Almost as soon as healthcare providers began ventilating neonates with respiratory distress syndrome, the problem of chronic lung disease began. How to manage these children in a way to promote lung growth and disease-free survival has been the question for those involved in the care of these infants since that time.

During the next 40 years the multifactorial nature of the processes that lead to chronic lung injury and bronchopulmonary dysplasia has been uncovered piece by piece. One of the important aspects that has been uncovered during the last four decades is the potentially injurious nature of mechanical ventilation itself.

How to best apply this life-saving therapy such that infants benefit without harm is now the focus of the healthcare team as we approach the care of infants with pulmonary disease.

This review summarizes the history of chronic lung injury in the neonate, looks at the supportive evidence for current clinical management strategies and which ventilation strategies are thought to be protective of the lung.

Abbreviations

- **RDS** - respiratory distress syndrome;
- **BPD** - bronchopulmonary dysplasia;
- **HMD** - hyaline membrane disease;
- **CLD** - chronic lung disease;
- **PEEP** - positive end expiratory pressure;
- **ARDS** - acute respiratory distress syndrome;
- **PaCO₂** - partial pressures of carbon dioxide;
- **RCT** - randomized clinical trial;
- **NCPAP** - nasal continuous positive airway pressure;
- **tcpCO₂** - transcutaneous pressures of carbon dioxide;
- **IVH** - isocapnic voluntary hyperventilation;
- **PIE** - pulmonary interstitial emphysema;
- **ROP** - retinopathy of prematurity.
History of chronic lung injury

The most common cause of neonatal death in the United States during the 1960s was hyaline membrane disease (HMD). Much was unknown about the disease at the time, but the next three decades would see an amazing growth in the understanding of the disease pathophysiology.

Surfactant deficiency and its role in the development of HMD was identified by Avery et al during the end of the 1950s [1]. Neonates suffering from HMD were recognized to have reduced lung compliance and functional residual capacity by Nelson et al soon thereafter [2].

Chu et al identified ventilation-perfusion mismatching and grunting as a mechanism for the infant to maintain recruitment and overcome ventilation-perfusion mismatching in hyaline membrane disease by the end of the 1960s [3].

Assisted ventilation of infants suffering from HMD soon followed. Initial strategies and technologies were crude and poorly met the infant’s needs. Initial experience showed that mechanical ventilation was able to change the course for some of these infants, but the survivors often suffered from chronic lung disease (CLD) [4-6].

Healthcare providers have been searching for methods to avoid the evolution of chronic lung disease associated with prematurity since the disease entity was first recognized and called bronchopulmonary dysplasia (BPD) by Northway et al in 1967 [7].

Despite advances in technology the development of lung injury secondary to the need for mechanical ventilation has continued to be a major problem for the preterm infant. BPD still affects 30-40 % of preterm infants needing mechanical ventilation [8].

BPD is a multifactorial condition related to the immaturity of the preterm infant’s lung and the injurious events that either accompany or follow the infant’s birth. The preterm infant’s lung and thorax are poorly equipped to handle the tidal volume breathing necessary once the infant is born.

The physical disadvantage of the infant’s thorax and the structural and biochemical immaturity of the lung lead to the need for mechanical support for adequate gas exchange.

Maintaining the proper inflation of the lung during the treatment of RDS is crucial in avoiding the atelectasis and trauma induced from the opening of collapsed alveoli. The importance of positive end expiratory pressure (PEEP) and its role in managing the infant with RDS has been known for quite some time [9].

It is now known that proper levels of PEEP are important in avoiding atelectotrauma and protecting the infant from developing BPD [9]. In 1974 Webb and Tierney reported that higher levels of PEEP were protective against the injury caused by higher inflation pressures in animals [10].

Others have since found the same findings in infants. In 1992 Van Mater et al reported their findings after examining the outcomes of infants from three different Harvard-associated nurseries. The authors found that infants exposed to higher levels of PEEP developed BPD less often [10].

Equally important in the evolution of BPD is the overdistention of alveoli that occurs when infants are ventilated at pressures that result in delivered tidal volumes above 4-6 mL/kg.

Volutrauma, as it has become known, is increasingly recognized as something to be avoided in an attempt to decrease the number of infants with BPD. Infants who experienced PaCO₂ levels below the physiologic range have an increased risk of BPD, grade III/IV intraventricular hemorrhage, cystic periventricular leukomalacia and cerebral palsy [11, 12].

