This is a summary of HFO strategies we use in the management of neonates. As with any new technology, the definition of optimal is dynamic and many issues remain to be resolved. Our goal is to communicate one approach.

In providing HFO support to over 400 critically ill neonates sent to Wilford Hall USAF Medical Center, we identified four categories of patients. These four groups consist of patients with diffuse homogeneous lung disease, nonhomogeneous lung disease, lung hypoplasia syndromes, and airleak syndromes. While these groups are distinct, several factors also play a role in determining the optimal HFO strategy to use in any specific patient. The three most important factors are: airleak, pulmonary hypertension, and poor cardiac performance.

Management of patients with severe airleak requires that a low pressure approach be considered. Pulmonary hypertension may be responsive to respiratory alkalosis and relative hyperoxia (PaO₂>80mmHg) and acceptable blood gas parameters must be adjusted accordingly.

ECMO candidates with meconium aspiration syndrome or sepsis are often hypotensive due to poor cardiac function. Their limited cardiac reserve requires careful assessment of the interaction between assisted ventilation, venous return and pulmonary blood flow. Increasing end-expiratory pressure during conventional mechanical ventilation (CMV) and increasing mean airway pressure during HFO can impede venous return and increase pulmonary vascular resistance. As a result, the patient with limited cardiac reserve can be made even less stable. Optimizing these patients’ intravascular volumes and vasopressor support is critical before initiating HFO.

The guidelines discussed below are not meant to replace individualized care. The most important advice we can offer is to never stop rethinking the patient’s problem.

**Diffuse Homogeneous Lung Disease**
Respiratory distress syndrome (RDS), pneumonia (especially Group B streptococcal), pulmonary hemorrhage, and adult type respiratory distress syndrome all may present with diffuse and homogeneous radiographic lung disease. The most common disease process producing diffuse homogeneous lung disease is RDS in the premature infant and pneumonia (especially that caused by Group B streptococci) in the term infant. In our series of 67 preterm infants with RDS and 45 term infants with pneumonia, we found that approximately 75% had improvements in gas exchange on HFO. In the term infants who meet ECMO criteria, 80% could be managed with HFO alone. In addition, controlled trials (1,2) have demonstrated a reduction in barotrauma when HFO is applied earlier in the course of respiratory failure. The pathophysiologic mechanisms common to these disease processes are edema, atelectasis, decreased lung compliance, and ventilation/perfusion mismatch. The goals of assisted ventilation in this group of patients are to improve lung inflation, compliance and ventilation/perfusion matching while avoiding barotrauma or compromise of cardiac output.

**Strategy in the management of diffuse homogeneous lung disease.**
Animal data (3,4,5) support the use of a HFO strategy that initially employs a high mean airway pressure to recruit collapsed alveoli, followed by judicious, but aggressive weaning of the mean airway pressure (PaO₂>80mmHg) and acceptable blood gas parameters must be adjusted accordingly.

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increased pressure during oscillation to re-expand atelectatic alveoli and to bring the lung onto the deflation limb of the pressure volume curve. The safe use of SI maneuvers in the management of infants with RDS requires that they be carefully controlled. Intermittent hand ventilation with a short inspiratory time is not a safe method of providing a SI. We prefer to use gradual increases in the mean airway pressure to SI maneuvers as a method of recruiting collapsed alveoli and improving oxygenation.

Our current clinical strategy in the management of infants with diffuse homogeneous lung disease is to initiate HFO at a mean airway pressure one to two cmH2O higher than that being used on CMV. We increase the mean airway pressure in one cmH2O increments until arterial oxygen improves by 20 to 30 torr, or there is a rise in central venous pressure with signs of decreased systemic blood flow, or until the chest radiograph shows evidence of normal lung inflation (eighth posterior rib level of expansion and decreased radiopacification). Once there is improvement in oxygenation, we hold the mean airway pressure constant and monitor the patient for clinical signs of decreased systemic perfusion. Capillary refill, blood pressure, central venous pressure, heart rate, and urine output are monitored hourly. Echocardiographic measurements of indices of myocardial performance are done daily.

Chest radiographs are obtained frequently to assess the degree of lung inflation. If the PaO2 continues to rise, the FiO2 is reduced until the level of support is less than 0.60. When the FiO2 is less than 0.60, mean airway pressure is given equal priority in the weaning process. If at any time the chest radiograph shows lung overinflation or there are signs of impaired cardiac output, weaning mean airway pressure is given priority over FiO2. The goal is to maintain optimal lung inflation and the lowest level of FiO2 necessary to maintain an oxygen saturation of 90-95%. It is important to recognize that adjustments in the mean airway pressure may not have an immediate effect on oxygenation. In the stable patient, make changes slowly and allow 30-60 minutes for the desired effect to occur.

