Mechanical Ventilation and Bronchopulmonary Dysplasia

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INTRODUCTION

MV is undoubtedly one of the key advances in neonatal care. Even in this era of noninvasive respiratory support, MV remains a mainstay of therapy in the extremely preterm population. Data from the Neonatal Research Network show that 89% of extremely low birth weight (ELBW) infants were treated with MV during the first day of life.1 Among survivors, almost 95% were invasively ventilated at some point during their hospital stay. In the Surfactant, Positive Pressure, and Oxygenation Randomized Trial...
(SUPPORT), 83% of the ELBW infants initially assigned to noninvasive support required endotracheal intubation and MV at some point.\(^2\) The CPAP or Intubation trial enrolled infants between 25 and 28 weeks of gestational age only if they had adequate respiratory effort at birth, but even in this group, 46% of the infants assigned to noninvasive support required endotracheal intubation and MV.\(^3\)

Although often lifesaving, MV has many untoward effects. Although this article focuses on the adverse effects of MV on the lungs, protracted MV is also strongly associated with adverse neurologic outcomes.\(^1\) In preterm baboons, 5 days of elective MV resulted in greater degree of brain injury compared with ventilation for 1 day.\(^4\) Cohort data from the Neonatal Research Network show that each week of additional MV is associated with a significant increase in the likelihood of neurodevelopmental impairment.\(^1\) Additionally, the endotracheal tube acts as a foreign body, quickly becoming colonized and acting as a portal of entry for pathogens, increasing the risk of ventilator-associated pneumonia and late-onset sepsis.\(^5\) For these reasons, avoidance of MV in favor of noninvasive respiratory support is seen as perhaps the most important step in preventing neonatal morbidity.

BPD was originally described by Northway and colleagues\(^6\) more than 45 years ago in large moderately and late preterm babies who survived MV. Thus, BPD has always been associated with the use of MV, but many other factors play an important role in the pathogenesis of BPD (Fig. 1). The classic, so-called old BPD occurred as a consequence of unsophisticated ventilatory support in infants with surfactant deficiency and was characterized by marked fibrosis, increased interstitium, marked airway alterations, and reactive airway disease.\(^7\) New BPD, characterized mostly by simplified lung architecture as a consequence of an arrest in pulmonary development, occurs in infants who are far more immature, received surfactant replacement therapy, and are likely to have been treated with antenatal steroids.\(^8\) Nevertheless, there is considerable overlap between the 2 forms, and old BPD has by no means disappeared from neonatal ICUs.

**Fig. 1.** The ultimate neonatal pulmonary outcome is affected by a variety of factors, beginning in utero. The immediate postnatal period is one of the most critical times, as indicated by the 3 exclamation marks. Adverse influences are listed in the upper part of the panel and mitigating factors in the lower portion. The multifactorial pathogenesis of BPD explains why no single therapeutic intervention is likely to have a large impact on its incidence. PDA, patent ductus arteriosus.
WHAT IS VENTILATOR-ASSOCIATED LUNG INJURY?

The huge number of articles published since the first description of ventilator-associated lung injury (VALI) highlights its importance and the incomplete understanding of this complex subject. The central role of MV and oxygen exposure in VALI and subsequent development of BPD have been recognized since the early days of neonatal medicine. In 1975, Alistair Philip described the etiology of BPD as “oxygen plus pressure plus time.”9 Although fundamentally this concept still holds, it has since been refined by recognizing that excessive volume, rather than pressure, is the most important factor that contributes to VALI, a concept that has been slow to gain complete acceptance, despite strong evidence in its favor.

