NEONATAL HIGH-FREQUENCY VENTILATION Past, Present, and Future

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Update on Mechanical Ventilation and Exogenous Surfactant

NEONATAL HIGH-FREQUENCY VENTILATION
Past, Present, and Future

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In the last two decades, high-frequency ventilation (HFV) has evolved from a physiologic curiosity to an established method of treating neonates with respiratory failure. After more than 20 years of laboratory and clinical experience with HFV, a great deal is known about how it works and about how it can be used. A Medline query of articles on HFV lists more than 1300 English language articles published between 1980 and 2000. Despite the huge number of publications, however, substantial controversy remains about when and how HFV should be used. At one end of the spectrum is a minority of clinicians who use it as a primary mode of ventilation for infants who require ventilatory support, whereas at the other extreme are those who view it strictly as a rescue technique, only to

be used when conventional ventilation has failed. Still others possess an intermediate level of enthusiasm, using HFV in an early rescue manner in infants judged to be at high risk for complications from conventional ventilation, or who have developed air leak, even though they are maintaining adequate gas exchange on conventional ventilation. This article represents a synthesis of the authors' interpretation of the published literature on HFV, and their clinical experiences with HFV to treat neonates since the early 1980s.

TYPES OF HIGH-FREQUENCY VENTILATION

There are three types of high-frequency ventilators commercially available in the United States for use in newborn infants. The LifePulse high-frequency jet ventilator (HFJV, Bunnell Inc., Salt Lake City, UT); the SensorMedics 3100A (SensorMedics Inc, Yorba Linda, CA), a high-frequency oscillatory ventilator (HFOV); and the Infant Star (InfraSonics Inc., San Diego, CA), a device which has been characterized as either a high-frequency flow interrupter (HFFI) or an HFOV. In Canada and Europe, several other types of HFOV are available, including the German made Dräger Babylog with HFV option, the British SLE 2000, and the French Dufour OHF 1. In Japan, the Hummingbird oscillator is widely used.

The Bunnell LifePulse HFJV delivers short pulses of heated and humidified gas at high velocity to the upper airway trough a narrow injector lumen in the LifePort adapter. This is a special 15-mm endotracheal tube adaptor that eliminates the previous need for reintubation with a triple lumen endotracheal tube. Pulses of high-velocity gas stream down the center of the airway, penetrating through the dead-space gas, which simultaneously moves outward along the periphery of the airway. Enhanced molecular diffusion probably plays an important role in the gas exchange occurring in the distal airways and alveoli. A pressure sensor placed in the patient box close to the LifePort adapter measures proximal airway pressure. The measured airway pressure is used to servo-control the driving gas pressure and maintain the desired peak inspiratory pressure. A conventional ventilator is used in tandem with the Life Pulse and serves as a source of bias gas flow and generates positive end-expiratory pressure (PEEP). When desired, it also provides intermittent sigh breaths in the form of background intermittent mandatory ventilation (IMV) breaths, typically at a rate of 2 to 10 breaths per minute. The amplitude of the HFJV breaths is determined by the difference between the jet peak inspiratory pressure and the conventional ventilator PEEP.

The SensorMedics 3100A HFOV generates a quasisinusoidal pressure wave with a diaphragm driven by an electromagnet. By varying the power applied to the magnet, both the excursion of the diaphragm and the frequency at which it moves can be adjusted. The sinusoidal pressure wave that is generated by the diaphragm is transmitted through the airways to the alveoli. The HFOV breaths are characterized primarily by their frequency; their amplitude (usually measured as "Δ pressure" at the hub of the endotracheal tube); and the mean airway pressure (also measured at the hub of the endotracheal tube). All three of these parameters can be independently adjusted. In addition, the bias flow and

inspiratory:expiratory ratio can be adjusted, although their adjustment is not a key part of the ventilatory strategy for most patients on HFOV.

The InfraSonics Infant Star is designed around microprocessor-controlled solenoids that open and close at high frequencies. The opening and closing of these solenoids generates a pulse of high-velocity gas, which is transmitted down the airways. The pulse of gas also leads to a small recoil in the ventilator circuit that leads to an active expiratory phase, similar to that caused by the movement of the diaphragm in HFOV. The amplitude of the expiratory phase is significantly smaller than the amplitude of the inspiratory phase, however, in contrast to the SensorMedics HFOV where the inspiratory and expiratory amplitudes are similar. In many ways, the InfantStar is a hybrid device with attributes of both HFJV and HFOV. Unlike HFJV, however, the pulses of gas are delivered at the airway opening without being accelerated to a high velocity by passage through a narrow orifice. The jet (venturi) effect that causes the pulses of gas generated by HFJV to stream down the center of the airway through the dead-space gas in the large airways is not produced.

The different mechanisms by which these three devices generate high-frequency breaths lead to some intrinsic differences in their function. Both the Bunnell and the InfraSonics devices allow high-frequency breaths to be combined with conventional ventilation, whereas the SensorMedics HFOV can deliver only high-frequency breaths. The SensorMedics oscillator is almost always used with a 1:2 inspiratory:expiratory ratio, whereas the Bunnell is typically used with a 1:6 ratio, and the InfraSonics with an approximately 1:5 ratio. These differences in inspiratory:expiratory ratios may play an important part in determining the relative efficacy and complications of the devices in different diseases. Additionally, these characteristics lead to different optimal frequencies for these devices in any given clinical situation.

PHYSIOLOGY OF HIGH-FREQUENCY VENTILATION

Although there are significant differences in the mechanisms by which these devices cause gas exchange to occur, there are also substantial similarities in how they function. With all three devices, the volume of individual breaths are near, or even less than, dead-space volume. Additionally, gas exchange partly occurs by enhanced molecular diffusion resulting from increased mixing of gases in the airways. The exact mechanisms by which this high-frequency mixing occurs has been most thoroughly studied with HFOV. The mechanisms, which include bulk flow, Pendelluft, Taylor-type dispersion, and radial diffusion, are beyond the scope of this article, and have been elegantly described in the classic paper by Chang.[6] In simplest terms, one can think of these small, rapid breaths as shaking the gas in the airways and the alveoli, causing extremely efficient mixing between the fresh gas delivered to the upper airway and the gas at the alveolar surface.

High-frequency devices, like other ventilators, are designed to improve both oxygenation and ventilation. As with other ventilators, the factors affecting oxygenation and

ventilation are interrelated, but distinct. In most neonatal lung diseases, the primary problem causing hypoxemia is diffuse atelectasis, which leads to ventilation-perfusion mismatch and intrapulmonary shunting. As mean airway pressure is increased, the degree of atelectasis is decreased and ventilation-perfusion matching is improved. In general, increasing mean airway pressure with any high-frequency device results in improved oxygenation. With the SensorMedics HFOV, mean airway pressure is adjusted directly. With the Bunnell and the InfraSonics devices, mean airway pressure is affected by multiple factors including end-expiratory pressure, inspiratory pressure, inspiratory:expiratory ratio, and the superimposed conventional breaths, without the ability to set the mean airway pressure directly.

The relationship between ventilation (CO_2 removal) and ventilator settings is more complex for HFV than it is for conventional ventilation. With conventional ventilation, which relies on bulk flow of gas to remove CO_2 from the alveoli, CO_2 removal is proportional to alveolar minute ventilation (i.e., the product of respiratory frequency [rate] and tidal volume [$f \times V_T$]). With HFV, however, CO_2 is removed largely by the extremely efficient mixing of gas in the airways, also referred to as *enhanced diffusion*. With all HFV devices, CO_2 removal is roughly proportional to the product of HFV frequency and the square of the HFV tidal volume ($f \times V_T^2$). This relationship between CO_2 elimination and the square of tidal volume has been validated in numerous animal models.[2] [58] [60] In practical terms, it means that small adjustments in HFV amplitude (usually measured as Δ P) or tidal volume have a large effect on CO_2 elimination. Consequently, for most patients, CO_2 elimination is relatively frequency-independent and is controlled primarily by adjusting HFV amplitude. With the SensorMedics HFOV, amplitude is set directly. With the Bunnell HFJV and the InfraSonics HFFI devices, HFV amplitude is the difference between the independently-adjusted PEEP and peak inspiratory pressure (PIP).

