Pathophysiology of premature lung injury

Introduction
In the premature infant who develops pulmonary disease, current perspectives consider each clinical diagnosis encountered as a separate entity. These familiar diagnoses include respiratory distress syndrome (hyaline membrane disease), pulmonary interstitial emphysema, gross air leak, oxygen toxicity, and chronic lung disease (bronchopulmonary dysplasia).

Exploration of current information on the development of pulmonary injury in the surfactant deficient premature infant will lay the ground work to develop rational treatment strategies for the use of new ventilator devices, such as high frequency oscillatory ventilation.

Sequelae of conventional ventilation
Currently available information allows us to interpret these diseases not as separate illnesses, but as an entire spectrum of complications which stem from the use of tidal volume ventilation in the noncompliant, surfactant deficient lung. The progressive nature of this disease spectrum more appropriately should be labeled as “pulmonary injury sequence.”

The pulmonary injury sequence of prematurity commences with the first tidal volume breaths in the infant who lacks surfactant, whether the breaths are spontaneous or mechanical in origin. Attempting to establish a gas exchange interface at the alveolar level through the use of tidal volume ventilation results in injury to the immature lung. The infant may then manifest a unique response to this injury due to its multi-organ system immaturity.

The continuum of pulmonary injury begins as gaseous tidal volumes are distributed heterogeneously within the surfactant deficient lung. This distribution occurs by way of bronchial paths which have the lowest flow resistance. Those distal gas exchange units which lack surfactant require significant opening pressures. Even if opening pressure is achieved, these units will tend to collapse on deflation. Subsequent breaths attempt to reopen atelectatic areas along these low resistance conducting airways. The result is that most of the tidal volume is increasingly distributed to airways which are more compliant than their associated non-expanded gas exchange units. Airway stretch and dilatation cause cellular membrane distortion and fracture of intercellular tight junctions. This is the start of barotrauma on a microscopic level.

The epithelial injury to the airway results in cytomorphological changes and in the development of proteinaceous edema. The histopathologic findings are those typical of hyaline membrane disease, including hyaline membrane formation, alveolar atelectasis and overexpansion of distal conducting airways. Edema protein may inactivate alveolar surfactant which can further worsen atelectasis. This requires that inspiratory
and mean pressures must increase in order to maintain the same degree of inflation and gas exchange. The increase in distending force can cause airway rupture at the juncture of the distal airway and atelectatic gas exchange unit. This is the region of greatest strain from airway overdistention. Airway rupture can be considered to be the onset of macrobarotrauma. Pulmonary interstitial emphysema results as gas moves through the airway rupture site and dissects into a peribronchiolar interstitium. Gross airleak can ensue if dissecting air is forced into potential intrathoracic and extrathoracic spaces. To maintain effective oxygenation, high levels of ambient oxygen are required to overcome significant diffusion barriers to the pulmonary capillaries. Cytotoxic injury from increased oxygen levels adds to the already present lung injury of both micro- and macrobarotrauma. In combination with continued barotrauma and oxygen injury, the reparative response of the immature lung results in the development of abnormal airway and parenchymal architecture, and corresponding abnormalities in pulmonary function. These chronic changes are representative of bronchopulmonary dysplasia.

**Figure 1.**

**Treatment for pulmonary injury sequence of prematurity**

Probably the most important points to conceptualize are that it may be possible to prevent the injury sequence, or it may be possible to interrupt the sequence so that it does not progress further. However, once injury is established, assisted ventilation even with an appropriate strategy will not be injury curative. At best, appropriate ventilator strategies will only be supportive to the extent that injury does not continue. Hopefully, the end result following the removal of the injury stimulus will be pulmonary healing, maturation, and the establishment of normal pulmonary function.

Based on the etiologies discussed, there are two ways in which the injury sequence might be prevented: correction of surfactant deficiency, or elimination of tidal volume respiration.

Surfactant replacement therapy has been one of the most intensely studied therapeutic advances in neonatology. The use of surfactant, particularly within the first hours of life, improves gas exchange and reduces neonatal mortality. However, there is much less agreement as to whether surfactant therapy consistently contributes to a reduction in chronic lung disease in treated infants. Therefore, use of exogenous surfactant as currently applied does not fully prevent nor interrupt the pulmonary injury sequence. Reasons for this ineffectiveness may include: 1) non-uniform distribution such that not all lung units receive surfactant, 2) administered surfactant becomes ineffective or nonfunctional, and 3) oxygen therapy continues to contribute to the injury process.

Recent studies suggest that the increase in functional residual capacity which is noted following surfactant replacement is mainly due to the recruitment and distention of previously open airspaces. It thus appears that administered surfactant may only be effective in reversing atelectasis in those gas exchange units directly accessible to open, low resistance pathways. Surfactant administration via endotracheal instillation therefore results in nonhomogeneous surfactant distribution. Uniform surfactant distribution may not be achievable with current administration techniques. If this is the case, then use of surfactant to prevent the initiation of the pulmonary injury sequence may not be possible.

