Early intervention in respiratory distress syndrome

Introduction

Since its availability in the late 1960s, mechanical ventilation has led to dramatic improvements in treating infants with hyaline membrane disease (HMD). Conventional mechanical ventilators provide relatively large tidal volumes to eliminate carbon dioxide and establish an adequate gas exchanging volume to reduce shunting. In 1959, Mead and Collier showed that without periodic inflation with lung volume recruitment, there was a progressive fall in compliance during prolonged mechanical ventilation. Since the introduction of this concept, clinicians have been searching for better methods of lung volume recruitment in acute lung disease. To achieve adequate lung volume recruitment, the lung has to be inflated past the pressure at which atelectatic alveolar units begin to open and then be maintained above their critical closing pressure. Positive pressure mechanical ventilation uses repetitive large convective flows to achieve lung volume recruitment. The lung volume in conventional ventilation is constantly changing. The repetitive stretching of distal conducting airways will cause over distention and a resultant lung injury which can become considerable.

High Frequency Oscillatory Ventilation (HFOV) has been shown to be an effective method for ventilation and oxygenation not only in experimental animals with and without lung disease, but also for neonates with respiratory failure. HFOV lung volume recruitment can be safely used by employing mean lung pressures greater than those used with conventional ventilation, but without exposing the lung to high peak pressures that can lead to injury. Lung recruitment can be accomplished while using tidal volumes less than dead space, delivered at supra-physiologic ventilatory frequencies.

Pulmonary injury sequence of prematurity

Pulmonary injury sequence (PIS) of prematurity is a continuum of disease which includes respiratory distress syndrome (RDS), pulmonary interstitial emphysema, pulmonary airleak syndrome, oxygen toxicity, and bronchopulmonary dysplasia (BPD).

This syndrome is initiated by either spontaneous or mechanical tidal volume breaths in an infant lacking surfactant. These convective tidal volumes are distributed heterogeneously within the lung and initiate the first phase of the pulmonary injury sequence. This tidal breathing induced injury has been described in detail in our previous Critical Care Review “Pathophysiology of Lung Injury”, published in 1992.

Based on the etiologies discussed in our review, there are two ways by which PIS of prematurity might be prevented, correction of surfactant deficiency (pulmonary immaturity) or elimination of tidal volume respirations. Surfactant replacement therapy is now generally considered to be a standard of care for infants with RDS, significantly reducing mortality. Because of this substantial improvement, many centers question the value of adding HFOV to surfactant for early intervention. But exogenous surfactant has not proven. A recent report from the New England Journal of Medicine clearly indicates that although surfactant has significantly decreased mortality from 24 to 20 percent following its introduction for treatment of RDS, morbidity...
remains high with the incidence of BPD increasing from 22 to 25 percent, intraventricular hemorrhage (IVH) from 17 to 23 percent, and patent ductus arteriosus from 24 to 27 percent. Benefits of using HFOV in conjunction with surfactant therapy have been demonstrated in three new animal studies and a new three year clinical trial. These studies also provide insight as to why surfactant works better with HFOV. Froese, et. al. evaluated high (optimal) and low lung volume strategies with both conventional and high frequency ventilation in a surfactant deficient lung injury rabbit model treated with exogenous surfactant. Phospholipid levels in lamellar bodies were used as one indicator of lung injury. The optimal lung volume strategy with HFOV maintained pre-injury levels (92 percent) of phospholipids, while low lung volume strategies had significant decreases with both mechanical ventilation (CMV) (33 percent) and HFOV (34 percent). The optimal lung volume strategy with conventional ventilation resulted in an intermediate reduction (52 percent) of phospholipid levels. The authors concluded that the ventilator strategy strongly influences exogenous surfactant efficiency and that high lung volume HFOV enables the lung volume to be stabilized, preventing both over-distention and atelectasis. The 1994 study by Jackson, et. al., reported the effects of both conventional and HFOV, with and without exogenous surfactant, on lung injury in a premature baboon model. They found that surfactant with HFOV was superior to surfactant with CMV, CMV alone or HFOV alone. Surfactant therapy with HFOV from the first breath dramatically reduced alveolar proteinaceous edema, alveolar debris, radiographic scores and oxygen index. They speculated the reduction in early lung injury may reduce the incidence or severity of BPD. Recently, Matsuoka, et. al., examined the levels of granulocytes in lung lavage fluid in surfactant depleted rabbits ventilated with CMV or HFOV. They demonstrated animals ventilated with conventional ventilation had significant increases in granulocytes while the HFOV group maintained baseline levels, supporting the theory that HFOV is useful for the prevention of lung injury related to activated granulocytes.

