

## Review

# Bench-to-bedside review: Ventilator strategies to reduce lung injury – lessons from pediatric and neonatal intensive care

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## Abstract

As in the adult with acute lung injury and acute respiratory distress syndrome, the use of lung-protective ventilation has improved outcomes for neonatal lung diseases. Animal models of neonatal respiratory distress syndrome and congenital diaphragmatic hernia have provided evidence that 'gentle ventilation' with low tidal volumes and 'open-lung' strategies of using positive end-expiratory pressure or high-frequency oscillatory ventilation result in less lung injury than do the traditional modes of mechanical ventilation with high inflating pressures and volumes. Although findings of retrospective studies in infants with respiratory distress syndrome, congenital diaphragmatic hernia, and persistent pulmonary hypertension of the newborn have been similar to those of the animal studies, prospective, randomized, controlled trials have yielded conflicting results. Successful clinical trial design in these infants and in children with acute lung injury/acute respiratory distress syndrome will require an appreciation of the data supporting the modern ventilator management strategies for infants with lung disease.

the adult population in their efforts to optimize outcomes in patients requiring mechanical ventilation.

Fortunately, the practice of lung-protective ventilation is not at all revolutionary in neonatal and pediatric intensive care units, where protective modalities such as continuous positive airway pressure (CPAP), high-frequency oscillatory ventilation (HFOV), and extracorporeal membrane oxygenation (ECMO) have been widely utilized over the past 20 years. In the same way that 'children are not just small adults', as the saying goes, they are also not just 'large babies'. Nevertheless, a thoughtful review of the evidence supporting current ventilator strategies used for neonatal respiratory distress syndrome (RDS), persistent pulmonary hypertension of the newborn (PPHN), and congenital diaphragmatic hernia (CDH) will help to guide the use of lung-protective strategies in the pediatric intensive care unit.

## Introduction

Although the first animal studies demonstrating the phenomenon of ventilator-induced lung injury (VILI) were published in the mid-1970s [1], it took 25 years to translate that information into a practice paradigm for treating adults with acute lung injury (ALI) and acute respiratory distress syndrome (ARDS) that is supported by a well designed, randomized, controlled clinical trial [2]. In the pediatric population, the smaller number of absolute cases of ALI/ARDS and lower mortality rate make it unlikely that a similar randomized, controlled clinical trial will be completed in the near future. For the moment, pediatric intensivists must extrapolate clinical trial results and ventilator algorithms from

## Respiratory distress syndrome in the preterm neonate

Nowhere is the potential harm caused by mechanical ventilation more evident than in the premature lung, which at birth is subject to the consequences of supplemental oxygen and mechanical ventilation. Although the ability to replace surfactant has reduced the severity of RDS and has permitted improved survival for even the most premature infants, the percentage of surviving infants who develop neonatal chronic lung disease (CLD) remains high [3,4]. As in adults with ARDS, the search for interventions that will improve outcomes in RDS has focused on determining the safest and most lung-protective means of providing mechanical ventilation to these infants.

ALI = acute lung injury; ARDS = acute respiratory distress syndrome; BPD = bronchopulmonary dysplasia; CDH = congenital diaphragmatic hernia; CLD = chronic lung disease; CMV = conventional mechanical ventilation; CPAP = continuous positive airway pressure; ECMO = extracorporeal membrane oxygenation; HFOV = high-frequency oscillatory ventilation; iNO = inhaled nitric oxide; PEEP = positive end-expiratory pressure; PPHN = persistent pulmonary hypertension of the newborn; RDS = respiratory distress syndrome; VILI = ventilator-induced lung injury.

### Animal studies

Although preterm lung volumes are small, significant inflation pressures are often necessary during resuscitation because of surfactant deficiency, immature structure, and fetal lung fluid. Animal studies in premature lambs have found that initial resuscitation with high tidal volumes augments abnormalities of lung mechanics [5–7], increases edema formation [8–10], increases inflammatory cytokine production [10], worsens histopathology [5,6], and leads to decreased surfactant production [11], even when used in combination with surfactant therapy [5–7,11]. The potential for overdistension is greater in the neonate because of a very compliant chest wall, which permits lung expansion beyond total lung capacity.