We use an initial rate of 10-15 Hz with a fractional inspiratory time of 0.33. Ventilation (PaCO2) is adjusted by changing the oscillatory pressure amplitude (power) delivered by the ventilator. If adequate PaCO2 cannot be achieved with the maximum power output, the rate is decreased to increase the tidal volume. If a patient is over ventilated at the lowest power setting, we increase the rate to decrease the ventilator’s tidal volume output. The typical operation range is 5-15 Hz at a fractional inspiratory time of 0.33.

Nonhomogeneous Lung Disease
Patients with nonhomogeneous lung disease have unilateral or patchy lung involvement. Meconium aspiration syndrome (MAS) and focal pneumonia are examples of this type of disease.

The pathophysiology shared by these diseases in nonuniform lung involvement where certain lung units are nearly normal while other areas are markedly abnormal. As a result, ventilator management is difficult. A strategy that is effective in opening damaged areas may result in overinflation and trauma to more normal areas of the lung.

Meconium Aspiration Syndrome
Patients with MAS are less responsive to HFO than patients with diffuse homogeneous lung disease. In our series of 51 patients with severe respiratory failure secondary to MAS, only 30% responded to HFO with an improvement in oxygenation. While the response rate was low, none of the patients who met ECMO criteria, but responded to HFO, required ECMO. In contrast, 94% of the patients who failed to respond to HFO required ECMO to support adequate gas exchange. Poor responsiveness to HFO may be due to the presence of meconium plugs within the airway. Patients least likely to respond to HFO are those with evidence of air trapping and overinflation on CMV. Currently employed strategies of HFO do not promote airway clearance of meconium or mucous plugs. Focal gas trapping may be accentuated by HFO and result in airway rupture and pneumothorax.

Another important problem in infants with severe MAS and respiratory failure is the presence of pulmonary hypertension. Persistent pulmonary hypertension may be associated with compromised cardiac output. Lung volume changes substantially during tidal breathing and CMV. During HFO, lung volume and pleural pressure remain relatively constant. The relative absence of lung volume changes results in nearly constant (and sometimes higher) intrathoracic pressure that may impede venous return and reduce
cardiac output. In patients with limited reserve, this can lead to clinical deterioration. ECMO candidates who do not respond to HFO have significantly worse indices of cardiac function. (9) While no specific index has a high positive predictive value in determining which patients will need ECMO, it is important to assess cardiac performance before a trial on HFO. The injudicious adjustment of assisted ventilation (CMV or HFO) in infants with air trapping and/or signs of severe pulmonary hypertension may cause pneumothoraces or cardiovascular compromise. These events may lead to severe irrecoverable hypoxemia and death. Close, readily available ECMO support is essential when managing critically ill patients with MAS and severe pulmonary hypertension.

An important subgroup of patients with MAS has clinical and radiographic finding more consistent with RDS. These patients tend to be older (>2 days) and usually have been exposed to prolonged high levels of oxygen and ventilator support. The chest radiograph typically shows lung underinflation and more homogeneous reticulogranular pattern. In these infants, echocardiographic evaluation often demonstrates normal myocardial performance, and they frequently respond well to HFO.

**Lung Hypoplasia Syndromes**
The most common associated diagnosis in this population of infants is congenital diaphragmatic hernia (CDH). Other less common associated diagnoses include Potters’ syndrome, prolonged rupture of membranes and hydrops fetalis. The common variable in this group of infants is small, often abnormal lungs. The theoretic advantage that HFO offers over CMV is a less traumatic method of supporting carbon dioxide elimination. In our series of 15 ECMO candidates with CDH, 27% responded to HFO and did not require ECMO.

Infants with lung hypoplasia are similar to those with MAS in that they frequently fail to have a sustained response to HFO. While gas exchange frequently improves on initiation of rescue therapy, the improvement is usually transient.(10, 11) There are two possible explanations for the poor response. The first is that patients with lung hypoplasia have inadequate lung tissue to support adequate gas exchange. Despite aggressive medical management (CMV or HFO), some infants die shortly after birth. These infants are usually not offered ECMO because they are felt to have inadequate lung tissue to support life or because they die before ECMO can be initiated. However, some infants with radiographic evidence of profound pulmonary hypoplasia on the first day of life have radiographs that show much less severe lung hypoplasia after several days of HFO. While it is unlikely that their lungs have grown in this time frame, it is possible that lung capacity improved because of adaptive factors and avoidance of lung injury. Therefore, we are aggressive in the early management of all infants with lung hypoplasia syndromes who do not have other lethal congenital anomalies.