An important difference between HFV devices and conventional ventilators is the relationship between the pressure amplitude measured at the hub of the endotracheal tube and the pressure amplitude that is delivered to the alveoli. With conventional ventilators operating at relatively low frequencies (e.g., < 40 to 60 breaths per minute), gas exchange occurs almost entirely by bulk flow (convection). In this situation, pressure applied at the airway opening is fully transmitted from the upper airway to the alveoli. As rates increase (e.g., to 75 to 150 breaths minute), however, with a proportional decrease in inspiratory and expiratory time, there is insufficient time within the respiratory cycle for the pressure to equilibrate fully between the upper airway and the alveoli. This is the mechanism for the gas trapping or inadvertent PEEP, which is seen at high rates with conventional ventilation. With HFV, this attenuation of the pressure amplitude between the upper airway and the alveoli becomes extreme. Gas exchange occurs predominantly by enhanced diffusion and the pressure amplitude or volume delivered to the alveoli is significantly less than the amplitude measured at the airway opening. As frequency increases, this attenuation of transmitted pressure becomes more pronounced. This is the reason that increasing the frequency of HFOV, with a concomitant decrease in inspiratory and expiratory time, decreases the amplitude of the pressure wave at the alveoli, and decreases CO_2 elimination. With the Bunnell HFJV or with the InfraSonics device, where

HFV inspiratory time is fixed and is independent of HFV frequency, excessively high frequencies can cause air-trapping when expiratory time becomes insufficient to achieve complete exhalation. This results in CO_2 retention and impairment of venous return because of increased intrathoracic pressure. Because of the inherent differences in the way in which gas delivery is accomplished, the optimal frequencies for HFJV are somewhat lower than those for HFOV.

With each patient and device, it is important to chose a frequency that achieves optimal gas exchange without air trapping. The optimal range of frequencies is dependent on both the size of the patient and the patient's intrinsic lung mechanics.[29] In general, the smaller the patient, the higher the optimal frequency, and vice versa. The most important aspect of lung mechanics in determining optimal frequency is the time constant, which equals the product of dynamic compliance and airway resistance ($C_{dyn} \times R_{aw}$). In general, patients with short time constants (low lung compliance or low airway resistance) can be ventilated effectively at higher frequencies than those with longer time constants (high lung compliance or high airway resistance). Unfortunately, there is no simple way to calculate ideal frequencies for each of the HFV devices for an individual patient; one must rely both on clinical experience and trial-and-error adjustments.

ANIMAL STUDIES OF HIGH-FREQUENCY VENTILATION

There are a wealth of data from animal studies dating back 20 years that suggest that in diseases primarily characterized by atelectasis, HFV leads to better lung inflation and less alveolar and airway damage than does conventional tidal ventilation.[12] [28] This has been demonstrated in both preterm animals and in animal models of surfactant deficiency and lung injury induced by saline lavage. Most of the animal studies have used HFOV, rather than HFJV or HFFI. Many of these results, however, can probably be generalized to include all HFV devices, as long as a similar strategy designed to optimize lung volume is used. Several key studies, in a variety of animal models, are summarized in Table 1 .

TABLE 1 -- SELECTED ANIMAL STUDIES OF PULMONARY EFFECTS OF HFV

Author and Year	Animal Model	Results
Hamilton et al, 1983	Lavaged rabbit	HFOV reduced pulmonary damage, decreased hyaline membranes, and improved gas exchange
Quan et al, 1984	Lavaged rabbit	HFJV improved gas exchange but did not improve histologic appearance of the lung
deLemos et al, 1987	Premature baboon	HFOV decreased

TABLE 1 -- SELECTED ANIMAL STUDIES OF PULMONARY EFFECTS OF HFV

Author and Year	Animal Model	Results
		barotraumas and increased lung expansion
McCulloch et al, 1988	Lavaged rabbit	HFOV with high alveolar volume decreased lung injury
Meredith et al, 1989	Premature baboon	HFOV improved gas exchange and decreased morphologic changes in the lung
deLemos et al, 1989	Premature baboon	Early HFOV use improved lung morphology, decreased edema and hyaline membranes
Niblett et al, 1989	Lavaged rabbit	HFOV led to normalization of pressure-volume curves
Kinsella et al, 1991	Premature baboon	HFOV improved oxygenation without decreasing cardiac output
Jackson et al, 1991	Monkey	HFOV improved gas exchange and decreased edema
Suzuki et al, 1992	Lavaged rabbit	HFOV had best results when initiated early using volume recruitment
Froese et al, 1993	Lavaged rabbit	HFOV with high-volume strategy improved surfactant effect
Jackson et al, 1994	Lavaged monkey	HFOV and surfactant replacement were synergistic
Yoder et al, 2000	Premature baboon(long-term ventilation)	Improved lung mechanics to 28 d, less inflammation, more uniform lung inflation

High-Frequency Ventilation and Surfactant-Deficient Lungs

Data from the late 1980s and early 1990s suggested that, rather than being simply a technique for rescuing patients with severe lung disease, early use of HFOV (and

presumably other forms of HFV) is actually protective, and leads to less severe histologic evidence of respiratory distress syndrome than does conventional ventilation. Meredith et al[44] used a premature baboon model of neonatal RDS to compare effects of HFOV instituted immediately following birth of the animal with the effects of conventional ventilation. All animals ventilated with conventional IMV had histologic findings of RDS, whereas only one animal in the HFOV group had such findings. Platelet activating factor, an inflammatory mediator that may be involved in lung injury, was elevated in all IMV animals, whereas only the HFOV animals with RDS demonstrated this elevation. Pressure-volume curves obtained on the lungs of all animals were markedly better in the HFOV group, compared with the tidal ventilation group. deLemos et al[13] subsequently used the same preterm baboon model to study the effect of instituting HFOV immediately after birth compared with instituting it after 3 hours of conventional IMV or treating animals only with IMV. Air leak developed in nearly half of the animals initially treated with IMV, but in none of the animals that were begun on HFOV immediately after birth. Ranking the clinical course of the animals by ability to wean ventilator settings and fraction of inspired oxygen (F_{IO_2}), the authors assessed early HFOV as having the best outcome, IMV followed by HFOV as intermediate, and IMV only as having the worst outcome. Histologic examination of the lungs when the animals were sacrificed at 24 hours of age also suggested that the animals treated with HFOV from birth had the least lung damage and the most normal-appearing histology.

Although some of the early work with HFV emphasized the potential advantage of using HFV to support ventilation with a low mean airway pressure, there is now a great deal of data suggesting that one of the key advantages of HFV is the ability to use relatively high mean airway pressures safely. For example, McCulloch et al[43] demonstrated better gas exchange, preservation of normal lung mechanics, and improved histologic appearance in saline-lavaged rabbits ventilated with HFOV at high lung volumes, compared with those on HFOV with low lung volume. The authors concluded that maintenance of alveolar volume is a key mechanism in the prevention of lung injury. The use of a strategy that includes lung volume recruitment, or volume optimization, seems to be an essential part of the HFV management of diseases characterized by atelectasis.[17] [18] [32] [40] [52]

Although the initial studies of HFV emphasized the role of HFV in decreasing lung injury in a surfactant-deficient animal, there is also evidence that HFV is superior to conventional ventilation in animals treated with surfactant.[33] This suggests that there is a role for clinical use of HFV, even in an era of routine surfactant treatment for preterm infants with RDS. A recent 28-day ventilation study in premature baboons demonstrated modest benefits in terms of lung mechanics, histologic appearance, and decreased inflammation in animals treated with HFOV.[66] Chronic lung disease similar to that of human infants, however, developed in both HFOV and conventionally ventilated animals. HFOV-treated animals did not seem to be protected from the decreased alveolization, which is typical of the sort of neonatal chronic lung disease (CLD) commonly seen in extremely preterm infants.

