

# Pulmonary Complications of Mechanical Ventilation in Neonates

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Mechanical ventilation is a common therapy to treat infants with respiratory insufficiency. Advances in pulmonary care such as surfactant replacement therapy and improved mechanical ventilation have reduced the mortality of infants, but important respiratory morbidities continue to affect preterm and term infants [1,2]. Lung and airway injury can be attributed to natural causes, such as pulmonary or systemic infection, or to complications of mechanical ventilation. Complications of mechanical ventilation include volutrauma, extrapulmonary air leak syndromes, traumatic injury to large airways, and endotracheal tube complications.

## **Volutrauma**

Experimental data demonstrate that mechanical ventilation using both high tidal volumes and high peak pressures can cause lung injury [3–6]; however, data from various investigators consistently demonstrate that, regardless of the peak pressure, markers of lung injury in animals are increased with high tidal volume ventilation but not with low tidal volume ventilation [7–10]. Only a few breaths of large tidal volume ventilation immediately after birth can reduce subsequent lung compliance and diminish the response to exogenous surfactant in surfactant-deficient lambs [11]. Furthermore, most experimental animal studies investigating ventilator-associated lung injury use high tidal volumes, not low tidal volumes, to induce the injury.

At the microscopic and molecular level, volutrauma caused by mechanical overdistention leads to a diverse array of abnormalities. Alveolar

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epithelial cell damage, alveolar protein leakage, altered lymphatic flow, hyaline membrane formation, and inflammatory cell influx can be seen in the lungs of animals after high tidal volume ventilation [12–15]. Volutrauma can also decrease lung compliance and alter surfactant structure and function [11,15–18]. The expression of genes involved in inflammatory signaling is up-regulated after mechanical ventilation with high tidal volumes [14,15,19,20]. These data suggest that changes at the microscopic and molecular level due to injurious mechanical ventilation could adversely affect the structure and function of the lung.

Because lung injury contributes to bronchopulmonary dysplasia (BPD), efforts to decrease volutrauma in preterm infants should decrease the risk of this disorder [21]. Most published randomized controlled trials in neonates testing “lung protective” strategies with conventional mechanical ventilation have compared volume-targeted modes with pressure-limited modes and have not used different predetermined tidal volumes in each treatment arm [22–25]. The assumption while using volume-targeted modes of conventional mechanical ventilation is that lower tidal volumes are delivered as compliance improves when compared with the volumes associated with pressure-limited ventilation. Over time, these lower volumes may translate into decreased volutrauma and decrease the risk of BPD. Various investigators have compared these two modes of ventilation to test the hypothesis that volume-targeted ventilation decreases the incidence of BPD. A meta-analysis of four such trials demonstrated a significant decrease in pneumothorax (2% versus 13%; relative risk [RR], 0.23; CI, 0.07–0.76; number needed to treat [NNT], 9) and trends toward decreased death and BPD [26]. The combined outcome of death or BPD was not reported in any trial included in the analysis. Other protective ventilatory strategies such as permissive hypercapnia have been tested using randomized controlled trials in preterm infants. Even though all three permissive hypercapnia trials aimed to decrease volutrauma, respiratory frequency, not tidal volume, was changed the most to achieve different  $PCO_2$  targets [27–29].

Only one recent prospective randomized controlled trial has evaluated the effects of using different predetermined tidal volumes to ventilate preterm infants. Lista and colleagues [30] used volume-guarantee ventilation and compared tracheal aspirate cytokine levels in 30 preterm infants ventilated with 3 mL/kg versus 5 mL/kg of tidal volume. The primary hypothesis was that, when compared with a tidal volume of 5 mL/kg, using low tidal volumes (3 mL/kg) would induce less inflammation, reduce ventilation time, and reduce the incidence of BPD. Interestingly, reduction of the tidal volume from 5 mL/kg to 3 mL/kg actually increased the markers of lung injury, prolonged the total time of mechanical ventilation, and did not change the incidence of BPD [30]. Another mechanism of lung injury is repeated collapse and re-opening of alveoli, but there are insufficient data in immature lungs [5]. The best ventilator strategy may consist of using adequate positive end-expiratory pressure (PEEP) to maintain functional

residual capacity (FRC) to avoid atelectrauma and using an optimal tidal volume to avoid volutrauma (Fig. 1) [31].

A single respiratory intervention (ie, using a particular ventilator mode or a specific tidal volume) may minimize lung injury from volutrauma but is unlikely to substantially decrease the incidence of a multifactorial disease such as BPD. To improve long-term respiratory outcomes, clinicians must focus on many aspects of neonatal care. Walsh and colleagues [32] designed a randomized controlled trial to test the hypothesis that care practices at hospitals with a low incidence of BPD (benchmark centers) could be emulated and to determine whether those practices would decrease the incidence of BPD. The respiratory practices at benchmark centers thought to be effective in reducing BPD were using lower tidal volumes and peak pressures, aggressively weaning infants from the ventilator to nasal continuous positive airway pressure, avoiding routine suction procedures, avoiding hand-bagging ventilated infants, accepting higher  $PCO_2$  values, and using surfactant early once an infant was intubated. Interestingly, the trial reported that successfully changing respiratory care practices did not reduce the incidence of BPD. A multifactorial benchmarking approach to neonatal respiratory care and ventilator management may help minimize lung injury from pulmonary complications such as volutrauma, but more data are needed to identify potential better care practices.