Many terms have been coined to describe the mechanism of lung injury in VALI. Barotrauma refers to damage caused by pressure. The conviction that pressure is the key determinant of lung injury has fostered a deeply ingrained “barophobia,” causing clinicians to focus on limiting inflation pressure, sometimes to the point of precluding adequate ventilation. There is convincing evidence, however, that high pressure by itself, without correspondingly high volume, does not result in lung injury. Rather, injury related to high inflation pressure is mediated through the tissue stretch resulting from excessive $V_T$. Dreyfuss and colleagues10 demonstrated more than 20 years ago that severe acute lung injury occurred in small animals ventilated with large $V_T$, regardless of whether that volume was generated by positive or negative inflation pressure. In contrast, animals exposed to the same high inflation pressure but with an elastic bandage over the chest and abdomen to limit $V_T$ delivery experienced much less acute lung damage. Hernandez and colleagues11 similarly showed that animals exposed to pressure as high as 45 cm H2O did not show evidence of acute lung injury when their chest and abdomen were enclosed in a plaster cast. Volutrauma refers to injury caused by overdistention and excessive stretch of tissues, which leads to disruption of alveolar and small airway epithelium, resulting in acute edema; outpouring of proteinaceous exudate; and release of proteases, cytokines, and chemokines, which in turn leads to activation of macrophages and invasion of activated neutrophils. Collectively, this complex process is referred to as biotrauma. Another important concept is that of atelectrauma, or lung damage caused by tidal ventilation in the presence of atelectasis.12 Atelectrauma exerts lung injury via several mechanisms. The portion of the lungs that remains atelectatic has increased surfactant turnover and high critical opening pressure. There are shear forces at the boundary between aerated and atelectatic parts of the lung, leading to structural damage. Ventilation of injured lungs using inadequate end-expiratory pressure results in repeated alveolar collapse and expansion (RACE), which rapidly leads to lung injury. Perhaps most importantly, when a large portion of the lungs is atelectatic, whatever $V_T$ is entering the lungs preferentially enters the aerated portion of the lung, which is more compliant than the atelectatic lung with its high critical opening pressure (Laplace’s law). This maldistribution of $V_T$ leads to overdistention of that portion of the lungs and regional volutrauma. Thus, it becomes clear that the risk of lung damage from MV is multifactorial and cannot be linked to any single variable.

The key concept regarding VALI is that the initiating event is biophysical injury from excessive tissue stretch, which in turn leads to biotrauma and initiates the complex cascade of lung injury and repair (Fig. 2). It is important to recognize, however, that VALI is only one of several mechanisms that may ultimately lead to BPD. Although infants with severe neonatal lung disease are more likely to develop severe BPD, it is well known that BPD also afflicts infants who require only minimal respiratory support in the first weeks of life.13 Exposure to intrauterine inflammation is known to result in
accelerated lung maturation in the short term but ultimately triggers biotrauma directly, initiating the cascade of injury and repair that leads to the development of moderate or severe BPD.\textsuperscript{14–16}

\textbf{MITIGATING VENTILATOR-ASSOCIATED LUNG INJURY}

Because some degree of impairment of normal pulmonary development is probably inevitable when an extremely preterm fetus is suddenly thrust into a hyperoxic (by fetal standards) environment and must initiate air breathing with lungs that are incompletely developed, it is unlikely that advances in neonatal care, including avoidance of MV, can completely prevent impairment of lung structure and function. Optimal respiratory and general supportive care, however, can minimize the overlay of ventilator-induced lung injury and facilitate lung growth and repair.

\textbf{IMPORTANCE OF THE GOLDEN FIRST HOUR}

The time immediately after birth when air breathing is initiated in a structurally immature surfactant deficient lung has been recognized as a critical time that may rapidly and irrevocably initiate the process of lung injury and repair. To achieve a successful transition to extraterrestrial life, newborn infants must rapidly aerate their lungs, clear lung fluid from the air spaces, and maintain a functional residual capacity (FRC), ultimately facilitating a dramatic increase in pulmonary blood flow. A healthy full-term infant is able to achieve this remarkable transition quickly and effectively,\textsuperscript{17} but this is often not the case in very preterm infants. Preterm infants may be unable to generate the critical opening pressure to achieve adequate lung aeration because of their limited muscle strength, excessively compliant chest wall, limited surfactant...
pool, and incomplete lung development. Additionally, their excessively compliant chest wall fails to sustain any lung aeration that may have been achieved spontaneously or with positive pressure ventilation. They may also be unable to generate sufficient negative intrathoracic pressure to effectively move lung fluid from the air spaces to the interstitium, lymphatics and veins. Consequently, subsequent tidal breathing, whether spontaneous or generated by positive pressure ventilation, takes place in lungs that are still partially fluid filled and partially atelectatic. This situation leads to maldistribution of the VT to a fraction of the preterm lung, which leads to volutrauma even when the VT is in a safe physiologic range.