The second method by which the pulmonary injury sequence may be prevented is by achieving gas exchange without tidal volume breathing. The concept that elimination of tidal volume breathing may prevent the development of lung injury has been approached from two different points of view. Using a premature lamb model, Kolobow, et. al., observed that with continuous positive airway pressure and cardiopulmonary bypass,
preterm animals failed to develop hyaline membrane disease. This is in contrast to the development of severe hyaline membrane disease when this animal model is supported with positive pressure ventilation.

Work by Meredith, et. al., in premature baboons was some of the first to suggest that HFOV can prevent this early injury phase. His work demonstrated that surfactant deficient premature animals ventilated using high frequency oscillation with a specific high mean airway pressure strategy had normal appearing lungs at 24 hours of age.

Thus, there is experimental evidence to suggest that if the early phasic airway pressure swings are eliminated (such as with cardiopulmonary bypass) or markedly reduced (such as with HFOV), the pulmonary injury sequence may be avoided in surfactant deficient lungs.

If prevention of the pulmonary injury sequence cannot be achieved, then interruption of the injury sequence must be a major therapeutic goal. The point at which this intervention occurs has obvious implications about the degree and type of pathophysiology to be treated, and the amount of residual pulmonary disease that can be expected. Both early intervention and late rescue are possible. How fast any one infant may progress in the injury sequence is highly variable and may range from a few hours to a few days. Thus, response to early intervention and late rescue correspond more closely to the extent of disease progression than to specific periods of time. In general, response and outcome for early intervention are superior to intervention at a later time when more severe injury has developed.

Human and animal studies with HFOV in the treatment of lung injury in the premature infant

Though it appears that surfactant administration alone may not completely prevent pulmonary injury, there are little data relating the efficacy of combining surfactant administration and high frequency oscillation to achieve this goal.

Preliminary data in an ongoing Japanese study compared conventional ventilation and HFOV in 51 premature infants, most of whom had received surfactant therapy prior to initiation of mechanical ventilation. Though patient numbers are small and overall morbidity is remarkably low, the group administered surfactant followed by high frequency oscillation had a lower incidence of bronchopulmonary dysplasia. This difference was not statistically significant at this sample size. In addition, patients treated with high frequency oscillation alone, an important control group, were not included in this study. It is thus difficult to distinguish between surfactant effects and HFOV effects in these data.

The only premature primate data at this time that looks at surfactant administration followed by high frequency oscillation is in unpublished data by Dr. Alice Gong of the University of Texas. It appears in these studies that animals administered natural baboon surfactant followed by high frequency oscillation did not have pulmonary physiology profiles better than the control group ventilated only with high frequency oscillation (personal communication).

Though there are numerous animal and clinical studies evaluating the use of exogenous surfactant combined with conventional ventilation, conclusive experiments testing the role of surfactant administration in combination with high frequency oscillation are not yet available.

Human clinical studies which evaluate eliminating tidal volume breathing by the institution of high frequency oscillation on the first breath immediately following delivery have not been reported. However, two studies in non-human primates have been published.

In 1989 Meredith, et. al., published data on five (5) premature baboons in whom HFOV (SensorMedics 3100A) was instituted immediately following delivery. These animals were compared with a control group of five (5) animals treated with conventional ventilation. Significant improvements were noted in the high frequency oscillation group with respect to clearing of chest radiographs, oxygenation, pulmonary mechanics, and pulmonary pathology (Figure 2).
At 24 hours of age, FiO₂ was typically < 28 percent and histopathology revealed the absence of hyaline membranes and the uniform inflation of airways and gas exchange units in these animals. Airway dilation, saccular atelectasis and typical hyaline membranes were seen in the lungs of animals treated with conventional ventilation. FiO₂ in the conventional ventilation group was typically 80 percent at 24 hours. Thus, immediate institution of high frequency oscillation prevented the development of early injury in these animals.

In 1990, Jackson, et. al., published data on 10 premature monkeys also treated with immediate institution of high frequency oscillation. These animals were compared to a similar group treated with conventional ventilation. Though study duration in these experiments was only six (6) hours, these investigators also noted more rapid clearing of chest radiographs and improved oxygenation. (Figure 3).

The above studies of Meredith and Jackson are complementary in their results. They demonstrate that the use of a ventilatory strategy that constantly maintains intrapulmonary pressure above alveolar closing pressure can successfully alter the development of early pulmonary injury. The result is significant recruitment and maintenance of lung volume which markedly improves gas exchange. This is referred to as a high lung volume strategy.

If prevention of the pulmonary injury sequence cannot be achieved, then interruption of the injury process must become the major therapeutic goal. Two large clinical studies have been accomplished which look at the effect of early intervention following development of hyaline membrane disease.