High-Frequency Ventilation and Other Lung Diseases

In addition to the studies on the role of HFV in animal models of respiratory distress syndrome (RDS), there are several studies of the effects of HFV in other conditions. Relevant for neonatologists are studies comparing HFV and conventional ventilation in animal models of meconium aspiration. The results are somewhat contradictory, with some studies showing apparent advantages of HFV and others showing no differences. These conflicting results are likely from differences in both the ventilatory strategies and the animal models used. Mammel et al[42] found no advantage of HFJV in a feline model of aspiration using HFJV at a relatively high frequency immediately after instillation of meconium. They noted difficulty with both ventilation and oxygenation, and documented elevated pulmonary artery pressures and pulmonary vascular resistance in the HFJV group. These findings are consistent with air-trapping secondary to airway obstruction and inadequate expiratory time. Trindade et al[55] also compared IMV with HFJV with a low airway pressure strategy in a meconium aspiration model, and showed no differences in gas exchange, lung mechanics, or hemodynamic variables.

In contrast, Keszler et al[39] studied both HFJV and HFJV combined with low-rate IMV in an infant canine model of meconium aspiration and found improved ventilation and oxygenation at lower mean and peak airway pressures, particularly in the animals ventilated with HFJV combined with low-rate IMV. There were no adverse hemodynamic effects of HFJV and no elevation of pulmonary vascular resistance. In contrast to the Mammel et al[42] and Trindade et al[55] studies, Keszler et al[37] used a slightly more dilute mixture of meconium; allowed the animals to stabilize for 30 minutes on conventional ventilation; suctioned the trachea before the onset of ventilation; and used a slower HFJV rate (i.e., longer expiratory time). The combined HFJV animals had significantly lower histologic lung injury scores, compared with the tidal ventilation group. The benefit of superimposed conventional breaths is probably the result of improved alveolar recruitment, made necessary by the fact that the meconium aspiration led to surfactant inactivation.

Wiswell et al[62] investigated the effects of four different ventilators on gas exchange and lung histology in newborn piglets and reported that animals ventilated with HFJV or with HFFI had significantly fewer histologic abnormalities than did those ventilated with conventional IMV. More recently, in a very elegant study, Wiswell et al[63] compared the effects of surfactant therapy with both HFJV and conventional ventilation on ventilator variables, gas exchange, and lung histology in a piglet model of meconium aspiration syndrome. Disappointingly, they were unable to demonstrate benefit of surfactant therapy or of HFJV, compared with conventional ventilation.

In combination, these studies suggest that there may be a role for HFV in the treatment of infants with aspiration syndromes, but that specific clinical circumstances and strategies used may uniquely affect the effectiveness of this approach. By extrapolation, one can assume that there may be a role for HFV in other disease states characterized by atelectasis.

CLINICAL TRIALS OF HIGH-FREQUENCY VENTILATION FOR INFANTS WITH RESPIRATORY DISTRESS SYNDROME

Despite the wealth of information on the advantages of HFV in animal models of RDS, the data from controlled clinical trials in infants are relatively sparse and have yielded inconsistent results. There have been 14 prospective, randomized clinical trials of HFV versus conventional ventilation for the treatment of premature infants with RDS. These trials and their pulmonary outcomes are summarized in Table 2 .

TABLE 2 -- PULMONARY OUTCOMES OF CONTROLLED TRIALS OF HFV IN PREMATURE INFANTS

Author and Year	N	Study Population	Results
HiFi, 1989	673	Respiratory failure, 750–2000 g (mean 1100 g)	HFOV did not improve outcome
Carlo et al, 1990	42	RDS, 1000–2000 g (mean 1420 g)	HFJV did not improve outcome
Keszler et al, 1991	144	RDS complicated by PIE, ≥750 g (mean 1336 g)	HFJV accelerated resolution of PIE; no decrease in CLD
Clark et al, 1992	83	RDS, ≤1750 g (mean 1100 g)	HFOV-only decreased CLD; HFOV × 72 hours followed by conventional ventilation did not decrease CLD
HiFO, 1993	176	Severe RDS, ≥500 g(mean 1739 g)	HFOV decreased incidence of new air leaks compared with conventional ventilation; no difference in CLD
Ogawa et al, 1993	92	Respiratory failure, 750–2000 g (mean 1200 g)	HFOV did not improve outcome
Wiswell et al, 1996	73	Severe RDS, ≤32 wk, >500 g (mean = 954 g)	HFJV did not improve outcome (no difference in air leaks, or CLD)
Gerstmann et al,	125	RDS, ≤35 wk (mean	HFOV improved

TABLE 2 -- PULMONARY OUTCOMES OF CONTROLLED TRIALS OF HFV IN PREMATURE INFANTS

Author and Year	N	Study Population	Results
1996		1510 g)	survival without CLD; reduced surfactant needs
Keszler et al, 1997	130	RDS, 700–1500 g ≤36 wk(mean 1020 g)	HFJV reduced incidence of CLD at 36 wk PCA and need for home oxygen; no decrease in air leaks
Rettwitz-Volk et al, 1998	96	RDS, <32 wk (mean 1100 g)	HFOV did not improve outcome
Plavka et al, 1999	43	RDS, 500–1500 g (mean 836 g)	HFOV did not reduce CLD at 30 d, but did reduce it at 36 wk
Thome et al, 1999	284	RDS, 24–30 wk, mean wt. 880 g	HFFI was associated with more air leaks and did not decrease CLD
Moriette et al, 2001	273	RDS, 24–29 wk (mean 985 g)	HFOV reduced need for surfactant, but did not decrease CLD
NVSG 2001	500	RDS, 601–1200 g, <4 h	HFOV decreased age at extubation, increased survival without CLD

CLD = Chronic lung disease; HFOV = high-frequency oscillatory ventilator; HFJV = high-frequency jet ventilator; RDS = respiratory distress syndrome; PIE = pulmonary interstitial emphysema; HFFI = high-frequency flow interrupter.

Rescue Trials

Two of the large clinical trials were aimed at determining the role of HFV in the treatment of infants with severe, established RDS.[30] [34] These late or rescue trials were performed before the introduction of routine surfactant replacement for the treatment of RDS, and examined a population that is not frequently seen today. The multicenter trial of HFJV by Keszler et al[34] focused on infants with RDS complicated by pulmonary interstitial emphysema. Consequently, the age at randomization was relatively high

(mean = 44 hours), and all of the infants had severe lung disease. HFJV led to faster and more frequent resolution of pulmonary interstitial emphysema. When crossover in infants who were failing conventional ventilation is accounted for, survival was improved with the use of HFJV (65% versus 47%, $P<0.05$). Gas exchange was also improved with HFJV, and there was a modest trend toward less CLD with HFJV (50% versus 67%).

The HiFO study was conducted on infants with severe RDS to determine if HFV would decrease the development or progression of air leaks.[30] These infants all had severe lung disease at the time of study entry, and were approximately 1 day old. The authors concluded that HFOV, using the SensorMedics ventilator and the lung recruitment ventilation strategy advocated by Froese[17] provided effective ventilation, improved oxygenation, and reduced the incidence of new air leak in infants with severe RDS. There was no difference, however, in the rate of progression or resolution of existing air leak.

