edema following mechanical ventilation. Am Rev Respir Dis 1993;148(5):1194–1203.
36. Muscedere JG, Mullen JB, Gan K, Slutsky AS. Tidal ventilation at low airway pressure can augment lung injury. Am J Respir Crit Care Med 1994;149(5):1327–1334.
37. Kacmarek R, Pierson DJ. Positive end expiratory pressure. Respir Care 1988;33(7):401–516.
38. Brooks-Brunn JA. Postoperative atelectasis and pneumonia: risk factors. Am J Crit Care 1995;4(5):340–349.
39. Fry DE. Postoperative pneumonia in the intensive care unit. Surg Gynecol Obstet 1993;177 Suppl:41–49.
40. Evidence-based guidelines for weaning and discontinuing ventilatory support: a collective task force facilitated by the American College of Chest Physicians, the American Association for Respiratory Care, and the Society of Critical Care Medicine. Respir Care 2002;47(1):69–90.

41. Brochard L, Rauss A, Benito S, Conti G, Mancebo J, Rekik N, et al. Comparison of three methods of gradual withdrawal from ventilatory support during weaning from mechanical ventilation. Am J Respir Crit Care Med 1994;150(4):896–903.
42. Esteban A, Frutos F, Tobin MJ, Alia I, Solsona JF, Valverdu I, et al. A comparison of four methods of weaning patients from mechanical ventilation. Spanish Lung Failure Collaborative Group. N Engl J Med 1995;332(6):345–350.
43. Ely EW, Meade MO, Haponik EF, Kollef MH, Cook DJ, Guyatt GH, Stoller JK. Mechanical ventilator weaning protocols driven by non-physician health-care professionals: evidence-based clinical practice guidelines. Chest 2001;120(6 Suppl):454S–463S.
44. Nava S, Ambrosino N, Clini E, Prato M, Orlando G, Vitacca M, et al. Noninvasive mechanical ventilation in the weaning of patients with respiratory failure due to chronic obstructive pulmonary disease: a randomized, controlled trial. Ann Intern Med 1998;128(9):721–728.

Discussion

Kollef: 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[1] because it's not clear to me how that all comes into play here. There is at least one study[2] 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.

REFERENCES

1. Kollef M. Ventilator-associated pneumonia and ventilator-induced lung injury: 2 peas in a pod (editorial). Crit Care Med 2002; 30(10):2391–2392.
2. Markowicz P, Wolff M, Djedaini K, Cohen Y, Chastre J, Delclaux C, et al. Multicenter prospective study of ventilator-associated pneumonia during acute respiratory distress syndrome: incidence, prognosis, and risk factors. ARDS Study Group. Am J Respir Crit Care Med 2000;161(6):1942–1948.

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?

MacIntyre: I studied the ARDS Network original data, trying to sort that out, and unfortunately it's very difficult to do, because VAP was not one of the specific things that was being followed. You can follow things like white blood cell counts, fevers, or antibiotic usage, but 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?

* David J Pierson MD FAARC, Division of Pulmonary and Critical Care Medicine, Harborview Medical Center, University of Washington, Seattle, Washington.

MacIntyre: Yes.

Pierson: So the clinical risk of increased atelectasis (as shown in a recent study[1]) 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

1. 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(4):1281–1291.

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—

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.

Also—and I think this is more important—is that people forget that in the high-tidal-volume protocol in the ARDS Network trial[2] the tidal volume could be turned down to 4 mL/kg to keep the plateau under 50 cm H_2O. 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.

REFERENCES

1. Cheng IW, Eisner MD, Thompson BT, Ware LB, Matthay MA, Acute Respiratory Distress Syndrome Network. Acute effects of tidal volume strategy on hemodynamics, fluid balance, and sedation in acute lung injury. Crit Care Med 2005;33(1):63–70.
2. 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(18):1301–1308.

MacIntyre: I am the first to agree that there are patients who are so hopelessly asynchronous with any strategy that you've got to sedate them. Large, small, or intermediate tidal volumes can be associated with asynchrony in some patients. Arguing from individual experiences is very problematic in trying to come up with a blanket recommendation. The fact of the matter is that when you consider all the patients, it seems to balance out.

There are people in the high-tidal-volume group who needed a lot of sedation; there are people in the low-tidal-volume group who needed a lot of sedation. And I would submit to you, having tried to adopt these philosophies in our unit since the study came out back in 1999, that we've paid a lot of attention to keeping people comfortable with ventilator strategies, not drugs. We like going to pressure-targeted ventilation, and—contrary to what some believe—you can set a pressure target to get 6 mL/kg tidal volume. The synchrony that you get for the pressure-targeted breath tends to be a little better than with a fixed-flow volume breath—*tends* to. That's not true all the time, but it tends to be.

So I think there are ways of playing with the ventilator a little bit to make it a little more comfortable. I would also point out that the low-tidal-volume strategy in the ARDS Network could actually go up to 8 mL/kg if there were a serious synchrony issue. That was added on later on in the trial, when people were complaining that 6 mL was a little difficult. As you probably know, we euphemistically named that change the "sucking wind" amendment, to address that particular issue. So when I recommend the 6-mL/kg strategy, I'm talking about the 6 mL/kg strategy with all of its ramifications.

Kollef: Are you worried that by allowing atelectasis to occur, particularly in patients without lung injury, that that just drives more antibiotic use, because people will see infiltrate, even though it's atelectasis—and there may be some low-grade fever with that—and call it pneumonia?

MacIntyre: You raise a very valid point, and I am worried about it. I hope that at the end of this conference we will be much better at separating out atelectasis that may not cause much harm at all from infection that truly needs to be treated. But you're right. It's yet another part of the tradeoff picture.

Branson: The reintubation issue to me has always been one of those things that is "true, true, and unrelated." When the patient gets reintubated, is that bad because they needed to be reintubated, or is it bad because of the reintubation process itself, and does anybody know if the microbiology data suggests that pneumonia after reintubation is caused by a bolus of oropharyngeal bacteria?

MacIntyre: I think intubation probably does introduce a bolus of bacteria into the tracheobronchial tree. So whether you're getting reintubated because you guessed wrong and the patient was really too sick to extubate, or you're reintubating because the patient developed post-extubation stridor, you have exposed the patient to that risk. The other side of the coin is what you were alluding to; if you have to reintubate because of respiratory failure, that in itself is an important independent marker of underlying lung injury, regardless of any specific reintubation risks that may be present.