Another important mechanism of VILI in the preterm lung is the repetitive opening and closing of atelectatic alveolar units, which is more pronounced in the preterm infant because of surfactant deficiency. A strategy to reduce this effect is the 'open-lung' strategy of maintaining lung volumes with positive end-expiratory pressure (PEEP) or HFOV. McCulloch and coworkers [12] compared HFOV using high and low mean airway pressures in rabbits after saline lavage-induced surfactant deficiency, and found that maintenance of lung volumes significantly improved lung compliance and reduced hyaline membrane formation. In the preterm lamb and newborn piglet surfactant washout models, an open-lung strategy improved histologic evidence of collapse, preserved lung function, improved surfactant function, and reduced inflammation [13–17].

Before the advent of surfactant therapy, many surviving premature infants developed bronchopulmonary dysplasia (BPD) – a disease described by Northway and coworkers [18] in 1967 as one of alveolar and bronchiolar fibrosis. After the advent of surfactant therapy and gentler ventilation techniques, the lung pathology in those infants who continue to require pulmonary support after RDS is characterized by arrested alveolar development with less fibrotic change [19]. This 'new BPD' with deficient alveolarization has been termed 'CLD of infancy', defined clinically as dependence on supplemental oxygen at postconceptual age 36 weeks. Recently, preterm lamb and baboon models that manifest abnormal alveolarization after surfactant and 3–4 weeks of mechanical ventilation have been developed [20,21]. Studies in these animal models have provided evidence that, in addition to improving other markers of lung injury, lung-protective ventilation improves alveolarization and lung development [20,22]. This finding has added fuel to the search for the most lung-protective ventilation strategies for extremely premature infants.

If small tidal volumes and lung volume maintenance are able to prevent VILI in the preterm lung, then HFOV should be an ideal mode of ventilation for preterm infants. The most extensive animal data on this subject come from a preterm baboon model that was characterized by Coalson and

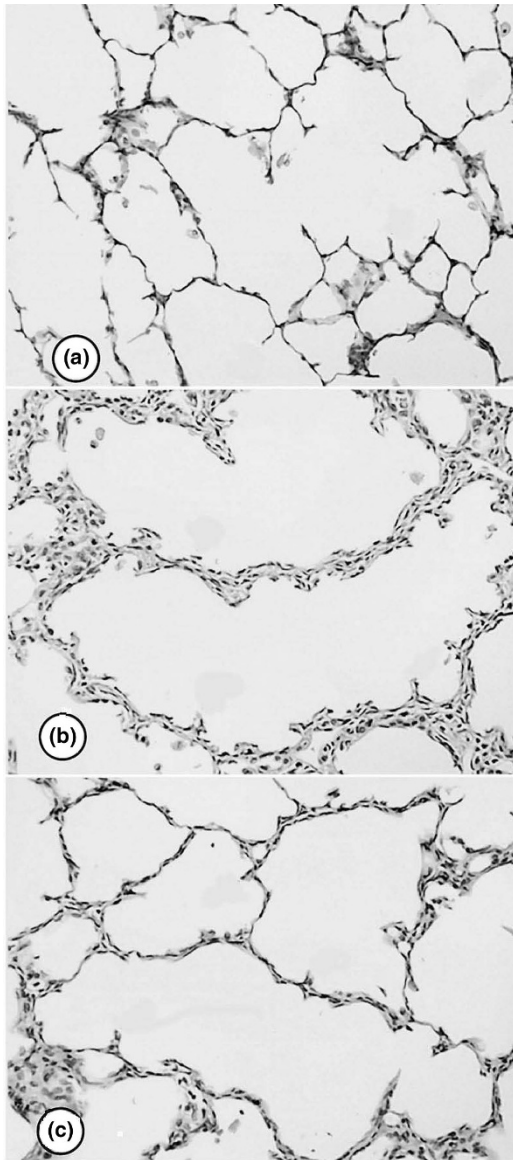
coworkers in 1982 [23–26]. Using this model, they showed that the pathologic changes of RDS occur more commonly after a high tidal volume and low PEEP strategy than after HFOV using a higher mean airway pressure [25]. Hamilton and coworkers [27] found similar results comparing HFOV with conventional mechanical ventilation (CMV) in the saline-lavaged rabbit model. More recent studies in the premature baboon have demonstrated HFOV to be associated with improvements in lung mechanics and histopathologic outcomes (Fig. 1) when compared with CMV using small tidal volumes and low PEEP [28]. Together, these animal data provide evidence supporting both theoretical advantages of HFOV, namely reduction in VILI associated with high tidal volumes and the repetitive opening and closing of atelectatic units.