Early Intervention Trials

More controversial than the role of HFV in patients with established severe RDS is the question of whether there is a role for the use of HFV as the primary treatment of preterm infants. As with many other aspects of HFV, the results are contradictory, probably because of the differences between devices, strategies, and populations in the clinical trials.

The National Institutes of Health–funded HiFi trial was the first controlled clinical trial of HFV, and also the largest to date.[29] The study showed no improvement in pulmonary outcome for infants in the HFV arm. This trial used an HFOV device that has never been released for use in the United States, and which provided a symmetric sinusoidal pressure waveform and a set inspiratory time of 50%. Patients were eligible for entry until they had received 12 hours of conventional ventilation. Lung recruitment was not a consistent part of the HFOV ventilation strategy. Possibly confounding this study was the fact that when the study was begun, in the mid 1980s, HFV was a new technique in most study centers. Unfortunately, because of the large numbers of enrolled infants, the results of the HiFi trial have a strong negative impact on meta-analyses of HFV.

The small HFJV trial by Carlo et al[5] also used a device that is not commercially available, and failed to show any benefit to the HFJV-treated patients. This trial, however, included only 42 patients and did not have the statistical power to show anything but extreme differences in outcome. Its negative conclusion is clearly susceptible to type II statistical error for smaller, yet clinically important differences in outcome.

Results from the single-center study by Clark et al[8] were dramatically different from those of the HiFi trial. Eighty-three infants were randomized to one of three groups: (1) HFOV only, (2) conventional ventilation only, or (3) HFOV for 72 hours followed by conventional ventilation. The incidence of CLD was significantly lower in the HFOV-only group (10% HFOV, 38% conventional ventilation), but not in the group that was treated with HFOV for 72 hours followed by conventional ventilation. This study used

the SensorMedics device with a 1:2 I:E ratio, and was carried out by a group of investigators with extensive experience in the application of HFOV. Lung recruitment was a key part of the HFOV strategy used in this study.

Ogawa et al[47] subsequently reported a smaller multicenter trial in premature infants with respiratory failure. Using the same HFOV equipment as in the HiFi trial but using a lung volume recruitment strategy, these investigators found that 9% of infants in the HFOV group developed CLD compared with 13% of those in the tidal ventilation group. This difference was not statistically significant, possibly because of the small sample size and low incidence of CLD in the control group.

The more recent studies by Gerstmann et al[23] and by Keszler et al[38] are of particular interest because they are multicenter studies that both suggest that HFV, when initiated early and used as the primary mode of ventilation, can decrease the incidence of CLD. Unlike the preceding studies, they were conducted in an era of routine use of exogenous surfactant to treat RDS. Gerstmann et al[23] found that the combined end point of survival without CLD at 30 days was 77% in the HFOV group and 56% in the IMV group ($P < 0.02$). They also found a markedly decreased need for exogenous surfactant in the HFOV group, and significantly reduced overall hospital costs for the HFOV group. Keszler et al[38] described a reduction in CLD at 36 weeks corrected age (20% versus 40%) and less need for home oxygen therapy (6% versus 23%) in infants treated with HFJV. A trial in which patients were enrolled during the same period as the previous two studies (early to mid-1990s) was that of Wiswell et al.[64] In this investigation, 73 mechanically ventilated premature infants were randomized to early treatment with either conventional ventilation or HFJV. The trial was halted for safety reasons. At 36 weeks' postconceptual age there were no differences in the incidence of CLD between groups (conventional ventilation 19%, HFJV 15%) or in the combined end point "survival without bronchopulmonary dysplasia" (conventional ventilation 69%, HFJV 57%). Of note, the population of infants enrolled in the latter trial consisted of premature infants of lower mean birth weight (954 g) and mean gestational age (26.8 weeks) than the aforementioned successful trials of Gerstmann et al[23] (1510 g, 30.9 weeks) and Keszler et al [38] (1020 g, 27.3 weeks).

Several more recent trials have assessed pulmonary outcomes using HFV. The rather small study of Plavka et al[48] used the SensorMedics HFOV device in a group of extremely premature infants with a mean birth weight of 836 g and showed a decreased incidence of CLD at 36 weeks. As with the Gerstmann et al[23] study, these investigators used a lung recruitment (optimal volume) strategy. On the other hand, the recent large study by Rettwitz-Volk et al[51] has not documented an advantage of HFOV, despite relatively early institution. There are a number of differences between the design of the Gerstmann et al,[38] Plavka et al,[48] and the Rettwitz-Volk et al[51] studies that could account for this. The HFOV devices studied were different, with the Gerstmann et al[38] and Plavka et al[48] groups using the SensorMedics, whereas the Rettwitz-Volk et al[51] group used a piston oscillator with a fixed 1:1 I:E ratio that was fitted into a standard circuit of a Stephan SHF 3000 conventional ventilator. The oscillatory frequencies of 15 to 20 Hz used in the Rettwitz-Volk et al[51] study were somewhat higher than those typically used with the SensorMedics in the United States today. Perhaps most importantly, in contrast

to the Gerstmann et al[38] and Plavka et al[48] studies, the Rettwitz-Volk et al[51] investigators may have used a strategy that did not optimally recruit lung volume. This is suggested by the fact that the distending airway pressures used with the oscillator were no higher than those in the conventional ventilation group (approximately 8.5 cm H_2O at entry, declining to approximately 7 cm H_2O at 6 hours and 6 cm H_2O by 24 hours).

Thome et al[53] recently reported the results of the first large prospective trial using the InfraSonics HFFI device in infants with RDS. In this study of 284 infants with RDS, the gestational ages ranged from 24 to 30 weeks and the mean birth weight was 880 g. HFFI did not improve outcome, as measured by failure of assigned therapy, survival, and development of CLD. In fact, those treated with HFFI were significantly more likely to develop air leaks. Another recent multicenter trial was that of Moriette et al.[45] Two hundred seventy-tree infants, 24 to 29 weeks' gestation, were randomly assigned at approximately 2.5 hours of age to receive HFOV with the Dufour OHF 1 oscillator or to synchronized conventional ventilation with the Draeger Babylog 8000 ventilator. The OHF 1, a piston oscillator, was used with a 1:1 I:E ratio and frequency of 15 Hz. An optimal volume strategy was used. Fewer infants in the HFOV group required repeated doses of surfactant, but there was no difference in pulmonary outcome (survival without supplemental oxygen at 28 days). It is impossible to say whether the apparent lack of effect in these latter recent trials resulted from differences in the patient population, the HFV device used, the strategy used, or whether HFV truly makes a difference when compared with synchronized conventional ventilation.

The largest clinical trial of HFV since the HiFi trial was the recently completed Neonatal Ventilation Study Group, trial which randomized 500 infants from 601 to 1200 g to HFOV or synchronized intermittent mandatory ventilation (SIMV) by 4 hours of age.[11] Infants in the HFOV arm were managed with the SensorMedics 3100A using a lung recruitment strategy, whereas infants in the control arm were treated with time-cycled, pressure-limited, SIMV using a strategy that emphasized careful control of tidal volumes within a narrow range. Infants in both groups were managed with standardized ventilation protocols that emphasized maintaining normal lung volumes, permissive hypercapnia, and aggressive weaning to extubation. Preliminary data from this study reveal that infants in the HFOV arm were successfully extubated at an earlier age (17.4 ± 16.6 versus 24.2 ± 19.2 days, $P < 0.0002$), and were more likely to be alive and free of respiratory support by 36 weeks' corrected age (57% versus 47%, $P < 0.05$).