**POSITIVE END-EXPIRATORY PRESSURE IN THE DELIVERY ROOM**

The use of positive end-expiratory pressure (PEEP)/continuous positive airway pressure (CPAP) during initial stabilization of preterm infants mitigates the effect of excessively compliant chest wall and surfactant deficiency by stabilizing alveoli during the expiratory phase and has been shown to help establish FRC. Siew and colleagues demonstrated the beneficial effects of PEEP by using phase-contrast radiography in preterm rabbits, showing that virtually no FRC was established after several minutes when PPV was delivered without PEEP. In contrast, FRC was rapidly established when 5 cm H₂O of PEEP was applied.

Both the Neonatal Resuscitation Program and International Liaison Committee on Resuscitation guidelines state, “PEEP is likely to be beneficial during initial stabilization of apneic preterm infants and should be used if suitable equipment is available.” The physiologic rationale and experimental evidence from preclinical studies is so persuasive that this practice has become the standard of care in much of the developed world. Provision of end-expiratory pressure alone, however, may not entirely address the inadequate muscle strength of the preterm infant or help clear lung fluid sufficiently rapidly to avoid regional volutrauma and atelectrauma, which can occur in minutes.

**SUSTAINED INFLATION**

Because liquid has much greater viscosity than air, resistance to moving liquid through small airways is orders of magnitude higher than that for air, making the time constants required to clear fluid from the airways much longer. Recognition of these factors supports the concept that a prolonged (sustained) inflation applied soon after birth should be more effective than short inflations in clearing lung fluid in the first minutes of life. Theoretically, ensuring effective lung recruitment with even distribution of VT immediately after birth should reduce VALI.

Despite a substantial body of evidence that supports the theoretic advantages of sustained inflation in extremely preterm infants, the evidence that this measure can substantially reduce VALI remains inconclusive. Additionally, the most appropriate way to deliver an sustained inflation is unclear. Therefore, the procedure cannot currently be recommended outside of well-controlled clinical trials.

**HYPEROXIC INJURY**

Preterm infants have immature antioxidant defenses, making them more susceptible to oxidative stress from relative or absolute hyperoxia. Several studies of early respiratory management in the delivery room evaluated whether reducing oxygen exposure results in improved respiratory outcomes. A single-center randomized clinical trial (RCT) in infants born at 24 to 28 weeks’ gestation demonstrated less oxidative stress,
lower proinflammatory cytokine levels, and a lower incidence of BPD (15.4% vs 31.7%; \(P<.05\)) in infants resuscitated with a fraction of inspired oxygen (Fi\(O_2\)) of 0.30, compared with 0.90, and then titrated to achieve target oxygen saturation as measured by pulse oximetry (Sp\(O_2\)) levels.\(^{25}\) Kapadia and colleagues\(^{26}\) compared rates of BPD in infants with gestational age of 24 to 34 weeks randomized to receive either 21% or 100% oxygen, which was then titrated to achieve the Neonatal Resuscitation Program recommended Sp\(O_2\) target of 85% to 94%. BPD rates were lower in the infants initially resuscitated with room air (7% vs 25%; \(P<.04\)). In contrast, the Room-Air Versus Oxygen Administration for Resuscitation of Preterm Infants study found no difference in BPD rates between preterm infants treated with room air, despite randomizing greater than 1000 infants.\(^{27}\) This may be in part because initiating resuscitation with room air in very preterm infants often resulted in inadequate response and a rapid increase to 100% oxygen. Therefore, the best approach probably is to initiate support with Fi\(O_2\) of 0.30 and avoid an excessively rapid increase, recognizing that several minutes are needed for Sp\(O_2\) to reach 90%.