Few clinical trials have investigated pulmonary and long-term outcomes using low versus high tidal volume ventilation in preterm infants. Current evidence from experimental studies suggests that volutrauma from high tidal volume ventilation or from inadequate maintenance of the FRC with PEEP is injurious to the preterm lung and should be avoided [5,7–10]. Although the

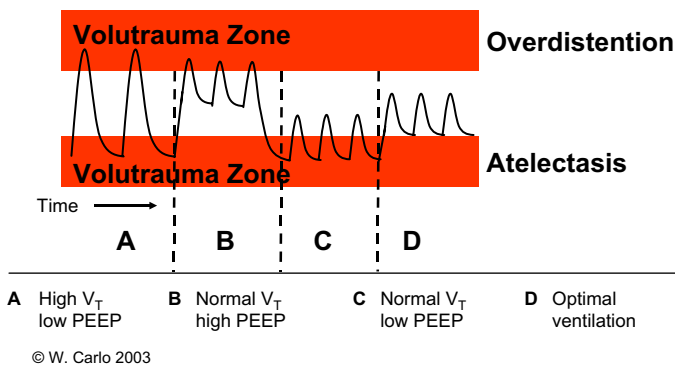


Fig. 1. Which volumes cause lung injury? (A) A large tidal volume ( $V_T$ ) with inadequate PEEP may cause lung injury due to overdistention and atelectasis. (B) A normal tidal volume with high PEEP may also cause volutrauma. (A and C) A low PEEP may cause lung injury secondary to collapse and reopening of alveoli. (D) Optimal ventilation with a tidal volume and PEEP that avoids both injury zones. (Courtesy of W. Carlo, MD, Birmingham, AL.)

pathogenesis of BPD is multifactorial, volutrauma caused by mechanical ventilation may be an important factor to minimize with ventilator strategies that avoid overdistention and atelectasis. The precise tidal volume required to minimize volutrauma is not known; however, efforts to limit tidal volume may be a beneficial practice in the neonatal intensive care unit [32].

### **Air leak syndromes**

Complications of mechanical ventilation related to volutrauma include various types of extrapulmonary air leakage, such as pneumothorax and pulmonary interstitial emphysema. Air leak syndromes are important causes of morbidity and mortality in neonates [33,34]. In fact, Powers and colleagues reported that infants weighing less than 1500 g and diagnosed with pneumothorax during the first 24 hours of life were 13 times more likely to die or have BPD [34]. Pneumothorax is associated with respiratory distress syndrome, meconium aspiration syndrome, and pulmonary hypoplasia but can also occur in non-ventilated neonates. The incidence of pneumothorax in infants weighing less than 1500 g during 1991 to 1999 in the Vermont Oxford Neonatal Network Database ranged from 8.6% in 1991 to 5.1% in 1996 [35]. Recent retrospective data from the National Institute of Child Health and Development (NICHD) Neonatal Research Network suggest that pneumothorax is more common in extremely low birth weight infants, but this is confounded by the higher need for mechanical ventilation and severity of lung disease in these infants [1]. The incidence of pneumothorax in the NICHD Neonatal Research Network from 1990 to 2002 was 13% in infants weighing 501 to 750 g and 2% in infants weighing 1251 to 1500 g [1].

Clinical data identifying risk factors associated with pneumothorax can be obtained from randomized controlled trials comparing different ventilator modes or strategies for preterm infants. Analysis of three randomized controlled trials comparing high rate positive-pressure ventilation (rate >60 breaths per minute) with conventional mechanical ventilation in neonates showed that using rates greater than 60 breaths per minute was associated with a decreased risk of air leakage (RR, 0.69; CI, 0.51–0.93; NNT, 11) [36]. Another analysis of four randomized controlled trials evaluating long versus short inspiratory times using conventional mechanical ventilation in intubated infants with respiratory distress syndrome showed that a long inspiratory time (>0.5 seconds) was associated with an increased risk of pneumothorax (36% versus 24%; RR, 1.56; CI, 1.24–1.97; NNH, 8) [37]. Elective high-frequency oscillatory ventilation has also been evaluated in multiple randomized controlled trials to determine whether this therapy is beneficial in preterm infants. An analysis of 16 trials comparing elective high-frequency ventilation with conventional ventilation showed a significant increase in air leakage in the high-frequency group (29% versus 24%; RR, 1.23; CI, 1.06–1.44; NNH, 28) [38]. This association was

consistent in the fixed effect model and random effects model in this analysis. One randomized controlled trial investigated the role of high-frequency oscillatory ventilation in preventing new air leaks in high-risk infants versus conventional mechanical ventilation [39]. This study reported a significant decrease in new air leaks (42% versus 63%;  $P < .005$ ; NNT, 5), although the incidence of air leaks in the control group with conventional mechanical ventilation was high (63%), and the majority of patients were not treated with surfactant [39]. High-frequency jet ventilation has also been studied as a means to decrease chronic lung disease. Two trials demonstrated a nonsignificant decrease in the risk for air leaks in favor of elective high-frequency jet ventilation (39% versus 32%; RR, 0.82; CI, 0.55–1.22) [40].