CLINICAL TRIALS SUPPORTING OTHER INDICATIONS FOR HIGH-FREQUENCY VENTILATION

It is the authors' impression that, in many nurseries, HFV is used as frequently to treat diseases other than RDS as it is to treat preterm infants. Despite this widespread use of HFV to treat these conditions, there are few large trials of HFV outside of the preterm population.

Rescue of Potential Extracorporeal Membrane Oxygenation Candidates

In a multicenter controlled trial 79 term infants who were potential candidates for extracorporeal membrane oxygenation (ECMO) Clark et al[9] randomized patients to HFOV or conventional ventilation. Twenty-four (60%) of 40 patients initially assigned to conventional ventilation met treatment failure criteria compared with 17 (44%) of 39 assigned to HFOV (no significant difference). Of the 24 patients in whom conventional ventilation failed, 15 (63%) responded to HFOV. In contrast, only 4 (23%) of the 17 in whom HFOV failed responded to conventional ventilation ($P = 0.03$). Interpretation of this study is difficult because of its crossover design and relatively small size. A similar single-center study of HFJV versus conventional ventilation for near-ECMO patients by Engle et al[15] enrolled only 24 infants. HFJV improved gas exchange and showed a trend toward less frequent need for ECMO. None of the nine HFJV survivors had CLD, compared with 4 of 10 conventionally ventilated survivors. These differences were not statistically significant, but the study was extremely small.

Bronchopleural and Tracheoesophageal Fistula

Gonzales et al[26] demonstrated a substantial decrease in leak though chest tubes in a group of infants with bronchopleural fistula when they were switched from conventional ventilation to HFJV.[25] Similarly, improved gas exchange and reduced flow through tracheoesophageal fistula was demonstrated by Donn et al[14] and by Goldberg et al.[24] There are other case reports and small series, particularly from the early days of HFV, which demonstrate the advantages of HFV in patients with gross air leak such as this. It is widely believed that the advantage of HFV in these patients may be in the ability to ventilate them with extremely short inspiratory times.

Abdominal Distention

Increased intra-abdominal pressure results in upward pressure on the diaphragm, reduces diaphragmatic excursion, and results in decreased compliance of the respiratory system in newborns with acute intra-abdominal disease, such as necrotizing enterocolitis, or postoperatively in infants with gastroschisis, omphalocele, or diaphragmatic hernia. Large tidal volume ventilation further exacerbates the hemodynamic compromise normally caused by positive pressure ventilation. Fok et al[16] documented improved gas exchange with HFOV in eight such infants who were failing conventional ventilation. Keszler et al[36] likewise reported improved ventilation and hemodynamic variables in 20 similar patients using HFJV. The role of HFV in supporting patients with increased intra-abdominal pressure is further supported by an animal trial by Keszler et al[35] that demonstrated improved gas exchange and better hemodynamics with HFJV in an animal model of increased intra-abdominal pressure.

Combined Therapy

Kinsella et al[41] were the first to recognize the potential of HFV to optimize delivery of inhaled agents, such as nitric oxide, as a result of its ability to optimize lung inflation. In

a large multicenter trial, they demonstrated that in infants with significant parenchymal lung disease HFOV in combination with inhaled nitric oxide was more effective than inhaled nitric oxide delivered with conventional ventilation. In the latter trial, however, there was no control group that was conventionally ventilated alone without inhaled nitric oxide.

SAFETY OF HIGH-FREQUENCY VENTILATION

One of the key controversies surrounding HFV is related to concerns about a possible role of HFV as a risk factor for the development of severe intracranial hemorrhage (ICH) or periventricular leukomalacia (PVL). Potential mechanisms include pulmonary hyperexpansion or high intrathoracic pressure leading to cerebral venous congestion, and hypocarbia resulting from the ease with which HFV usually is able to ventilate the patient.

Animal studies have not explored the impact of HFV on the central nervous system, at least in part, because of the fact that few good animal models of ICH-PVL exist. Raju et al[50] studied HFOV effects on intracranial pressure in healthy adult cats and concluded that intracranial pressure dynamics were not affected. More recently, Walker et al[61] used newborn lambs to evaluate intracranial pressure and cerebral perfusion pressure during HFOV and tidal ventilation while incrementally increasing mean airway pressure. They found no significant differences between groups.

The conclusions of the published controlled clinical trials of HFV in human infants regarding this question are summarized in Table 3 . Many of these trials only assessed for the presence of ICH and not PVL. Moreover, most trials did not standardize the number or frequency of neuroimaging studies, nor were results from such studies interpreted by masked reviewers. Of the four HFJV trials, two showed no increase in ICH,[34] [38] whereas the trial by Wiswell et al[64] found a substantial increase in the incidence of both severe ICH and PVL. In the latter study, the mean age at randomization was 7 hours, and the incidences of ICH and cystic PVL were two of the primary outcome variables evaluated. Severe ICH occurred in 22% of the conventional ventilation infants and 41% of HFJV infants; cystic PVL occurred in 6% of conventionally ventilated infants and 31% of HFJV infants. Unlike virtually all other trials, a comprehensive number of standardized, sequential cranial sonograms were performed (essentially one or more per week). Moreover, a radiologist with special expertise in interpretation of neonatal ultrasounds and masked to study group interpreted the scans. This study was stopped by the Data Monitoring and Safety Committee because of the high incidence of deaths, ICH, and PVL in the HFJV patients.[64] In contrast, Keszler et al[34] found no difference in ICH in their earlier sample of very sick infants with pulmonary interstitial emphysema, or in their more recent trial in infants with RDS.[38] This latter study differed from the Wiswell et al[64] trial in that an HFV strategy aimed at optimizing lung volume was specified. Unfortunately, there were protocol deviations from this therapy in 44% of the HFJV

population (HFJV infants were not treated with optimal lung volumes), a fact the complicates the interpretation of the results.

TABLE 3 -- NEUROLOGIC OUTCOMES OF CONTROLLED TRIALS OF HFV IN PREMATURE INFANTS

Author and Year	Ventilator Type	N	Results
HiFi, 1989	HFOV	673	Significant increase in both severe ICH and PVL
Carlo et al, 1990	HFJV	42	No difference in ICH *
Keszler et al, 1991	HFJV	144	No difference in ICH *
Clark et al, 1992	HFOV	83	No difference in ICH *
HiFO, 1993	HFOV	176	Signficant increase in severe ICH *
Ogawa et al, 1993	HFOV	92	No difference in ICH *
Gerstmann et al, 1996	HFOV	125	No difference in ICH or PVL
Wiswell et al, 1996	HFJV	73	Significant increase in both severe ICH and cystic PVL
Keszler et al, 1997	HFJV	130	No difference in ICH or PVL
Plavka et al, 1997	HFOV	43	No difference in ICH or PVL
Rettwitz-Volk et al, 1998	HFOV	96	No difference in ICH or PVL
Thome et al, 1999	HFFI	284	No difference in ICH *
Moriette et al, 2001	HFOV	273	Significant increase in severe ICH
NVSG, 2001	HFOV	500	No difference in severe ICH or PVL

HFOV = High-frequency oscillatory ventilator; ICH = intracranial hemorrhage; PVL = periventricular leukomalacia; HFJV = high-frequency jet ventilator; HFFI = high-frequency flow interrupter.

*Did not check for periventricular leukomalacia.