The second explanation for the failure of HFO to produce an improvement in gas exchange in patients with pulmonary hypoplasia is the presence of profound pulmonary hypertension. As described in patients with MAS, HFO may compromise cardiac output. In the patient with limited cardiac reserve, any change that effects cardiac output (e.g., agitation, pneumothorax, increasing end-expiratory pressure) can cause acute irreversible deterioration. It is exceedingly important to have immediate access to ECMO therapy for the infant with pulmonary hypoplasia and marginal gas exchange. Acute deterioration can be associated with severe irreversible hypoxemia.

While HFO has not been a very effective mode of rescue for infants with lung hypoplasia who are failing CMV, it may be an effective ventilatory strategy in the early management of these infants. HFO improves ventilation and allows the use of lower pressure amplitudes. The use of HFO early in the management of lung hypoplasia could reduce ventilator associated barotrauma and improve pulmonary recoverability and long term outcome. This hypothesis is currently being studied. Until further data are available, the use of HFO early in the management of patients with CDH must be considered investigational.

**Strategy in the management of non-homogeneous lung disease and pulmonary hypoplasia syndromes**
Initiation of HFO in this group of infants must be done with care. Evaluation of the degree of lung inflation on chest radiograph, degree of lability in gas exchange, the severity of existing pulmonary hypotension and the adequacy of cardiac performance must be performed before starting HFO. In addition, these patients must have access to ECMO. In our own nurseries we accomplish this by notifying the ECMO team before we offer a trial of HFO.
The goal of HFO in these patients is to improve oxygenation at the lowest possible mean airway pressure. Care must be taken to avoid lung overinflation. Estimating optimal lung inflation is more difficult in this group of infants than in patients with homogeneous lung disease. In initiating HFO in these patients, we start at the same mean airway pressure that was being used on CMV. Central venous pressure, oxygen saturation and systemic blood pressure are monitored continuously during the trial of HFO. If the patient remains stable for five minutes, an arterial blood gas is obtained. If oxygenation has not improved, the mean airway pressure is increased by one cmH\(_2\)O increments every five to ten minutes until the arterial oxygen tension improves. Once there is an improvement in PaO\(_2\), the mean airway pressure is held constant at that level. In general, once oxygenation begins to improve it will continue to improve, and increasing the mean airway pressure further can result in lung overinflation. If at any point during the trial there is a significant increase in the central venous pressure, a decrease in the systemic arterial pressure, or a drop in the arterial oxygen saturation, the infant is returned to CMV at the same settings as were present before the trial of HFO. When initiating a second trial of HFO in these patients, we start at a mean airway pressure one to two cmH\(_2\)O lower than that required on CMV and then follow the same protocol.

Within an hour of initiation of HFO, a chest radiograph is obtained to look for signs of lung overinflation. For patients without lung hypoplasia, lung overinflation is diagnosed when the lung fields are expanded to a level of more than eight posterior ribs, or are hyperlucent, or when the diaphragms are flattened. Assessment of lung overinflation in neonates with lung hypoplasia is more subjective. If there are sings of lung overinflation, attempts are made to decrease the mean airway pressure. If lung overinflation persists, the rate being used on HFO is decreased by one to two Hz. By reducing the rate, the lung is allowed more time to empty and problems with gas trapping are reduced. The patient is returned to CMV if these procedures fail to result in resolution of lung overinflation.

Ventilation is controlled by adjusting oscillatory pressure amplitude and ventilator rate. As in patients with homogeneous lung disease, we initiate HFO at a rate of 10-15 Hz, a pressure amplitude that produces perceptible chest wall movement and a fractional inspiratory time of 0.33. If the infant remains stable, an arterial blood gas is obtained. If ventilation is inadequate and the chest x-ray shows normal inflation, the pressure amplitude is increased. If the chest x-ray shows overinflation, the ventilator rate is decreased allowing increased times for exhalation. If adequate ventilation cannot be achieved at five Hz and maximum power output, the infant is returned to CMV. Faster rates, larger tidal volumes, and longer inspiratory times all increase the propensity for gas to become trapped within the lung. Avoidance of this complication is crucial to the safe use of HFO in infants with heterogeneous lung disease and/or pulmonary hypoplasia.