In a new clinical study, the Provo multicenter controlled trial entered patients at approximately three hours of age. The incidence of moderate to severe chronic lung disease and/or death was 50 percent less in the HFOV-surfactant treatment group than in the CMV-surfactant group. These new data strongly support the argument that the combination of surfactant and HFOV is more effective for treating RDS than either HFOV alone or surfactant with CMV.

**HFOV strategy in early intervention**

The lung volume on HFOV remains relatively constant. Recruitment of lung volume is achieved by raising MAP to move lung inflation past the critical opening pressure at which atelectatic alveolar units begin to open. Inflation is maintained above the closing pressure of the alveoli and airways.

Achieving the correct lung volume and maintaining it throughout the respiratory cycle improves ventilation/perfusion ratio (V/Q) matching in several ways. In CMV, the alveolar gas exchange area is reduced and the time for gas exchange is short. With an optimum lung volume strategy during HFOV, the lung volume is held above the critical closing pressure throughout the respiratory cycle, the gas exchange area is enlarged, and the time for gas exchange is prolonged. Both can significantly improve the ventilation side of the V/Q relationship. Optimizing pulmonary blood flow is critical to improving V/Q matching. This can only be achieved when pulmonary vascular resistance (PVR) is minimized and cardiac output is not compromised. It has been shown that physical expansion of the lung contributes to pulmonary vasodilatation. At low lung volume, alveoli spontaneously collapse due to loss
of interstitial traction. This triggers an associated decreased functional residual capacity, decreased alveolar stability, and acute hypoxemia. At a low lung volume, PVR increases secondary to a decreased cross-sectional area of the extra alveolar vessels.14,15 As the lung increases from a low to an optimum lung volume, there is an increase in radial traction to the walls of the large extraalveolar pulmonary vessels resulting in an increase in cross-sectional area and a reduction in PVR. If the lung becomes over distended, there is increased alveolar pressure compressing the alveolar vascular bed. This results in increased PVR. Thus at both under and over inflated lung volume, PVR is increased, but PVR is minimized at optimum lung volume (Figure 2). V/Q can be monitored by changes in arterial oxygenation.

In general, lung volume while on CMV at the time of transfer to HFOV usually is on the inflation limb of the pressure volume curve as depicted by point “A” in Figure 3. We increase MAP in 1 cmH2O increments to increase lung volume along the pressure volume curve. These incremental changes are performed until arterial oxygen shows marked improvement, or there is a rise in central venous pressure with signs of decreased systemic blood flow, or overinflation is found on the chest radiograph. During the patient stabilization period, ventilator adjustments are made every 15, 30 or 60 minutes depending on the patient’s condition and whether they are high or low on the pressure volume curve. As these incremental MAP increases are performed, FiO2 is decreased to keep the PaO2 in the 50 to 55 torr and O2 saturation in the 91 to 93 percent range. Because of concerns with diffuse oxygen toxicity in the fully recruited neonatal lung, the FiO2 is reduced to a level of oxygen support that is less than 30 percent. Chest radiographs for assessment of lung volume are obtained every 2 to 6 hours as needed until lung volume is optimized. Optimal lung inflation on chest radiographs generally correlates with obtaining an 8 to 9 posterior rib level expansion on the right hemidiaphragm and decreased lung opacification.

Ventilation is adjusted by changing the power that varies the oscillatory pressure amplitude delivered by the ventilator. Increasing the power increases the oscillatory amplitude which increases tidal volume. The need to adjust oscillatory amplitude is based on observed chest movement (vibration) and arterial blood gas results. We use a rate of 10 Hz and an I:E ratio of 1:2 in most neonates. In very low birth weight infants, we use 15 Hz to enable finer control of tidal volume and to prevent over ventilation.
Figure 4. *Follow arrows on protocol. Letters do not necessarily follow in sequence.
Transcutaneous monitoring of carbon dioxide levels facilitates the decision making process and is extremely beneficial in preventing inadvertent hyperventilation. It is important to remember as one increases MAP and approaches an optimum lung volume, compliance improves and tidal volume increases. This compliance improvement can be rapid, requiring an almost immediate decrease in oscillatory amplitude. Therefore as we increase MAP to establish an optimal lung volume, we adjust oscillatory amplitude to keep PaCO₂ approximately 45 torr until lung volume is optimized. We then adjust oscillatory amplitude to fine tune PaCO₂ to 40 torr. In severe respiratory failure, if adequate PaCO₂ cannot be achieved with maximum power output, decreasing the oscillatory frequency will increase tidal volume and improve ventilation. However, frequency changes are generally not needed, and 10 Hz usually provides an adequate range of tidal volume output. In extremely low birth weight infants, over-ventilation at low power output is occasionally seen and increasing the frequency will result in more attenuation of the tidal volume, reducing ventilation.