It is probably not possible to draw definite conclusions about the relationship of HFJV to ICH-PVL from these HFJV trials. The relatively small sample size in the study by Wiswell et al[64] gives rise to the possibility of a type II statistical error (even though post hoc calculated power was 70%). Although multiple obvious confounders, such as hypocarbia, were considered in the analysis, perhaps a larger sample size might demonstrate a role for this or other factors. A previous publication from the same institution that included several patients from the randomized trial and other patients treated with HFJV did demonstrate that prolonged exposure to severe hypocapnia was a predictor for neuroimaging abnormalities in HFJV patients.[65] Earlier anecdotal data from Thomas Jefferson University described a dramatically increased incidence of PVL and cerebral palsy in conventionally ventilated preterm infants exposed to marked hypocapnia,[20] findings that are consistent with other studies.[4] [19]

The 1991 HFJV rescue trial of Keszler et al[34] showed no difference in the incidence of ICH. This trial, however, enrolled patients up to 7 days of age and pre-enrollment cranial sonograms were not obtained on all patients. Because ICH is most likely to occur within the first 48 to 72 hours of life, it is possible that most ICH in both groups might have occurred before study entry, making it possible to miss a treatment effect. In their more recent trial, Keszler et al[38] showed no overall increase in ICH or PVL, but there was an interesting difference between two subgroups of HFJV patients. Even though a well-defined optimal volume strategy of HFJV was prescribed, the 44% of the HFJV patients were not managed this way; rather, they were ventilated using a traditional low-pressure strategy of HFJV, similar to that used in the Wiswell et al[64] study. Although this protocol deviation detracted somewhat from the quality of the study, it provided an opportunity to compare the two strategies of HFJV. This post hoc analysis must be interpreted with caution, but it demonstrated a much lower incidence of ICH-PVL in the optimal volume subgroup (9%) compared with the low-pressure HFJV group (33%) and the conventional group (28%). The low-pressure subgroup of HFJV had significantly lower $PaCO_2$, compared with both conventional ventilation and the optimal volume HFJV subgroup during the first 24 hours (mean values of 32 to 35 versus values of 37 to 40 mm Hg).[38]

Interpretation of the results from the 10 trials evaluating HFOV and HFFI are similarly complex. The HiFi trial suggested that HFOV is associated with an increased incidence of ICH or PVL.[29] Variations in ventilation management and HFOV experience across study sites in the HiFi trial may have contributed to the large intercenter differences in ICH, and have led some to question the validity of these results.[3] Possible inadvertent hyperventilation could also explain some of these findings, but unfortunately the blood gas data were not reported. The constellation of the complications observed in the HFOV patients (more air leaks, ICH, PVL hypotension, and poor gas exchange leading to crossover) is also consistent with inadvertent air-trapping and increased intrathoracic pressure. The latter may occur when using a 1:1 I:E ratio and a frequency of 15 Hz, as was done in that study.[22] [31] [54] This increased intrathoracic pressure might not have been

detected, because pressure is not measured distal to the endotracheal tube. In the HiFO study, infants were severely ill and entered into the study at an average age of nearly 24 hours.[30] Pre-enrollment cranial sonograms, however, were obtained on nearly all infants. Infants with pre-existing severe ICH were not entered into the trial. There was no difference in the incidence of grade I or II ICH between groups before study entry (12% HFOV, 11% tidal ventilation). Although infants in the HFOV groups had a significant increased incidence of severe ICH during the trial, overall numbers were small (6 of 81 HFOV versus 2 of 84 tidal ventilation). It is of interest, however, that Pa_{CO_2} was lower in the HFOV patients during the initial 24 hours compared with conventionallyventilated patients (mean values of 38 to 40 versus 40 to 42 mm Hg).

By contrast, the early study of Clark et al[8] and recent studies of Gerstmann et al,[23] Rettwitz-Volk et al,[51] Plavka et al,[48] and Thome et al[54] all found no increase in the incidence of ICH or PVL in the HFV group. The trial by Gerstmann et al[23] found that for tidal ventilation the incidence of severe ICH was 11% compared with 4% for HFOV, whereas PVL incidence was 6% versus 8%. The latter is a trial of large premature infants (mean birth weight 1510 g). Additionally, the recently completed Neonatal Ventilation Study Group trial comparing HFOV with SIMV in 601- to 1200-g infants found no difference in the incidence of severe ICH or cystic PVL.[11] Nevertheless, the results of these latter investigations are somewhat contradicted by the recently published study of Moriette et al.[45] Despite using an optimum volume strategy of HFOV there was a significant increase in severe ICH (14% for conventional ventilation versus 24% for HFOV, OR 1.94, CI 1.05 to 3.60, $p<0.05$). The difference was no longer significant when presence of maternal hypertension was factored in. On the other hand, when infants who received only conventional ventilation were compared with those who received HFOV either by primary assignment or as a result of crossover, severe ICH was significantly more common in the latter group (9.5% versus 24.9%, $p<0.002$). The mean Pa_{CO_2} in the conventional ventilation group was significantly higher than that of the HFOV group 6 hours after randomization (39 versus 35 mm Hg, $P<0.001$). The relevance of this latter finding is unclear, however, because there was no difference in the incidence of PVL.

The authors cautiously suggest that HFV, as it is currently used in most institutions in the United States, does not increase the risk for ICH, severe ICH, or PVL. Based on the available information, it seems prudent to use the optimal volume strategy with HFV and pay careful attention to avoiding inadvertent hypocapnia.

CHOICES OF HIGH-FREQUENCY VENTILATION

Decisions about the use of HFV come down to two main questions: (1) which patients should be treated with HFV and, (2) if multiple types of HFV are available, which type should be used in a given patient? The second question is the easier to answer. Despite their mechanical and physiologic differences, all three of the HFV devices available in the United States (Bunnell LifePulse HFJV, SensorMedics HFOV, and InfraSonics HFFI) have some similarities. All three of them provide the advantage of using extremely small

tidal volumes to avoid the larger cyclic volumes changes that are required with conventional ventilation. All the devices can be used with a strategy aimed at optimizing lung volume. The outdated concept that HFJV does not achieve good oxygenation stemmed from the emphasis on low airway pressures that became a standard approach to the use of HFJV. This strategy was appropriate for the treatment of airleak, which was the predominant use of HFJV in the early days, but is not an inherent feature of HFJV. The user's familiarity with the operation of the particular device and attention to the choice of a ventilatory strategy that is best suited to the patient's pulmonary condition is probably more important than the differences between the devices in most patients. Because of these similarities, all three of these devices can be used to treat most patients.

There are several important differences, however, between the devices. In broad terms, the InfraSonics HFFI device is the least powerful of the three, and is less well suited to managing large-term infants with severe lung disease. In contrast, the SensorMedics device is the most powerful, and can be easily used to ventilate both infants and pediatric patients. Another major difference between the devices is their inspiratory:expiratory ratio. There is some evidence that one of the key elements in treating pulmonary interstitial emphysema is a short inspiratory time. In this area, the LifePulse and InfraSonics devices with their approximately 1:6 or 1:5 inspiratory:expiratory ratio may have an advantage over the SensorMedics with its 1:2 inspiratory:expiratory ratio. Also, because of the manner in which the inspiratory gas flow travels down the center of the airway at high velocity with little lateral pressure on the airway wall, HFJV could be more suitable for ventilation of infants with disruptions of the large airways. It is the authors' opinion that in centers with access to both HFJV and HFOV, HFJV is the preferred device for treatment of severe air leak. Finally, it should be noted that compared with HFOV or HFJV, there are far fewer publications (trials or anecdotal data) assessing effectiveness of the InfraSonics HFFI.

The question about which patients should be treated with HFV is somewhat more complex, partially because of the differing results of the clinical studies, and partially because we now have available therapeutic options, such as exogenous surfactant and other ventilatory modes that were not available when the early studies of HFV were conducted (e.g., patient-triggered ventilation, volume and pressure support ventilation, and so forth). Although there is a wide variation in how the published data are interpreted and, consequently, in how HFV is used in the United States, the authors believe that several general conclusions can be drawn.