Although avoidance of oxidative stress is desirable, it has turned out to be a more complicated issue than was initially thought. A series of RCTs that compared lower versus higher Sp\(O_2\) targets (SUPPORT, Canadian Oxygen Trial, and Benefits of Oxygen Saturation Targeting II) failed to show a significant reduction in BPD and, unexpectedly showed a higher mortality rate in the low Sp\(O_2\) target group.\(^{28-30}\) A recent meta-analysis of those trials confirmed a significant increase in mortality and necrotizing enterocolitis and a decrease in the rate of severe retinopathy of prematurity in low compared with high oxygen saturation target infants.\(^{31}\) No differences in physiologic BPD, brain injury, or patent ductus arteriosus were noted between the groups. Based on these results, definitive recommendations regarding saturation targets during continued care of preterm infants are difficult to make. Nevertheless, it seems prudent to target functional Sp\(O_2\) at 90% to 95% in infants with gestational age less than 28 weeks until 36 weeks’ postmenstrual age. Most NICUs have revised their saturation targets to be close to this higher range, with alarm limits slightly wider, or approximately 88% to 97%. Anecdotally, this change has again increased the risk of significant retinopathy of prematurity.

**NONINVASIVE RESPIRATORY SUPPORT**

There is little doubt that avoiding MV reduces iatrogenic lung injury superimposed on the inevitable arrest of pulmonary development. Although earlier cohort comparisons of CPAP or MV suggested a large reduction in the risk of BPD,\(^{32}\) a series of more recent RCTs showed a much more modest benefit of avoiding MV. A meta-analysis of 4 recent RCTs\(^{2,3,33,34}\), that enrolled nearly 2800 preterm infants showed that BPD rates were not significantly reduced by the use of different types of nasal CPAP (32.4% vs 34.0%).\(^{35}\) A modest benefit with the use of CPAP, however, was demonstrated for the combined outcome of death or BPD with a reduction of approximately 10% (relative risk [RR] 0.91; 95% CI, 0.84–0.99); with 1 additional infant surviving to 36 weeks without BPD for every 25 babies treated with nasal CPAP in the delivery room rather than being intubated. This latter finding is more important because death and BPD are competing outcomes and, therefore, should be evaluated in combination. There was also a significant decrease in the duration of MV and a nonsignificant trend toward shorter duration of oxygen exposure with early CPAP in the 2 largest trials.\(^{2,3}\)

Nasal intermittent positive pressure ventilation may be able to augment an immature infant’s inadequate respiratory effort without the complications associated with
endotracheal intubation.\textsuperscript{36} In theory, this approach offers the benefit of avoiding the use of an endotracheal tube, thus reducing the incidence of VALI and ventilator-associated pneumonia and avoiding the contribution of postnatal inflammatory response to the development of BPD.\textsuperscript{37} Although a meta-analysis of several small single center studies concluded that nasal intermittent positive pressure ventilation was superior to CPAP,\textsuperscript{38} a recent large pragmatic multinational RCT in infants with birth weight less than 1000 g failed to substantiate these benefits, showing no reduction in BPD, mortality, or the combined outcome.\textsuperscript{39}

LESS INVASIVE SURFACTANT ADMINISTRATION

Traditionally, the avoidance of intubation and MV and the use of noninvasive respiratory support have meant a trade-off between the presumed benefits of this approach and the well documented benefits of surfactant replacement therapy. Early surfactant trials suggested that prophylactic surfactant administration was superior to rescue use\textsuperscript{40}; thus, some clinicians still intubate very premature infants in the delivery room for the sole purpose of administering surfactant. It must be recognized, however, that most surfactant RCTs were done many years ago in a different population of infants and with a less sophisticated approach to delivery room stabilization. A recent meta-analysis comparing prophylactic versus selective surfactant use in the modern era concluded that a prophylactic approach was associated with increased risk of BPD (RR 1.13; 95\% CI, 1.00–1.28).\textsuperscript{41}