Another strategy to limit VILI is with a combination of permissive hypercapnia and early extubation to CPAP. In the preterm lamb model, 2 hours of CPAP or CMV immediately after birth were compared; animals managed with CPAP exhibited higher lung volumes and reduced inflammatory cell infiltrate [28]. In the baboon CLD model, long-term management with CPAP led to a dramatic improvement in lung development with similar alveolarization to that in an animal killed after normal term delivery [22].

### Human studies

Before the surfactant era, Kraybill and coworkers [29] showed that early hypocapnia was associated with a higher incidence of BPD in a retrospective study, and after the advent of surfactant therapy another retrospective study found that hypocapnia before surfactant administration was associated with similar adverse outcomes [30]. These studies formed the basis of the hypothesis that more aggressive ventilation might be causally related to the development of CLD in infants. Two prospective trials of permissive hypercapnia were designed to test this hypothesis; both studies demonstrated decreased ventilator days in the hypercapnic group but neither found a significant difference in CLD development, death, or development of intraventricular hemorrhage [31,32]. Several authors have evaluated differences in CLD prevalence among neonatal intensive care units [33–35] and concluded that ventilator strategies designed to reduce VILI can explain these discrepancies.

Although the animal studies of HFOV support its use to improve RDS and prevent CLD, studies in preterm infants have not been as convincing. Many early trials did not use prenatal steroids or surfactant, and later studies used HFOV with low mean airway pressures and therefore did not take advantage of the open-lung benefits of HFOV. Two large multicenter, randomized controlled trials of early HFOV versus CMV for the prevention of CLD in preterm infants [36,37] were recently published simultaneously. Although Courtney and coworkers [36] found no differences in survival among 500 infants with birthweight under 1200 g, survival without CLD was improved from 47% in synchronized

**Figure 1**

Representative lung histopathology in (a) term baboons, (b) preterm baboons treated with a low tidal volume, low positive end-expiratory pressure strategy, and (c) preterm baboons treated with high-frequency oscillatory ventilation. Hematoxylin and eosin; 100 $\times$ . With permission from Yoder and coworkers [63].

intermittent mandatory ventilation-treated infants to 56% in HFOV-treated infants. HFOV-treated infants were successfully extubated a week earlier on average. In contrast, Johnson and coworkers [37] found no significant differences in overall survival or CLD among 787 infants at 23–28 weeks of gestation.

The differences in results for these two studies probably reflect the fact that Courtney and coworkers [36] defined a

disease threshold for enrollment (mean airway pressure of at least 6 cmH<sub>2</sub>O and 0.25 fractional inspired oxygen within the first 4 hours of life), used more closely defined ventilator algorithms and extubation criteria, targeted hypercapnia (partial carbon dioxide tension 40–65 mmHg) and maintained patients on their assigned ventilator until extubation, and the patients had a mean duration of HFOV of more than 6 days. In contrast, Johnson and coworkers [37] did not define a severity of illness threshold for enrollment, did not define algorithms for ventilator management and targeted normocapnia (partial carbon dioxide tension 34–53 mmHg), and the mean duration of HFOV was 3 days. Although Courtney and coworkers studied a more well defined population of infants who were sicker, the study by Johnson and colleagues may more accurately reflect the actual practice of HFOV across neonatal intensive care units [38].