First, HFV may be preferable to conventional ventilation for the treatment of the following air leak syndromes: pulmonary interstitial emphysema and bronchopleural or tracheoesophageal fistula. The data from animal studies, case reports, the HFJV data of Gonzales et al,[26] and the Keszler et al[34] controlled trial all support this conclusion. The authors believe that any patient with such air leaks should be treated with HFV until at least 24 hours after the air leak has resolved. In institutions where multiple modes of HFV are available, there are theoretical advantages to using the LifePulse HFJV device rather than the SensorMedics HFOV device, given the former's extremely short inspiratory times and the evidence from a controlled clinical trial. The InfraSonics HFFI

device has similar short inspiratory time, but there are no published data supporting its efficacy treating air leaks.

Second, HFV may be preferable to conventional ventilation for patients with severe uniform non-RDS lung disease, such as pneumonia or persistent pulmonary hypertension. The data from animal studies and from the HiFO trial support the argument that use of small tidal volumes at high frequencies allows more uniform lung inflation and causes less damage to severely noncompliant lungs than do the larger tidal volumes of conventional ventilation. As a rough guideline, the authors believe that most patients with uniform lung disease who require inspiratory pressures above 20 to 25 cm H_2O or F_{IO_2} above 0.4 to 0.6 could benefit from HFV.

Third, HFV may also be useful in patients with severe nonuniform disease, such as aspiration syndromes. The studies by Wiswell et al[62] [63] using the piglet model of meconium aspiration syndrome[62] [63] and that of Keszler et al[37] using a canine model suggest that HFV causes less damage to these lungs than does conventional ventilation. Although HFV management of aspiration syndromes has not been well studied in humans, anecdotal experience suggests that at least some infants with severe nonhomogeneous disease do well with HFV. It is important to recognize that meconium aspiration syndrome is a heterogeneous syndrome that evolves over time. Airway obstruction may predominate in the early stages. Although HFJV may facilitate mobilization of secretions, the presence of debris in the airways may interfere with efficient ventilation. In infants in whom the surfactant inhibitory effect of meconium predominates and in the subsequent inflammatory stages of meconium aspiration syndrome, HFV may be quite effective. The authors suggest that patients with severe aspiration syndromes should be considered for a trial of HFV. Nevertheless, it is critical to emphasize that infants with these disorders are at high risk for air trapping (and air leaks) and that air trapping is more likely to occur with HFV. When HFV is used in infants with aspiration syndromes, slower frequencies should be used because of the longer time constants, to minimize the chance of air-trapping.

Fourth, HFV may have a role in patients with pulmonary hypoplasia, such as is seen with diaphragmatic hernia. Although this has not been well studied, some clinicians believe there is improved gas exchange with HFV in such infants. Clearly, it is reasonable to assume that the ideal method of ventilating these small lungs is with a high-frequency device that allows one to maintain adequate gas exchange while using extremely small tidal volumes.

Fifth, HFV could be a preferred mode of ventilation when severe chest wall restriction or upward pressure on the diaphragm from abdominal distention interferes with tidal ventilation and causes hemodynamic embarrassment. Although there are no peer-reviewed publications supporting this contention, the preliminary data look promising.[35] [36]

Sixth, the authors believe that a trial of HFV is appropriate in term infants with severe respiratory failure who are potential candidates for ECMO. Patients with significant parenchymal lung disease who require inhaled nitric oxide therapy may benefit from the

improved lung aeration afforded by HFV to optimize the delivery of the therapeutic agent at the alveolar level.[41]

Finally, an argument can be made that HFV may be the preferred mode of ventilation for preterm infants with RDS. The enthusiasm for the routine use of HFV as a primary mode of ventilation must be tempered, however, by the lingering concerns about the reports of increased brain injury and the ease with which inadvertent hypocapnia can occur.

WEANING AND HIGH-FREQUENCY VENTILATION

One area of HFV management that has not been well studied is the question of when (or whether) patients on HFV should be weaned to conventional ventilation. The only clinical trial that directly addressed this issue was the one by Clark et al,[8] which demonstrated that infants who were treated with HFOV alone did better than infants who were changed from HFOV to conventional ventilation after 72 hours. Although there are some advantages to having a patient on conventional ventilation (e.g., tidal volumes can be accurately measured, fewer chest radiographs may be needed, it may be easier for the parents to hold the infant), there are few compelling physiologic reasons to change infants from HFV to conventional ventilation during the acute stage of the disease. The authors have successfully managed patients on both HFOV and on HFJV for up to several weeks, and have been routinely extubating patients directly from HFV. In general, the authors suggest continuing HFV until extubation or for as long as the patient is continuing to improve. For the occasional patient who is no longer improving at more than 2 to 4 weeks of age, a trial of an alternative mode of ventilation is indicated. At this stage of the lung disease, increased airway resistance is likely to have developed and this may render HFV less effective. If the decision is made to continue HFV, lower frequencies may be appropriate in these patients to accommodate the longer time constants. Data regarding the effectiveness of HFV in infants with chronic lung disease compared with conventionally managed controls are lacking.

VENTILATORY STRATEGIES OF HIGH-FREQUENCY VENTILATION

The way in which HFV is used has evolved over time, both because our understanding of the interaction of the ventilator and the pulmonary pathophysiology has increased and because the patient population treated today is different than it was 15 years ago. In the early days of HFV, the technique was used for rescue of patients failing conventional ventilation and was seen primarily as a means of reducing airway pressure and the lung injury associated with overdistention. With the elegant studies by the groups led by deLemos et al[13] [40] and Froese et al,[17] [18] [43] and subsequently confirmed by a number of controlled clinical trials, has come the understanding that the greatest advantage HFV offers is the ability to achieve uniform lung expansion and to support a patient at higher

mean airway pressures without excessive tissue stretching and overexpansion. With the growing understanding that avoiding atelectasis is as important as avoiding overdistention, the general approach to most patients treated with HFV (and with conventional ventilation) emphasizes lung recruitment and maintenance of the distending airway pressure above the critical closing pressure. This should be equally true for all types of HFV, although the concept has been adopted more slowly by the users of HFJV.

When HFOV was first used in the mid-1980s on patients with severely noncompliant lungs, frequencies of 15 Hz (900 breaths per minute) were usually used without causing air trapping. Now that HFOV is frequently being used on patients who are less critically ill and, consequently, have better lung compliance and longer time constants, however, frequencies of 6 to 10 Hz are more commonly used. Similarly, the frequencies used with HFJV are now more likely to be around 5 to 7 Hz (300 to 420 breaths per minute), rather than 7 to 10 Hz, as may be appropriate in infants with very short time constants. In general, the larger the patient and the more compliant the lungs, the lower the frequency with HFV.

The following guidelines for the use of the SensorMedics HFOV and the LifePulse HFJV are based on the authors' clinical experience with these devices, and on the input from other clinicians who have used them over the past two decades. They represent an approach to maintain lung volumes within the narrow ideal range between atelectasis and overdistention, and to aggressively wean patients from mechanical ventilation. These guidelines address the typical premature infant with predominantly atelectatic lung disease. As with all guidelines, they work most of the time and for most of the patients, but not for all patients or all of the time. It is critical that the clinician carefully assess an individual patient's pulmonary pathophysiology and determine which mechanisms are predominantly responsible for the gas exchange defect (atelectasis, airleak, airway obstruction, air trapping, decreased pulmonary blood flow, and so forth). Only then can one design the optimal ventilation strategy that is appropriate for a particular patient at this time. The evolution of the disease process must be re-evaluated frequently and the ventilatory strategy adjusted accordingly.