In recent years, a variety of approaches have been proposed to preserve the benefits of avoiding delivery room intubation while still providing surfactant therapy. These include the intubation-surfactant-extubation approach (INSURE) and several methods of administering surfactant through small catheters under direct laryngoscopic visualization.\textsuperscript{33,42–45} Although these techniques avoid endotracheal intubation, they still require direct laryngoscopy, typically without sedation and thus are still invasive. Administration of nebulized surfactant during CPAP is a potentially attractive approach that is currently under investigation.\textsuperscript{46}

LUNG-PROTECTIVE STRATEGIES OF MECHANICAL VENTILATION

There are numerous modes and modalities of MV and little high-quality evidence to guide clinicians in selecting the optimal method. A detailed discussion of these techniques is beyond the scope of this article; interested readers are referred to several recent reviews of the topic.\textsuperscript{47,48} Key principles of lung-protective strategies, however, are outlined.

\textit{Volume-targeted Ventilation}

Pressure-controlled ventilation (PCV) became the standard mode of ventilation in neonates because early attempts at volume-controlled ventilation proved ineffective in small preterm infants using equipment available at the time. PCV remains the accepted mode of ventilation in neonatal ICUs because of its simplicity, ability to ventilate despite a large endotracheal tube leak, and improved intrapulmonary gas distribution due to the decelerating gas flow pattern.\textsuperscript{49,50} Perhaps most importantly, clinicians continue to hold onto the belief that directly controlling peak inflation pressure is important. The danger of using PCV is that $V_T$ varies with changes in lung compliance. Rapid improvement in compliance may occur rapidly in the immediate postnatal period as a result of resorption of lung fluid, recruitment of optimal lung volume, and surfactant replacement therapy, leading to hyperventilation and volutrauma from excessively large $V_T$. Insufficient $V_T$ may develop because of decreasing lung
compliance, increasing airway resistance, airway obstruction, air-trapping, and/or decreased spontaneous respiratory effort. Inadequate VT leads to hypercapnia, tachypnea, increased work of breathing and oxygen consumption, agitation, fatigue, atelectasis/atelectrauma, and possibly increased risk of intraventricular hemorrhage (IVH) and thus should also be avoided. Low VT also leads to inefficient gas exchange due to an increased dead space:VT ratio. These factors suggest that tight control of VT delivery during MV is highly desirable and are the reason volume-controlled ventilation remains the standard of care in adult and pediatric respiratory support.

There are many ways to regulate VT delivery during MV. Although there are important differences in how volume targeting is performed, it is likely that the primary benefit of volume-targeted ventilation (VTV) rests in the ability to regulate VT, regardless of how that goal is achieved. When VT is the primary control variable, inflation pressure decreases as lung compliance and patient inspiratory effort improve. This process results in real-time weaning of pressure, in contrast to intermittent manual lowering of pressure in response to blood gas measurement, avoiding volutrauma, hypocapnia, and shortening the duration of MV. Volume guarantee, introduced in the 1990s as an option in the Babylog ventilator (Draeger Medical, Telford, Pennsylvania), is the most thoroughly studied form of VTV and the basic control algorithm is increasingly adopted by other ventilator manufacturers.48 Among the benefits documented in 2 recent meta-analyses that encompassed several different modalities of VTV are significant reduction in the combined outcome of death or BPD, the risk of pneumothorax, shorter duration of MV, and lower rate of severe IVH and periventricular leukomalacia (Table 1).51,52 Although encouraging, these meta-analyses cannot provide definitive evidence of the superiority of VTV, because the clinical trials in these analyses were small and used different devices, and some key outcomes reported in the meta-analysis were not prospectively defined. In some studies, other variables besides volume versus pressure targeting also differed. All the included studies focused on short-term physiologic outcomes rather than BPD. Only 1 study provided some long-term pulmonary and developmental outcomes, but this was based only on a parental questionnaire. Nonetheless, this is more evidence than currently available for any other approach to MV.