**HFOV weaning**

After radiographically optimizing lung volume with an FiO₂ less than 0.30, we slowly begin to reduce mean airway pressure. Because of the hysteresis of the pressure volume relationship of the lung on the deflation limb, the reduction in MAP will generally not result in a significant loss of lung volume and will maintain oxygenation. If weaning is overly aggressive, the lung may drop below the critical closing pressure and oxygenation may suddenly fall. Because the lung volume has now shifted back to the inflation limb, it may require more than simply increasing MAP 1 to 2 cm to re-recruit the lung. Re-recruiting the lung volume must be done by increasing pressure up the inflation limb to an optimum lung volume and then slowing decreasing MAP and lung volume on the deflation limb. An alternative recruitment method would be to open the lung with sighs.

Increasing the MAP along the pressure volume curve will result in increasing lung volume. When lung volume increases above the critical opening pressure, lung compliance will improve. Over time, lung compliance will continue to improve, and when not compensated for by decreased MAP, will result in continued lung volume increases and eventually, overdistension. This causes compression of the alveolar vascular bed and increased PVR, or decreased venous return, and decreased cardiac output. Chest radiographs are utilized to evaluate lung over-inflation. We consider the lung over-inflated radiographically when the diaphragm is flattened, or when bulging is noted in the intercostal spaces. If hypovolemia is present, a negative effect on pulmonary circulation may be experienced at an otherwise normal appearing lung volume.

The weaning strategy we follow is depicted in Figure 5. We decrease MAP in 0.5 to 1 cmH₂O increments as long as FiO₂ remains < 30. Chest radiographs are followed for lung volume assessment. Oscillatory amplitude is weaned per arterial carbon dioxide values. Because of the work by Clark, et. al., showing a decreased incidence of bronchopulmonary dysplasia in patients ventilated entirely with HFOV, it is our preference to maintain infants on HFOV until they are weaned to continuous positive airway pressure (CPAP).
HFOV weaning problems are usually evidenced by restlessness, increased retractions, fluctuations in mean airway pressure and a decrease in saturation. These may be related to inadequate lung inflation.

Some patients fail to wean successfully to CPAP from HFOV and these patients are changed to conventional ventilation. They remain on conventional ventilation if they can maintain FiO₂ less than 0.30 and mean airway pressure less than 8 cmH₂O for infants weighing less than 1,000 gms; or a mean airway pressure less than 10 cmH₂O for infants weighing more than 1,000 gms. We do not hesitate to place an infant back on HFOV if they fail a CMV trial.

If mucus plugging of the airways is a serious problem in the recovery phase of illness, this type of patient may also be changed from HFOV to conventional ventilation to improve mucus transport and recovery.

During HFOV, we monitor closely for signs of decreased systemic perfusion. Studies have shown that carefully increasing mean airway pressure as we have previously described, is similar to conventional ventilation in its effect on cardiac output. However, many of our patients may have limited cardiac reserves and these require careful echocardiographic assessment: indices of myocardial function such as shortening fraction, ejection fraction and estimates of chamber sizes, ductal shunting, pulmonary artery pressure and cardiac output. Our clinical experience in these patients has been that infants placed on HFOV are less tolerant of myocardial dysfunction or hypovolemia than conventionally ventilated newborns. If the patient has myocardial dysfunction or hypovolemia and inotropics or appropriate blood volume expansion are not given, there may be ventilation perfusion mismatches which will counter the positive oxygenation effects of optimal lung volume recruitment.

Suctioning while on HFOV currently requires disconnecting the circuit to suction through the endotracheal tube. This will result in a fall in MAP and loss of lung volume and Functional Residual Capacity (FRC) if the patient is surfactant deficient. Once HFOV is reinstated, mean airway pressure may need to be increased above the previous mean airway pressure settings to obtain re-recruitment. This is usually accomplished at a MAP 1 to 2 cm higher than the baseline MAP with weaning to the baseline MAP as oxygenation improves. In our experience with early institution of HFOV, frequent suctioning is not required in the first 24 to 48 hours; however, as compliance improves, we routinely suction every 4 to 6 hours.

As previously mentioned, surfactant replacement therapy is now considered to be a standard of care for infants with RDS. However, to instill exogenous surfactant into the endotracheal tube while on high-frequency oscillation currently requires interrupting the circuit with loss of mean lung volume. This necessitates re-recruitment of lung volume after instillation. Re-recruitment can usually be accomplished over time with the same mean airway pressure or by temporarily increasing mean airway pressure by 1 to 2 cmH₂O from the previous baseline and then weaning back to baseline mean airway pressure as oxygenation improves. Since our ventilatory strategy results in a rapid reduction in FiO₂ to less than 0.30 (i.e., below surfactant replacement indication levels), subsequent doses of surfactant are less frequently needed for HFOV ventilated infants.

**Potential complications**

All therapeutic ventilatory modalities have potential adverse effects, and HFOV is not different in this respect. Major factors that have been studied or proposed as potential complications of HFOV are focal obstruction/ mucus impaction, over inflation of the lung, impaired cardiac output, and intraventricular hemorrhage.