Two articles published in 1989 and 1995 retrospectively evaluated the effects of hypocarbia on the outcomes of premature infants and found that it was associated...
with a greater risk of BPD [13, 14]. Wanting to avoid overdistention and hypocarbia and avoiding them are often two separate issues.

The disease processes affecting a newborn are often moving targets and the clinical indicators lag behind the improving lung disease. Currently the best signs that an infant is receiving too much support are evidence of added pressure without continued increase in volume on the pressure-volume loop, and the laboratory evidence of hypocarbia (Fig. 1).

The result of preterm birth, atelectotrauma, volutrauma and the exposure to oxygen is inflammation. Ogden et al in 1984 and Arnon et al in 1993 published evidence that mechanically ventilated infants who developed BPD had persistently elevated levels of neutrophils in bronchial lavage samples [15-17].

Other inflammatory mediators are also elevated in infants that develop BPD, including leukotrienes, platelet-activating factors and fibroblast-activating factors [18].

This inflammatory response starts the cascade that leads to parenchymal injury and remodeling that becomes BPD.

Clinical reasoning for permissive hypercapnea

During the past decade methods of management have changed to include more gentle ventilation, but only recently have results of randomized trials been published evaluating the approach of permissive hypercapnea.

The first experience with permissive hypercapnea as a strategy for managing patients needing assisted ventilation was in the treatment of adult respiratory distress syndrome during the late 1980s and early 1990s.

Studies in adults suffering from acute respiratory distress syndrome (ARDS) reported increased survival and fewer days on the ventilator in patients treated with pressure-limited ventilation to minimize potential barotrauma and allowing hypercapnea [19-21].

The first pediatric experience involved a patient suffering ARDS secondary to burn injuries treated successfully with a strategy involving pressure-limited ventilation and hypercapnea [22].

A subsequent retrospective study supported this approach to ventilation as potentially beneficial for pediatric patients suffering from ARDS secondary to burn injury [23].

The initial experience with permissive hypercapnea in the treatment of newborns came in the management of congenital diaphragmatic hernia. Centers began to move away from managing congenital diaphragmatic hernia with aggressive hyperventilation and alkalosis and employing a strategy involving lower peak inspiratory pressures or high frequency oscillatory ventilation and hypercapnea.

Infants treated in this way had improved outcomes and decreased mortality [24]. During the same period that authors were exploring the clinical application in children and infants, investigators started to examine the effects of elevated partial pressures of carbon dioxide (PaCO₂) in models of lung injury.

Animal data suggests that hypercapnea is protective against multiple types of lung injury including ventilator-induced, endotoxin-induced and ischemia-reperfusion-induced lung injury [25-27].
There is no data to suggest harm from moderately elevated levels of PaCO$_2$.

**Randomized controlled trials**

It was not until the late 1990s, however, that authors published results of randomized studies testing the hypothesis that gentle ventilation would yield improved results as compared to strategies pursuing normal carbon dioxide levels when treating preterm infants with respiratory distress.

Carlo *et al* published the results of a study that included 220 preterm infants ranging in birth weight from 501 to 1000 grams who were all mechanically ventilated at less than 12 hours of life. If the infants were between 751 and 1000 grams, they then had to require more than 30% inspired oxygen and have received surfactant to be included in the study.

Infants were then randomized into two groups. The intervention group was managed with a strategy that included a target PaCO$_2$ of > 52 mmHg, and a target of PaCO$_2$ of < 48 mmHg was maintained in the control group [28].

These infants were part of a multicenter, randomized controlled trial of both the ventilatory strategies and early postnatal corticosteroids. The infants were managed in this regard for ten days. Definition of BPD in this group was oxygen requirement at 36 weeks postmenstrual age.

Mariani *et al* published the results of a study that included 49 newborn infants ranging in birth weight from 601 to 1250 grams. The infants all had RDS and were all mechanically ventilated at less than 24 hours of age.

The intervention group was managed to maintain PaCO$_2$ values between 45 and 55 mmHg and maintain pH values > 7.2. The control group was managed with a strategy that included PaCO$_2$ values from 35 to 45 mmHg and pH values > 7.25.

Infants were managed this way for 96 hours after which infants in the control group were managed simply to maintain pH values above the set criteria, allowing higher PaCO$_2$ values in the control group [29].

Definition of BPD in this group was an oxygen requirement and abnormal x-ray on the 28th day of life.

Table I summarizes the findings of these trials.