Table 1
Summary of major outcomes assessed in the meta-analysis of 11 randomized clinical trials of volume-targeted versus pressure-limited ventilation

<table>
<thead>
<tr>
<th>Outcome</th>
<th>No. of Studies</th>
<th>No. of Subjects</th>
<th>RR (95% CI) or Mean Difference (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mortality</td>
<td>11</td>
<td>767</td>
<td>0.73 (0.51–1.05)</td>
</tr>
<tr>
<td>Any IVH</td>
<td>11</td>
<td>759</td>
<td>0.65 (0.42–0.99)*</td>
</tr>
<tr>
<td>Grade 3–4 IVH</td>
<td>11</td>
<td>707</td>
<td>0.55 (0.39–0.79)*</td>
</tr>
<tr>
<td>BPD at 36 wk</td>
<td>9</td>
<td>596</td>
<td>0.61 (0.46–0.82)*</td>
</tr>
<tr>
<td>Cystic PVL</td>
<td>7</td>
<td>531</td>
<td>0.33 (0.15–0.72)*</td>
</tr>
<tr>
<td>Pneumothorax</td>
<td>8</td>
<td>595</td>
<td>0.46 (0.25–0.86)*</td>
</tr>
<tr>
<td>Failure of assigned mode</td>
<td>4</td>
<td>405</td>
<td>0.64 (0.43–0.94)*</td>
</tr>
<tr>
<td>Any hypocapnia</td>
<td>2</td>
<td>58</td>
<td>0.56 (0.33–0.96)*</td>
</tr>
<tr>
<td>Duration of supplemental O₂ (d)</td>
<td>2</td>
<td>133</td>
<td>−1.68 (−2.5 to −0.88)*</td>
</tr>
</tbody>
</table>

*P<.05.

Importance of the Open Lung Strategy

The benefits of VTV cannot be fully realized unless the VT is evenly distributed into an open lung, avoiding atelectrauma. Adequate PEEP is widely recognized as a means of mitigating lung injury. The admonition of Burkhard Lachman more than 20 years ago to “OPEN THE LUNG AND KEEP IT OPEN!”\textsuperscript{53} has been ignored by many during conventional MV despite a sound physiologic basis and strong experimental evidence in its favor. Caruso and colleagues\textsuperscript{54} demonstrated that when using PEEP of 0 cm H\textsubscript{2}O, lung injury in rats was not reduced by the use of low, compared with high, VT. Tsuchida and colleagues\textsuperscript{55} showed that in the presence of atelectasis, the nondependent (ie, aerated) lung was the most injured area. This is because, as seen in Fig. 3, if partially atelectatic lungs are ventilated, the VT entering only the open alveoli inevitably leads to overexpansion of this relatively healthy portion of the lung with subsequent volutrauma/biotrauma even when the VT is in the normal range. Additionally, atelectasis leads to exudation of protein-rich fluid with increased surfactant inactivation and release of inflammatory mediators. Shear forces and uneven stress in areas where atelectasis and overinflation coexist add to the damage. Thus, the open lung concept (OLC),\textsuperscript{56} which ensures that the VT is distributed evenly throughout the lungs, is a fundamental component of any lung-protective ventilation strategy.