Focal obstruction secondary to mucus impaction has been reported after prolonged use of HFOV. The small tidal volumes of HFOV may not breathe “through” mucus plugging effectively. Loss of chest wall movement may be an indication of mucus plugging which would require suctioning. When mucus secretions are not responsive to frequent suctioning, we often transfer the patient to conventional ventilation for short periods of CMV, or for continuous CMV if necessary. We have noted some patients on prolonged HFOV who have a large mobilization of secretions after return to conventional ventilation. These usually have been infants who had significant barotrauma before HFOV rescue. Mucus impaction may also be related to inadequate humidification.
Early enthusiasm for high-frequency ventilation was tempered by a concern high lung volumes could have an adverse effect on venous return and cardiac output. Studies comparing cardiac output during high-frequency and conventional ventilation have failed to reveal differences between the two techniques. However, lung over-distention can cause cardiovascular compromise. We have noted in many of our patients the need for more fluids during the first 24 hours of HFOV than we would usually need during conventional ventilation. Monitoring for adverse hemodynamic effects should include continuous heart rate, blood pressure, and central venous pressure monitoring. Frequent echocardiographic evaluations for measurement of myocardial function and blood volume status are extremely helpful. In addition, frequent lung volume assessment with serial chest x-rays should be performed. With careful attention to blood volume status and correction of myocardial dysfunction, we have found HFOV to be an effective method of ventilation and oxygenation even in septic infants.

Animal studies evaluating central venous pressure, cerebral blood flow and intracranial pressure have not shown differences when HFOV has been compared to conventional ventilation. In the very premature infant, HFOV can result in elevated pleural pressure and fluctuations of arterial venous pressure which may increase the risk of intraventricular hemorrhage. In the multicenter National Institutes of Health High-Frequency Oscillation (HIFI) trial, infants treated with HFOV had an increased incidence of severe intraventricular hemorrhage compared to those managed with conventional ventilation. These infants had varying periods of conventional ventilation before HFOV and their ventilator approach was probably more a low than a high lung volume strategy. In addition, there was a large difference between centers in Grade 3-4 IVH. A two year neurodevelopmental follow-up of those patients demonstrated no statistical difference in outcome between groups.

In 1993, the University of Iowa reported on the use of HFOV with surfactant in RDS as compared to infants treated with conventional ventilation and surfactant. Despite a lower birth weight (762 grams vs. 1003 grams) and more severe RDS, defined as MAPxFiO2 (9.7 vs. 7.1), in the HFOV treated patients, they had non-significant but lower incidences of pneumothorax (7.7 percent vs. 16 percent) and severe IVH (15 percent vs. 24 percent).

Three other studies, all in infants with severe respiratory distress syndrome using an optimum lung volume strategy, have not found a significant increase in severe intraventricular hemorrhage. A recent single center review of their two-year HFOV experience reported a drop in severe IVH in the first 104 infants with RDS treated with HFOV compared to their previous experience with conventional ventilation. They found the incidence of Grade 3 to 4 IVH to be down to 3.1 percent in their infants treated with HFOV, a reduction from 7.4 percent during previous use of CMV only.

At the 1994 High Frequency Ventilation (HFV) meeting at Snowbird, UT, Alan Spitzer, M.D., from Jefferson University Hospital in Philadelphia, reported on their analysis of high frequency ventilation relationships to neurological complications. They found that low PaCO2s had the highest correlation to neurologic complications. It may be that HFV is such an effective ventilator that unmonitored hyperventilation may set up some infants for vascular lesions.

**Summary**

We believe HFOV is an important tool in the management of neonates with respiratory distress and is effective in breaking the continuum of pulmonary injury sequence. There is a definite learning curve to the safe introduction of HFOV. As with any new technology, there is an ongoing process of determining optimum ventilation strategies for clinical management of neonates with varying types of respiratory failure. In the infant with RDS, early use of HFOV with a strategy to achieve effective, i.e., “optimal” lung recruitment, in combination with exogenous surfactant administration, may be the best treatment combination currently available.
References


Dale R. Gerstmann, MD: Dr. Gerstmann is the Director of Neonatal Research and is staff Neonatologist at the newborn intensive care unit at Utah Valley Regional Medical Center in Provo, Utah.

Stephen Minton, MD: Dr. Minton is the Co-Director of Newborn Services at Utah Valley Regional Medical Center in Provo, Utah. He is an Adjunct Professor of Pediatrics at Weber State University in Ogden Utah.

Ronald A. Stoddard, MD: Dr. Stoddard is the Co-Director of Newborn Services at Utah Valley Regional Medical Center in Provo, Utah. He is an Adjunct Professor of Pediatrics at Weber State University in Ogden Utah.

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