Although the jury remains out concerning how best to practice lung-protective ventilation in order to reduce the incidence of CLD in preterm infants, it is clear that VILI contributes heavily to CLD. Any successful future strategies will undoubtedly employ the concepts of lung-protective ventilation described above.

### **‘Gentle ventilation’ for persistent pulmonary hypertension of the newborn**

Full-term infants are also susceptible to the injurious effects of mechanical ventilation. PPHN has been well recognized as a clinical syndrome of high pulmonary vascular resistance and right-to-left shunting since the 1950s. The responsiveness of the pulmonary vasculature to acid–base status was elucidated in the 1960s, and led directly to the use of hyperventilation to produce hypocapnia and alkalosis in the management of PPHN [39]. Two case series reported in the early 1980s [40,41] showed that hyperventilation of infants with PPHN increased arterial oxygen tension over several hours. This approach was associated with reported mortality rates of 40% in all infants and 80–90% in infants with severe PPHN [42,43].

Given the emerging animal data regarding the significance of VILI [1], Wung and coworkers [44] at Babies’ Hospital in New York City began to manage PPHN without hyperventilation in an attempt to protect the lung from high peak inspiratory pressure and tidal volume. This was before the advent of inhaled nitric oxide (iNO) therapy. Those investigators reported 100% survival in 15 infants with severe PPHN ventilated with target partial carbon dioxide tension of 40–60 mmHg. Dworetz and coworkers [43] applied the lessons from the study by Wung and coworkers, and compared 23 infants from the era of hyperventilation versus 17 infants from the era of ‘gentle ventilation’. They found that overall survival improved from 65% to 88% as the management changed, and survival in the sickest infants (who met criteria and were eligible for ECMO but did not receive it) improved from 0% to 89%.

**Table 1**

<b>Death rates in infants with congenital diaphragmatic hernia</b>					
Period	Boston	Survival	Toronto	Survival	<i>P</i>
1981–1984	Immediate repair without ECMO	45%	Immediate repair	53%	NS
1984–1987	Immediate repair with postoperative ECMO	53%	Delayed repair	52%	NS
1987–1991	Delayed repair, preoperative ECMO	44%	Delayed repair	52%	NS
1991–1994	Delayed repair, permissive hypercapnia	69%	Delayed repair, permissive hypercapnia	61%	NS
		<i>P</i> = 0.007		<i>P</i> = NS	

Shown are mortality rates for infants with congenital diaphragmatic hernia (CDH) at Children's Hospital, Boston ( $n = 285$ ) and The Hospital for Sick Children, Toronto ( $n = 223$ ) during four eras of CDH management strategy. Extracorporeal membrane oxygenation (ECMO) was rarely used for CDH at Toronto. *P* values were determined by student's *t* test;  $P < 0.05$  was considered statistically significant. NS, not significant. Adapted from Azarow and coworkers [47].

Infants with PPHN often present with severe hypoxemic respiratory failure, and as soon as HFOV and ECMO became available in the late 1970s and early 1980s they were put to use in this population of infants with very high mortality rates. Although originally employed as a means to improve arterial oxygen content and systemic oxygen delivery, HFOV and ECMO also provided a means by which the lungs of these infants could be protected from injurious mechanical ventilation. Once iNO became available, HFOV provided a means by which atelectatic lungs could be efficiently recruited and enhance alveolar delivery of this selective pulmonary vasodilator. Kinsella and coworkers [45] found that the response to iNO therapy plus HFOV was better than the response to iNO or HFOV alone in 205 neonates in a randomized, controlled trial. Overall improvement in mortality rates and reduction in need to use ECMO in these infants is probably related to both lung-protective ventilation (regardless of modality) and iNO therapy. Gupta and colleagues [46] used gentle CMV with permissive hypercapnia and iNO and reported an overall mortality rate of 9.8% in infants with meconium aspiration syndrome and PPHN – a figure comparable to that in studies combining HFOV and iNO therapy [45].