In 1990, the HiFi collaborative study group published results from 10 participating centers combining the findings on over 300 premature infants with respiratory distress treated with HFOV. All infants had been on conventional ventilation for less than twelve (12) hours. Ventilator frequency was set at 15 Hz and I:E ratio at 1:1. Initial mean airway pressure on high frequency oscillation was the same as that used for conventional ventilator stabilization. Average mean airway pressure in the high frequency oscillation group was 8.6 cmH₂O over the first 72 hours with a mean FiO₂ of 43 percent. No other information is available on initial ventilator settings or the acute physiologic response to institution of high frequency oscillation. The study concluded that there was no difference in the incidence of bronchopulmonary dysplasia between conventional and HFOV groups at 28 days of age. Though no formal high frequency strategy was specified as part of this study protocol, most centers chose a strategy similar to that used with conventional ventilation. Such a strategy emphasizes the minimization of intrapulmonary pressures as much as possible. This study is thus representative of a low mean airway pressure (8 to 9 cmH₂O), or therefore a low lung volume approach to the management of existing pulmonary injury. This strategy appears to offer little advantage over conventional ventilation, as the incidence of continued pulmonary injury (bronchopulmonary dysplasia) was not different. There was no evidence to suggest that the pulmonary injury sequence had been interrupted.

A second clinical study by Clark, et. al., evaluated the effectiveness of HFOV in the treatment of respiratory distress syndrome. Eighty-three (83) patients were divided into three treatment groups: conventional ventilation, HFOV with early weaning to conventional ventilation, and HFOV alone. The purpose of the two high frequency groups was to evaluate the process of weaning from high frequency oscillation. By chance, patients with more severe disease were randomized to the two high frequency oscillation groups. Patients in the early weaning group were typically treated with HFOV for three to four days, whereas for the other high frequency oscillation group, treatment on this ventilator continued for approximately seven (7) days. Mortality and nonpulmonary morbidity were the same for all groups. The most significant finding of the study was the reduction in incidence of chronic lung disease at 30 days and 36 weeks post conception age in the high frequency oscillation only group. The group of patients

![Figure 3. Oxygenation index in ten premature monkeys](image)
on HFOV who were weaned early appeared to have intermediate benefit with reduction in the incidence of chronic lung disease. These improvements with HFOV occurred despite the fact that patients with more severe pulmonary disease were randomized to the high frequency oscillation groups.

These two studies are in marked contrast, reflective of the ventilatory strategies chosen. Volume recruitment through use of higher mean airway pressures was a stated goal in Clark’s study, consistent with a high lung volume approach to early pulmonary injury. With reduction in the incidence of chronic lung disease, it appears that the high lung volume strategy interrupted the pulmonary injury sequence. This was not the case with the HiFi study, which utilized a low lung volume strategy resulting in ineffective volume recruitment.

A series of premature baboon experiments by deLemos, et al., examined the effectiveness of institution of high frequency ventilation following development of significant pulmonary injury after eight (8) hours of tidal breathing. This is a situation similar to the actual clinical application in the previous two studies.

Significant time related improvements in oxygenation accompanied the institution of high frequency oscillation. All animals had morphologic evidence of hyaline membrane disease at 24 hours of age, though there was more uniform saccular aeration and less small airway dilatation in the high frequency oscillation intervention group. The authors conclude that high frequency oscillation did not reverse the pulmonary injury that had occurred during the initial eight (8) hours of tidal ventilation, but that the progression of injury appeared to have been interrupted.

In 1986 Clark, et al., published work describing the use of HFOV in the rescue of 27 premature infants who had developed pulmonary interstitial emphysema and ventilatory failure on conventional ventilation. The average age at intervention with high frequency oscillation was 96 hours. Though no control group was included, surviving patients had immediate improvement in blood gas parameters with ability to decrease inspired oxygen concentrations and mean airway pressure. Pulmonary interstitial emphysema resolved, but nonsurvivors developed chronic pulmonary insufficiency from which recovery was not possible.

At the 1991 Conference on High Frequency Ventilation, Minton, et al., presented data from the HiFO Study Group on 176 patients in severe respiratory failure treated either with continued conventional ventilation or intervention with high frequency oscillatory ventilation. The mean age at entry was 22 hours. The authors found significant improvement in oxygenation and ventilation in the group to the patients treated with HFOV compared of patients treated with continued conventional ventilation. Additionally, in those patients without pre-existing airleak syndrome, significantly fewer patients developed airleak when treatment was changed to high frequency oscillation.

The animal data by deLemos provides significant background for the interpretation of the two clinical studies. The clinical studies by Clark and the HiFO Study Group supported by the baboon intervention study showing improved lung morphology, provide evidence that strategies which maintain lung recruitment and eliminate tidal volume ventilation alter progression of the pulmonary injury sequence, even if pulmonary injury is already present.

**Summary**

We have introduced the concept that in the surfactant deficient premature infant, tidal volume ventilation can lead to a well defined pulmonary injury sequence and there is experimental evidence that this injury sequence may be prevented. Clinical and non-human primate data support the concept that interruption of this injury sequence is possible. Though the exact extent of pathologic injury is difficult to assess in the clinical setting, use of high frequency oscillation appears to be able to interrupt the progress of injury when used with a treatment strategy which emphasizes maintenance of recruited lung volume and elimination of the barotrauma associated with tidal volume ventilation.
References

5. Personal communication.

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