Target Ranges for Blood Gas Values

The target range for oxygen is based on postductal pulse oximetry, with the ideal value for most patients being a S_{PO_2} of approximately 88% to 96%. Assuming modest permissive hypercapnia is not harmful, the Pa_{CO_2} should be approximately 40 to 55 mm Hg in most patients without pulmonary interstitial emphysema, gross air leak, hyperinflation, or chronic changes on chest radiograph. Higher Pa_{CO_2} values may be tolerated in patients with these complications. In most patients, arterial pH should be at least 7.25, although pH in the range of 7.20 to 7.25 may be acceptable. Nevertheless, one must emphasize the dearth of controlled trial data supporting the concept that Pa_{CO_2} values greater than 55 mm Hg and pH values of 7.20 to 7.25 are not harmful. Additionally, at lower pH, the Pa_{O_2} has to be higher to maintain adequate oxygen saturation.

Target Ranges for Lung Inflation

It is difficult accurately to measure lung volumes on HFV, but they can be approximated from chest radiographs. Evaluation of lung inflation should take into account the position of the diaphragms, the relative flatness of the diaphragms, whether the heart silhouette is narrow, and evidence of regional differences in lung density. As a first approximation, however, the position of the hemidiaphragms is a reasonable marker for lung inflation. The authors have found that it is effective to define ideal lung inflation for most patients as of the top margin of the dome of the right hemidiaphragm located between the bottom of the eighth rib and no more than midway between the ninth and tenth ribs. For patients with pulmonary interstitial emphysema or bronchopleural fistula, the ideal lung inflation is defined as one rib less than for patients without air leak.

Initial High-Frequency Ventilation Settings

Initial settings on the SensorMedics HFOV include inspiratory time of 33%; mean airway pressure at least 2 cm H_2 O greater than patient was receiving on conventional ventilation (this is a correction for an HFOV pressure measurement artifact); frequency of 8 to 10 Hz; and amplitude (ΔP) adjusted based on adequacy of chest wall movement or transcutaneous P_{CO_2} monitoring. The LifePulse HFJV is typically started at a frequency of 7 Hz (higher or lower rate may be appropriate, depending on time constants) and inspiratory time of 0.02 seconds. The PEEP is increased to the range of 6 to 8 cm H_2 O, depending on the degree of atelectasis and oxygen requirement. Historically, reluctance to use adequate PEEP has hindered the effectiveness of HFJV in RDS. It should be remembered, however, that one of the key advantages of HFV is the ability to use higher mean and end-expiratory pressure safely, because of the lower ΔP. Background IMV at a rate of two to five breaths per minute is initiated with an inspiratory time of 0.4 to 0.5 seconds. The PIP is initially maintained at the original value on both the HFV and conventional ventilation to achieve alveolar recruitment. within a few minutes, however, the improved lung expansion commonly results in better lung compliance. If this occurs, the PIP should be lowered promptly by 10% to 20% to avoid overventilation. Further weaning of PIP should be guided by adequacy of chest wall movement or transcutaneous P_{CO_2} monitoring. The inexperience of the authors and the lack of published data regarding the InfraSonics HFFI, precludes recommending initial settings when it is used.

Adjusting Settings to Optimize Lung Inflation-Oxygenation

In the early stages of uncomplicated RDS, hypoxemia is the result of ventilation-perfusion mismatch and is readily corrected when optimal lung expansion is reached. In such patients the adequacy of oxygenation is an excellent guide to the need for mean airway pressure. This strategy consists of progressive increases in mean airway pressure (directly with HFOV, indirectly by raising PEEP in HFJV and HFFI) until adequate oxygenation occurs and F_{IO_2} less than 0.35 is reached. If this is not readily achieved with several mean airway pressure increases of 10% to 20%, further changes in mean airway pressure should be guided by chest radiographs. Radiographic assessment of lung volume is also essential in patients with more complex pulmonary pathophysiologies. With this

approach, the authors caution that there is potential to increase intrathoracic pressure to a degree that interferes with venous return and decreases cardiac output.

Because optimizing lung inflation is a key part of the strategy of HFV, patients on HFV usually need fairly frequent chest radiographs during the initial phase of their course, and at least daily chest radiographs when they become more stable. The magnitude of mean airway pressure adjustment should be proportional to the degree of underinflation or overinflation. The usual increment is 10% of the initial value. Particularly at the lower portion of the lung inflation curve, relatively small changes in mean airway pressure can result in significant changes in lung inflation. If a small change in mean airway pressure results in a significant change in F_{IO_2}, a chest radiograph should be obtained to evaluate lung inflation. It is important to recognize that once atelectasis occurs as a result of excessive weaning, it becomes necessary to re-expand the lungs by some form of volume recruitment maneuver. With HFOV the mean airway pressure must be transiently increased at least 2 to 3 cm H_2O above the most recent setting. This is because the critical opening pressure must be reached before recruitment occurs. With HFJV, the background IMV rate produces intermittent sigh breaths, which open the alveoli on inspiration. It is critical, however, to increase the PEEP sufficiently to maintain this recruitment.

Adjusting Settings Based on Pa_{CO_2}

At a given HFV frequency, Pa_{CO_2} is primarily determined by HFV amplitude. Once a frequency appropriate for the infant's size and clinical condition is chosen, changes in frequency should be reserved for situations in which there is reason to believe that the patient's condition has changed in a way that impacts the time constants. Adjustment of amplitude should be guided by adequacy of chest wall movement or transcutaneous P_{CO_2} monitoring, in addition to blood gases. The magnitude of amplitude changes should be proportional to the desired change in Pa_{CO_2}. The usual range is 5% to 10%. Repeated small adjustments may be preferable to infrequent large changes.

Weaning

Assuming the goal is actively to wean the patient toward extubation, patients who are stable within the target ranges for lung inflation and blood gases should be weaned on a regular basis. It is important to balance the desire to wean these patients with the need to avoid causing atelectasis by dropping below the critical closing pressure of the lungs. The F_{IO_2} should be weaned first in response to good oxygenation. In most cases, mean airway pressure should not be weaned until the F_{IO_2} is less than 0.4. Attention to these principles is particularly important with the LifePulse and the InfraSonics device where weaning peak inspiratory pressure to decrease amplitude also results in a decrease in mean airway pressure, which may not be desirable. This inadvertent drop in mean airway pressure can be avoided by simultaneously increasing the PEEP as needed to maintain a constant mean pressure. In general, the authors have found that with stable patients in the first week or two of their disease, an attempt should be made to wean mean airway pressure or

amplitude at least every 6 to 12 hours. Patients with chronic disease may not tolerate this aggressive a weaning schedule.

Very low-birth weight infants can usually be extubated as soon as they have been weaned to mean airway pressure of 6 to 8 cm H_2O and F_{IO_2} less than 0.25 to 0.30. Older, larger infants can be extubated from somewhat higher settings.

SUMMARY

High-frequency ventilation has become established as an effective treatment modality in a variety of clinical situations. The laboratory and clinical investigations of these techniques have contributed tremendously to our understanding of the pathophysiology of respiratory failure and the important concept of maintaining adequate lung volume. Clinicians have come to appreciate better the factors involved in lung injury and the potential for damage to distant organs.

The place of HFV in the therapeutic armamentarium will undoubtedly continue to evolve in the years to come. Of particular interest is the advent of advanced modes of fully synchronized and volume-targeted conventional mechanical ventilatory modes, along with the trend to use smaller tidal volumes and higher levels of PEEP with conventional ventilation. With these developments there seems to be a certain convergence of HFV and tidal ventilation that is the logical result of our improved understanding of respiratory pathophysiology. The available controlled trials of HFV versus tidal ventilation do not clearly differentiate whether improved outcomes are the result of HFV per se, or a reflection of the effects of optimizing lung volume, a benefit that may not be unique to HFV.[25] [56] [57]

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