High-frequency Ventilation: Evidence-based Practice and Specific Clinical Indications

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High-frequency Ventilation: Evidence-based Practice and Specific Clinical Indications

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Dr Keszler disclosed that he has served as a consultant to and received a research grant from Draeger Medical, Lubeck, Germany, and is an unpaid consultant to Bunnell, Inc, Salt Lake City, Utah.

Objectives

After completing this article, readers should be able to:

1. Summarize the basic rationale for the use of high-frequency ventilation (HFV).
2. Summarize the findings of the most important clinical trials of HFV.
3. Described the basic characteristics of the various HFV devices available.
4. Explain potential problems with interpreting the results of multiple clinical trials comparing HFV with standard therapy.
5. Make well-informed choices in the use of HFV.

Introduction

Chronic lung disease (CLD) remains the leading cause of prolonged hospitalization as well as significant respiratory and developmental handicap in neonates. Consequently, many efforts in modern neonatal care have focused on methods that might reduce the incidence of this dreaded complication. High-frequency ventilation (HFV) appeared to hold much promise in this area because of its ability to provide excellent gas exchange with lower pressure amplitude. During the 1990s, both high-frequency oscillatory ventilation (HFOV) and high-frequency jet ventilation (HFJV) became firmly established as important tools in the therapeutic armamentarium of neonatologists, based primarily on their potential for reducing the incidence of CLD and effectiveness in treating air leak, respectively. However, despite more than 20 years of laboratory and clinical research, the role of HFV remains controversial. At one end of the spectrum, a minority of clinicians uses HFV as a primary mode of ventilation; at the other extreme are those who view it strictly as a rescue technique, to be used only when conventional ventilation has failed. Most clinicians appear to have an intermediate degree of enthusiasm, using HFV in an early rescue mode for infants who are at high risk of complications with conventional ventilation or who have developed air leak, even though they are maintaining adequate gas exchange on conventional ventilation.

Abbreviations

BPD:	bronchopulmonary dysplasia
CLD:	chronic lung disease
ECMO :	extracorporeal membrane oxygenation
HFOV:	high-frequency oscillatory ventilation
HFJV:	high-frequency jet ventilation
HFFI:	high-frequency flow interruptor
HFV:	high-frequency ventilation
ICH:	intracranial hemorrhage
MAS:	meconium aspiration syndrome
PIP:	peak inspiratory pressure
PEEP:	positive end-expiratory pressure
PVL:	periventricular leukomalacia
RDS:	respiratory distress syndrome

Types of HFV

Three types of high-frequency ventilators are widely in the United States for newborns: the Life Pulse® high-frequency jet ventilator (Bunnell Inc, Salt Lake City, Utah), the SensorMedics 3100A® high-frequency oscillatory ventilator (SensorMedics Inc, Yorba Linda, Calif.), and the Infant Star® (InfraSonics Inc, San Diego, Calif.) high-frequency flow interrupter (HFFI). With the recent withdrawal of support for the Infant Star® device, the field has effectively narrowed to two, although the Bronchotron® flow interrupter (Perucssionaire Corp, Sandpoint, Idaho), a pneumatically operated transport ventilator based on an early 1980s design, has gained some popularity. However, published data about its safety and efficacy are lacking at this time. In Canada, Europe, and Japan several other types of HFOV devices are available.

High-frequency ventilators share many characteristics, although there are some important differences in the mechanism of gas delivery. Their basic characteristics are illustrated in Figure 1.

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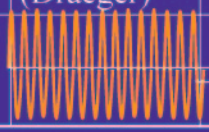
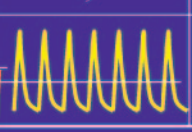
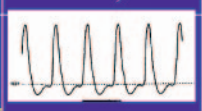
	HFOV	HFJV	HFFI
HF pulses generated by	Piston or other means	Pinch valve, Injector cannula	Solenoid valve
I : E ratio	1:1 or 1:2	1:4 to 1:8	1:3 to 1:6
Opt. Freq.	8 to 15 Hz	5 to 10 Hz	8 to 12 Hz
Ability to superimpose a sigh	No (SM) Yes (Draeger)	Yes (able to interrupt HF or not)	Yes (with interruption of HFV)
Waveform			

Figure 1. Types of high-frequency ventilation devices and their basic characteristics. HFOV=high-frequency oscillatory ventilation, HFJV=high-frequency jet ventilation, HFFI=high-frequency flow interruptor, I:E=inspiratory-to-espiratory.