### Ventilation for congenital diaphragmatic hernia

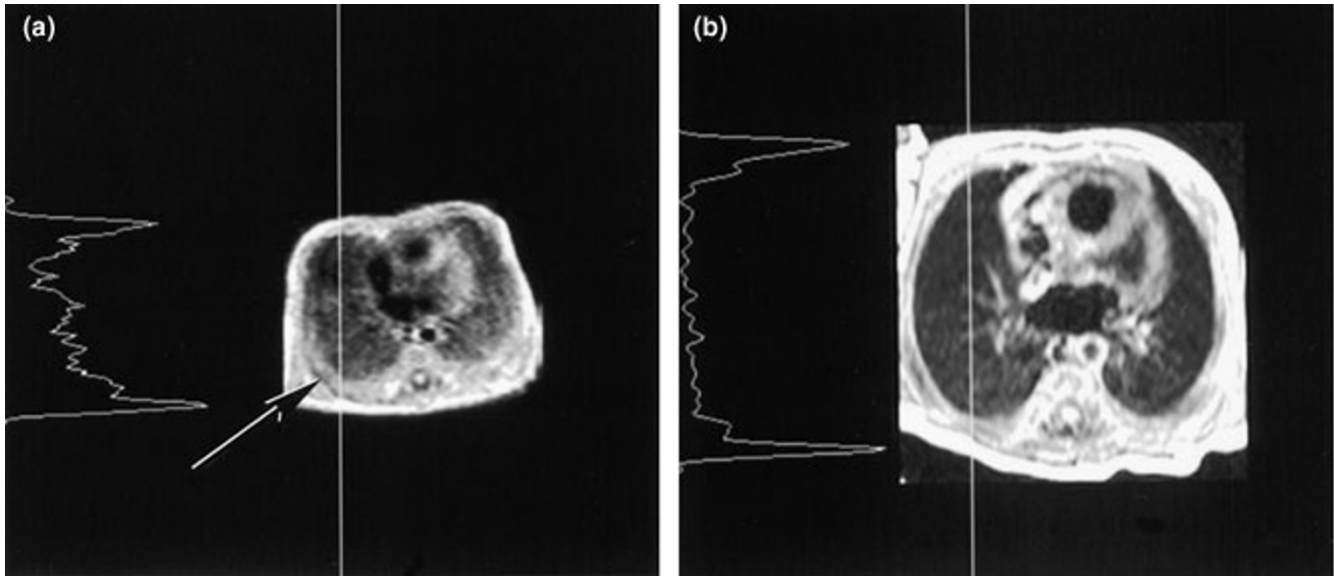
CDH is another excellent example of the negative impact that aggressive ventilation can have on morbidity and mortality in neonates with lung disease. Despite best efforts to improve survival in the 1980s with delayed surgical repair and other modern technologies such as synchronized intermittent mandatory ventilation, HFOV, surfactant replacement, iNO, and ECMO, mortality rates in infants with CDH remained between 48% and 66% as recently as 1991 [47]. During this time, management strategies included hyperventilation and induced alkalosis in order to reduce pulmonary vascular resistance and limit right-to-left shunting. The application of 'gentle ventilation' principles to the CDH population helped to decrease mortality rates to 31–39% by 1994 (Table 1)

[47,48], 20% in one center by 1998 [49], and 7% in another center by 2002 [50].

'Gentle ventilation' is likely to benefit the infant with CDH because, like the preterm lung, CDH lungs are immature and total lung capacity is small. Even when born full term, infants with CDH have lungs that are immature in structure and biochemistry. Type II pneumocytes have fewer lamellar bodies and surfactant is deficient [51]. An autopsy study found that both alveolarization and surfactant were deficient in CDH lungs, with the affected side being more immature than the unaffected side [52]. An analysis of autopsy specimens from 68 out of 101 infants who died from CDH at one institution from 1981 to 1994 showed that 91% of infants had hyaline membrane formation, which was more prominent in the ipsilateral, severely affected lung [49]. Of the six infants who did not die with prominent hyaline membranes in that study, five were treated with HFOV shortly after birth. The prominent hyaline membranes were postulated to be a result of lung immaturity and VILI [47,49].