**Airleak Syndromes**

Airleak syndromes (pneumothoraces, pneumopericardium, pneumoperitoneum, pneumomediastinum, and pulmonary interstitial emphysema) are a common complication of CMV in the management of respiratory failure. In the premature infant, the most common airleak syndrome associated with severe respiratory failure is pulmonary interstitial emphysema (PIE). The most common airleak syndrome in the near-to-term infant is pneumothorax. The occurrence of airleak usually results in further deterioration of the patient. In patients with intractable airleak, a significant portion of the volume delivered during a positive pressure breath can be lost through the leak. If this air accumulates in a closed space, it can compromise vital structures and cause death. Venting the airleak can restore function by decompressing the trapped gas. However, evacuation of the airleak may also result in the loss of delivered tidal volume through the vent. A cycle can develop whereby adequate gas exchange requires the use of higher ventilator settings that, in turn, increases the airleak and reduces the amount of gas available to participate in gas exchange. If this cycle is not interrupted, gas exchange becomes ineffective. Frequently, HFO achieves adequate ventilation at lower peak and/or mean intrapulmonary pressure than CMV and can break the cycle of airleak and need for high pressures on assisted ventilation. In our series of 127 preterm infants with PIE, 78% responded to HFO with an improvement in gas exchange.
**Strategy in patients with airleak syndromes**

In the management of PIE, we have found two distinct groups of patients based on their clinical presentation and response to HFO. The first group of infants has chest radiographic changes consistent with small focal bubbles surrounded by diffuse atelectasis represented by dense radiopacification and low lung volumes. The pathologic correlates in these infants are dilated distal bronchioles and diffuse alveolar collapse. (12) The management of these infants is the same as that outlined for patients with homogeneous lung diseases. Again, the goal is to improve lung inflation and avoid lung overinflation that may cause rupture of the dilated distal airway and produce PIE and/or pneumothorax.

The second group of patients has chest radiographs that show large tortuous cysts. Lung involvement may be focal or diffuse, unilateral or bilateral. Pathological examination of lungs from these infants shows true interstitial collections of gas. (12) As the cysts dilate, they may compress surrounding lung tissue and act like a tension pneumothorax. Our goal in the management of these patients is to allow reabsorption of the interstitial air. In these patients, every attempt is made to use the lowest possible ventilator settings and to accept low arterial oxygen (45-60 torr) and high carbon dioxide (50-65 with pH > 7.25) levels. The infant is placed on HFO at a mean airway pressure equal to or less than that being used on CMV. The mean airway pressure is reduced in one cmH2O increments until the target PaO2 is reached or the chest radiograph demonstrates normal inflation and signs of airleak resolution. In these infants weaning mean airway pressure is given priority over weaning FiO2.

Ventilation is adjusted as discussed previously. The use of low oscillatory pressure amplitudes (compared to PIP or CMV) often leads to resolution of the airleak without requiring great reductions in mean airway pressures. The most severely affected lung is placed in the dependent position to increase resistance to gas delivery to that lung. We avoid hand bagging and SI maneuvers in these patients because they can be associated with worsening of the PIE. (13, 14)

Another important issue in treating infants with PIE is when to wean back to CMV. In patients who resolve their PIE, we continue HFO for an additional 24 - 48 hours. We feel this allows for the complete reabsorption of interstitial air and decreases the possibility of the recurrence of PIE. In patients whose PIE fails to resolve or evolves into a radiographic picture of bronchopulmonary dysplasia, we attempt to wean back to CMV once the patient is on less than 50% oxygen, and can be supported on peak pressures less than 30 cmH2O and a rate less than 30 breaths per minute. Most patients will improve following their switch to CMV. This improvement is often temporarily associated with mobilization of pulmonary edema and clearance of airway secretions.

Our approach to the infant with gross airleak (recurrent pneumothoraces) is the same as that employed to manage the preterm infant with PIE. As in patients with PIE, we first decide if the predominant problem is poor lung inflation or airleak. In patients whose primary problem is poor lung inflation, our goal is to improve inflation. Therefore when switching from CMV to HFO, we use a higher mean airway pressure to accomplish this goal. In infants whose primary problem is severe airleak, our goal is to allow resolution of the airleak. In these patients, we use the lowest mean pressure that will allow adequate gas exchange. In either case, it should be reiterated that the oscillatory pressures are substantially lower than the peak inspiratory pressures of CMV.

**Concluding Remarks**

As with any new therapy, this technology has a learning curve. The safe introduction of HFO requires careful education of all those involved with its application. This includes, but is not limited to, nurses, respiratory therapists, physicians and ECMO specialists. We would like to emphasize all the complications seen during CMV can be seen on HFO. Hospital in-services reduce the learning curve’s effect on these complications. While adjusting this HFO is simple, defining optimal lung volume and patient specific ventilatory strategies can be difficult. We encourage animal laboratory experience before clinical use.

We believe that HFO is an important adjunct to CMV in the management of neonates with respiratory failure. However, its optimal application requires continued research into the definition of disease-specific HFO strategies. We hope this paper, based on our clinical experience and animal experiments, has helped clarify the current state-of-the-art.
REFERENCES
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