Although some of the data imply that there may be both beneficial and harmful effects of permissive hypercapnea, none of the findings reached significance and no conclusions can be drawn from these data.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Mariani <em>et al</em></th>
<th>Carlo <em>et al</em></th>
</tr>
</thead>
<tbody>
<tr>
<td>Death before discharge</td>
<td>1.04</td>
<td>1.06</td>
</tr>
<tr>
<td>BPD at 28 days</td>
<td>0.67</td>
<td>N/A</td>
</tr>
<tr>
<td>CLD at 36 weeks</td>
<td>1.05</td>
<td>N/A</td>
</tr>
<tr>
<td>Death or CLD at 36 weeks*</td>
<td>0.94</td>
<td>0.94</td>
</tr>
<tr>
<td>IVH all grades*</td>
<td>0.82</td>
<td>0.82</td>
</tr>
<tr>
<td>IVH grades III/IV</td>
<td>1.46</td>
<td>0.78</td>
</tr>
<tr>
<td>Periventricular leukomalacia</td>
<td>1.04</td>
<td>1.06</td>
</tr>
<tr>
<td>Air leak</td>
<td>0.52</td>
<td>N/A</td>
</tr>
<tr>
<td>Pneumothorax</td>
<td>N/A</td>
<td>2.29</td>
</tr>
<tr>
<td>PIE</td>
<td>N/A</td>
<td>1.08</td>
</tr>
<tr>
<td>ROP grade 2 or above</td>
<td>1.04</td>
<td>N/A</td>
</tr>
</tbody>
</table>

**Current ventilation strategies**

Although, to date, there is no evidence from randomized clinical trials (RCTs) that in human preterm infants a strategy including permissive hypercapnea leads to benefit, there is evidence in both humans and animals that pursuing normal PaCO$_2$ levels with higher pressure and tidal volume is deleterious.

There is also evidence that several physiological states may actually be benefited by higher partial pressures of
carbon dioxide. Because of these factors, the approach to ventilation has changed over the last decade to be more protective of the lung.

In our opinion, the goal for the premature neonate is to achieve a delivered tidal volume of 4-6 mL/kg delivered with a frequency that is appropriate for an infant, 40-60 breaths per minute.

The goal of this ventilation approach is no longer to have a ‘normal’ blood gas, but rather to achieve a PaCO$_2$ range of 48-55 mmHg and a pH > 7.2. The inspired fraction of oxygen is aggressively decreased to maintain oxygen saturation values above 92 % and PaO$_2$ levels > 60 mmHg.

Mechanical breaths are withdrawn from the infant as he/she contributes to the overall minute ventilation with spontaneous respiration; the ultimate goal being ventilation without assistance.

These goals are accomplished with a combination of newer ventilator technologies and the early use of a therapy that has been around for thirty years now: nasal continuous positive airway pressure (NCPAP).

The set pressure in time-cycled pressure-limited ventilation becomes a derivative of the infant’s disease state and response to therapies. Once the infant has reached sufficiently low support, extubation to NCPAP allows for spontaneous respiration while stabilizing the infant’s thorax and preventing atelectasis.

One of the most important additions to ventilator technology has been the addition of a pneumotachometer into the circuit itself. Not only does the information gathered give important insight into the disease process, but it also allows the care team to carefully deliver physiological tidal volumes.

A collection of the newer ventilators now incorporate the information from the pneumotachometer and a set tidal volume to deliver a consistent volume at the lowest possible pressure. This mode of ventilation has a variety of names depending upon the manufacturer, and the settings are slightly different among the different makers, but the concept is the same.

The patient receives a set volume every breath and the ventilator determines the pressure needed to deliver that breath based upon measurements made during prior delivered breaths. These breaths are delivered along with the patient’s own effort in a synchronized fashion.

The potential benefits are great to the neonate, allowing weaning from the support of the machine as the infant’s lung disease improves. This could be particularly beneficial to the newborn premature infant that has recently received surfactant.

A recent study published by Herrera et al demonstrated the effectiveness of this mode in a population of very-low-birth-weight infants.

In this study the short-term use of volume guarantee led to automatic weaning from mechanical support while maintaining ventilation and oxygenation [30].

Approaching the management of infants with lung disease in this manner is still evolving, and more randomized controlled trials need to be conducted to establish the benefit and safety of this approach.

Ideally, the management strategy for infants with lung disease would combine the above-mentioned approaches and technologies with available continuous monitoring of the infant’s PaCO$_2$ by either end tidal carbon dioxide measurements or transcutaneous measurement of the tc$p$CO$_2$.

In combination with continuous monitoring of the infant’s hemoglobin saturation via pulse oximetry this would allow the care team to be more responsive to the changing nature of the infant with lung disease while facilitating rapid adjustments in the infant’s support.
References