Interestingly, lung disease in those survivors of CDH with pulmonary morbidity closely resembles BPD. In a study of 45 survivors of CDH repair reported in 1993, 15 had clinical and radiologic evidence of BPD [53]. Animal studies indicate that the pathogenesis of VILI is similar in preterm infants and infants with CDH. The lungs of rats with nitrofen-induced CDH who are exposed to mechanical ventilation have abnormally high elastin deposition [54], which is similar to preterm lambs exposed to injurious mechanical ventilation [55]. More abnormal deposition is present in lambs ventilated with a slow rate and large tidal volume as compared with a faster rate and small tidal volume [20]. Abnormal elastin deposition is present in autopsy specimens of lungs of infants with BPD [56,57], and abnormal layout of elastin deposition has been proposed to play an important role in the impairment of alveolarization seen in BPD [58]. The effects of mechanical ventilation on elastin production and deposition may explain impaired alveolarization in the CLD seen in both



**Figure 2**

Transverse T1-weighted magnetic resonance images at the level of the left atrium in (a) a 4-day-old, 26-week gestation infant, and (b) a 2-day old, term infant. In the planes of the superimposed vertical white lines, signal intensity is graphed to the left of the images and shows that the preterm infant has a gravity-dependent increase in signal intensity as compared with the homogeneous pattern in the term infant. The arrow in panel a points to an area of dependent thickened pleural margin. With permission from Adams and coworkers [60].

premature infants and those with CDH. The improvements in mortality in the era of gentle ventilation of infants with CDH may be in part related to improved alveolar development in these infants, but this has not yet been studied.

### Conclusion

The evidence presented above strongly supports the use of lung-protective ventilation in the management of neonatal lung disease. Neonates with RDS, meconium aspiration syndrome, or CDH are thought to have more homogeneous lung pathology than the patchy, heterogeneously aerated pattern seen in ARDS [59], but recent magnetic resonance imaging evidence indicates that RDS has a similar distribution of dependent atelectasis and lung water to ARDS (Fig. 2) [60]. This evidence gives more credence to the concern for alveolar overdistention in the nondependent, aerated regions of the neonatal lung. It is clear that the use of lung-protective ventilator strategies similar to the algorithms developed for adults with ALI/ARDS can have a significant impact on outcomes. The non-neonate with ALI/ARDS and heterogeneous lung mechanics may be particularly susceptible to lung overdistention because of small absolute lung volumes and a highly compliant chest wall. Furthermore, large tidal volumes and elevated airway pressures in these patients may induce regional overdistention and lung stretch that is much more significant than in adults, whose noncompliant chest wall and increased abdominal compartment pressures may limit transpulmonary pressures. In patients younger than 5 years, the closing capacity of the lung is very close to the functional residual capacity. In the

setting of lung disease and mechanical ventilatory support, the young patient is likely to suffer significant alveolar instability and atelectasis. Children with ALI/ARDS may therefore benefit even more than adults from the lessons learned in the animal laboratory and adult clinical trials.

As clinical trial networks in the pediatric population evolve and mature [61], data relevant to the child with ALI/ARDS will emerge. Successful design of these trials will depend on knowledge gained from neonatal animal and human studies. An excellent example is a recent study from Dobyns and coworkers [62], who took lessons from the PPHN population [45] and studied the combined effects of HFOV and iNO on oxygenation in pediatric patients with acute hypoxemic respiratory failure. Although a prospective, randomized, controlled trial with important outcome measures is necessary to draw conclusions about this therapy, data from infants with PPHN have clearly helped to frame the important questions about this novel therapy. In the pursuit of excellent outcomes for children with ALI/ARDS, pediatric investigators and practitioners alike will benefit from a thorough understanding of relevant neonatal and adult animal and clinical data.

### Competing interests

The author(s) declare that they have no competing interests.

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