In practical terms, the open lung is achieved by applying adequate PEEP.\textsuperscript{57} One of the most important obstacles to optimizing the way conventional MV is practiced is the persistence of “PEEP-o-phobia”, the fear of using adequate levels of end-expiratory pressure. This may be in part because the OLC has not been extensively evaluated in the clinical setting.\textsuperscript{58} There is no single optimal PEEP level. The level of end-expiratory pressure must be tailored to the degree of lung injury (ie, lung compliance). For infants with healthy lungs and thus normal lung compliance, PEEP of 3 cm H\textsubscript{2}O may be appropriate; PEEP of 6 cm H\textsubscript{2}O may well lead to overexpansion of normal lungs with circulatory impairment and elevated cerebral venous pressure. On the other hand, atelectatic, poorly compliant lungs may transiently require PEEP levels as high as 8 to 10 cm H\textsubscript{2}O or more to achieve adequate alveolar recruitment and optimize ventilation/perfusion ratio. Because infants with healthy lungs are seldom ventilated, PEEP of less than 5 cm H\textsubscript{2}O should be uncommon.

High-frequency Ventilation

In contrast to conventional ventilation, the importance of optimizing lung inflation has been recognized since its early days by users of HFV, where the optimal lung volume strategy has become standard practice and is widely understood to be critical to its success.\textsuperscript{59,60} HFV includes several modes of ventilation, including high-frequency oscillatory ventilation (HFOV), high-frequency jet ventilation, and high-frequency percussive ventilation, that have been used in neonatology since the 1980s. The benefit of HFV is believed to be a function of reduced pressure and volume swings transmitted to the periphery of the lungs. For optimal effectiveness, the lungs need to be recruited and then stabilized with the lowest possible mean airway pressure. Several early animal studies demonstrated the short-term benefits of HFOV with an optimal lung volume strategy.\textsuperscript{51} More recently, Yoder and colleagues\textsuperscript{62} compared the effect of more prolonged HFOV and low VT positive pressure ventilation using the immature baboon model for BPD, demonstrating that prolonged use of HFOV significantly improved early lung function with sustained improvement in pulmonary mechanics up to 28 days of life and less pulmonary inflammation in the recovery phase of their RDS. Several RCTs of HFOV and high-frequency jet ventilation showed improved outcomes, including reduction in BPD and/or duration of MV,\textsuperscript{55-67} whereas
other trials showed no improvement.\textsuperscript{68–72} Interpretation of RCTs of HFV is made more challenging by the fact that most were done many years ago in patient populations that differ markedly from infants treated today and compared HFV with less sophisticated (more injurious) modes of CMV than those in use today.\textsuperscript{58} The only HFV trials that showed benefit were those that used the optimal lung volume strategy. Thus, there were 2 key differences between study and control strategies: higher frequency and use of the OLC in the intervention arm and lower frequency with lower distending pressure. The latter may be the more important difference. HFOV used without the open lung strategy was relatively ineffective in reducing lung injury\textsuperscript{73} and several animal studies have indicated that conventional ventilation, when used with the OLC, can achieve similar degrees of lung protection as HFOV, suggesting that optimizing lung volume, rather than frequency, is the key factor.\textsuperscript{74–76} Clinical application of the OLC with conventional ventilation, however, may not be an easy task and has not been extensively evaluated in clinical trials.\textsuperscript{77}

![Fig. 3. Tidal ventilation in the presence of extensive atelectasis leads to lung injury via multiple mechanisms. Although lung pathology in an infant with respiratory distress syndrome is commonly thought of as homogeneous, based on an anteroposterior radiograph (right lower corner), the lung is heterogeneous due to gravitational effects, as seen on the CT scan (left lower corner). This results in 2 populations of alveoli with very different critical opening pressures, illustrated in cartoon form in the upper panel. From Laplace’s law, it is known that the already aerated alveoli (white arrow) have a lower critical opening pressure; therefore, gas enters the already aerated portion of the lung preferentially, causing overexpansion with each inflation (black arrow in lower left corner). This results in volutrauma even with a normal $V_T$, whereas the atelectatic portion is also damaged by outpouring of protein-rich edema fluid that inactivates surfactant. The ventilated but unstable alveoli undergo repeated alveolar collapse and expansion (RACE) and shear forces at the boundary between aerated and un-aerated lung further add to damage. Adequate lung volume recruitment and keeping the lung open throughout the respiratory cycle achieve even distribution of $V_T$ and mitigate all the factors involved in VALI.](image-url)
With the inclusion of more recent clinical trials that reflect advances in conventional ventilation strategies, the protective effect of HFOV is less clear than earlier studies suggested. A recent meta-analysis of individual patient data from several RCTs did not demonstrate any superiority of HFOV over conventional ventilatory strategies. The analysis also did not support the selection of a specific subgroup of preterm infants who might uniquely benefit from HFOV on the basis of gestational age, birth weight for gestation, initial lung disease severity, or exposure to antenatal corticosteroids. The long-term pulmonary follow-up from the United Kingdom Oscillation Study, however, which demonstrated less severe long-term pulmonary abnormalities in the HFOV group, suggests that the dichotomous outcome of BPD versus No BPD is too blunt a tool to assess possible benefits of lung-protective ventilation strategies.