Retrospective data can also help define care practices or risk factors associated with extrapulmonary air leakage. In a case-control study of very low birth weight infants from 1997 to 2002, pneumothorax developed in 10.9% of infants. Multivariate analysis showed that maximal peak inspiratory pressures during the 24 hours before diagnosis (odds ratio [OR], 2.84; CI, 1.6–5.4) and the number of suction procedures during the 8 hours before diagnosis (OR, 1.56; CI 1.09–2.23) were both independently associated with pneumothorax [41]. Other studies that included both ventilated preterm and term infants in the analysis identified low birth weight (OR, 19.3; CI 2.3–160.2), the administration of bag and mask ventilation (OR, 29; CI 3.6–233.5), endotracheal tube displacement (64% in infants with air leaks versus 18.5% in controls,  $P < .05$ ), and an increase in clinical interventions including suction procedures, chest radiography, reintubation, and chest compressions as variables associated with pneumothorax [42–44]. Watkinson and Tiron [42] analyzed data from 606 ventilated neonates and reported that overventilation (defined as a  $\text{PaCO}_2 < 30$  mm Hg) was not associated with pneumothorax. Regardless of whether associated variables are causative or merely a result of an undiagnosed air leak, identifying those infants at highest risk is important and may improve long-term outcome if subsequent air leak is prevented.

Pulmonary interstitial emphysema is another form of air leak that is associated with increases in mortality and morbidity in preterm infants [34,45]. It is characterized by leakage of gas from the alveoli that becomes trapped inside the interstitial spaces of the lung. Pulmonary interstitial emphysema is diagnosed based on the presence of coarse, non-branching, radiolucencies on chest radiography that project toward the periphery of the lung in a disorganized fashion [46]. This appearance must not be confused with an air bronchogram, a classic radiographic sign of respiratory distress syndrome. Air bronchograms show long, smooth, branching radiolucencies that follow normal anatomic distributions similar to the bronchial tree [46]. The incidence of pulmonary interstitial emphysema in the randomized controlled trials evaluating prophylactic versus rescue surfactant therapy was about 3% to 5% [47]. In one recent retrospective study, risk factors for pulmonary

interstitial emphysema included a higher maximum inspired oxygen concentration and higher mean airway pressures when compared with that in control subjects, and these factors were associated with an increased risk of death in infants weighing less than 1000 g [34].

### **Tracheal injury and endotracheal tube complications**

Subglottic stenosis is a complication that occurs in approximately 1% to 2% of intubated neonates [48,49]. In one study, the incidence of subglottic stenosis was greater if the ratio of the external diameter of the endotracheal tube divided by the gestational age of the infant in weeks was more than 0.1 [50]. A recent case series described subglottic cysts as an abnormality often seen in conjunction with subglottic stenosis. Subglottic cysts are a recognized complication of intubation in preterm infants and may develop many months after extubation [51]. Tracheal perforation is a rare complication of endotracheal intubation. The data identifying risk factors and the incidence of tracheal perforation are limited to case reports. The mortality associated with this complication is high (75% in one study) and is likely due to vascular, cardiac, and respiratory compromise secondary to air leak [52]. Palatal deformities such as palatal grooves, asymmetry, and a high-arched palate also occur after long-term mechanical ventilation [53]. Despite subsequent palatal growth and remodeling after extubation, abnormalities can persist for many years [53,54]. Tracheal trauma and endotracheal tube complications may be minimized by using smaller endotracheal tubes, by minimizing reintubation attempts, and by aggressively weaning preterm infants off of mechanical ventilator support.

### **Summary**

Mechanical ventilation is necessary and life saving in many neonates. Most complications are inherent to this intervention and cannot be confused with iatrogenic errors in judgment or care practices by clinicians. Clinical data suggest that complications such as volutrauma and air leak syndromes can negatively affect long-term pulmonary and non-pulmonary outcomes. One specific intervention or strategy is unlikely to decrease complications of mechanical ventilation. Careful attention to many aspects of neonatal care, such as delivery room resuscitation, ventilatory support, and routine care practices, is needed to decrease pulmonary complications of mechanical ventilation. Clinical research is needed to improve mechanical ventilator strategies to reduce pulmonary complications and improve long-term outcomes.

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