**PUTTING IT ALL TOGETHER**

Based on the key concepts discussed previously, certain general guidelines for the use of MV can be formulated. The overarching goal is to support adequate gas exchange with the minimum of adverse effects on the infant’s lungs, hemodynamics, and brain. Longer duration of ventilation is associated with increased likelihood of chronic lung disease, late-onset sepsis, and neurodevelopmental impairment; therefore, successful extubation at the earliest possible time is desirable. Ventilation strategies should be individualized to address each patient’s specific condition, but optimizing lung volume and preventing atelectasis, which improve lung compliance, minimize oxygen requirement, avoid surfactant inactivation and achieve even VT distribution, remain fundamental imperatives. The second key element of lung-protective strategy is to avoid excessively large VT, which minimizes volutrauma and hypocapnia, 2 potentially preventable elements of lung and brain injury. This is best accomplished by the use of one of the volume-targeted modes available on most widely used ventilators. When high distending and inflation pressures are needed to achieve these goals, HFV is a reasonable option.

Mild permissive hypercapnia and minimal FIO₂ to achieve adequate oxygen saturation are generally considered appropriate, but PCO₂ greater than 60 mm Hg should be avoided in the first 3 days of life due to increased risk of IVH. There is no evidence to support the routine use of sedation and, therefore, infants should be allowed to breathe spontaneously. Routine suctioning should be avoided, because it leads to derecruitment, transient hypoxemia, and perturbation of cerebral hemodynamics. Only when secretions are detected by auscultation or by perturbation of the flow waveform is gentle rapid suctioning without instillation of normal saline indicated.

In the absence of definitive evidence from RCTs, the choice of synchronized intermittent mandatory ventilation (SIMV) or assist/control (A/C) remains a matter of personal preference and practice style. There is little difference between the two in the acute phase of respiratory failure or in a patient who has little or no respiratory effort but becomes more pronounced during weaning, especially in the smallest infants with narrow endotracheal tubes. Prolonged ventilation with low SIMV rates should be avoided in these infants, because of the mechanical inflations it imposes an undesirably high work of breathing. SIMV also results in larger VT compared with A/C, because small preterm infants typically do not generate adequate spontaneous VT resulting in a high dead space:VT ratio. To a significant degree, this problem may be overcome by adding pressure support ventilation (PS) to the spontaneous breaths during SIMV. Although this approach is effective, it adds complexity and does not seem to have any advantage over A/C or PS used alone as long as atelectasis is avoided by using adequate level of PEEP. Additionally, it is important to recognize
that volume targeting is only applied to the SIMV inflations when using SIMV with PS and volume guarantee.

**SUMMARY**

Although even with optimized respiratory care it is likely that some degree of lung injury is inevitable in ELBW infants, the wide variation in the risk-adjusted incidence of BPD among the academic medical centers that comprise the Neonatal Research Network suggests that MV and other clinical practices are potentially modifiable risk factors.\(^{82,83}\) Although the evidence to guide respiratory support strategies remains incomplete, the key concepts outlined in this review are based on the best available evidence and physiologic rationale and may provide an opportunity to minimize adverse respiratory outcomes in ELBW infants requiring respiratory support.

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