The 3100A HFOV device generates a quasisinusoidal pressure wave with an electromagnetically driven diaphragm. Varying the power applied to the magnet allows adjustment of the excursion of the diaphragm and the frequency at which it moves. The sinusoidal pressure wave is propagated down the airways to the alveoli, albeit with much dampening of the pressure amplitude. The frequency, amplitude, and mean airway pressure can be adjusted independently. In addition, the bias flow and inspiratory-to-expiratory ratio can be adjusted, although this usually is not necessary.

The HFJV device delivers short pulses of heated and humidified gas at high velocity to the upper airway through a narrow injector lumen in a special endotracheal tube adaptor that eliminates the need for reintubation with a triple-lumen endotracheal tube, as previously required. Pulses of heated and humidified high-velocity gas stream down the center of the airway, penetrating through the dead-space gas, which simultaneously swirls outward along the periphery of the airway. Enhanced molecular diffusion probably plays an important role in gas exchange that occurs in the distal airways. A pressure sensor placed in the "patient box" close to the adapter measures proximal airway pressure, which is used to servocontrol the driving gas pressure and maintain the desired peak inspiratory pressure (PIP). A conventional ventilator is used in tandem with the HFJV device to generate positive end-expiratory pressure (PEEP) and, when desired, provides 2 to 5 breaths/min of intermittent sigh breaths. The amplitude of the HFJV breaths is determined by the difference between the jet PIP and the PEEP controlled by the conventional ventilator.

The Infrasonics HFFI device was designed around microprocessor-controlled solenoids that open and close at high frequencies, generating a pulse of gas, which is transmitted down the airways. A small negative pressure deflection is generated by the device, similar to that caused by the movement of the diaphragm in HFOV, although the amplitude of the "expiratory" phase is much smaller than the amplitude of the inspiratory phase, in contrast to HFOV, in which the inspiratory and expiratory amplitudes are more similar. Thus, in many ways, the HFFI device is a hybrid with attributes of both HFJV and HFOV. However, unlike HFJV, the pulses of gas are delivered at the airway opening without being accelerated to a high velocity by passage through a narrow orifice. Thus, the jet 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 does not occur.

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

Gas Exchange During HFV

Although there are important differences in the mechanisms of gas exchange among the devices, there are also significant similarities in how they function. With all three devices, the "breaths" are near, or even less than,

dead-space volume, and gas exchange occurs in part by enhanced molecular diffusion resulting from increased mixing of gases in the airways. In simplest terms, the small, rapid pulses/oscillations "stir" the gas in the airways, causing extremely efficient mixing between the fresh gas delivered to the upper airway and the gas at the alveolar surface. Details of the mechanisms by which such high-frequency mixing occurs are beyond the scope of this article; they have been described in the classic paper by Chang and, more recently, by Venegas and by Pillow. The factors that affect oxygenation and ventilation are interrelated, but possibly are more distinct than with conventional ventilation.

Oxygenation

In most neonatal lung diseases, the primary problem causing hypoxemia is diffuse atelectasis, which leads to ventilation-perfusion mismatch and intrapulmonary right-to-left shunt. As mean airway pressure is increased, more alveoli are recruited, and ventilation-perfusion matching is improved. Thus, increasing mean airway pressure with any high-frequency device generally improves oxygenation. With the HFOV device, mean airway pressure is adjusted directly. With the HFJV device, similar to conventional ventilation, mean airway pressure is affected by multiple factors, including end-expiratory pressure, inspiratory pressure, inspiratory-to-expiratory ratio, and superimposed sigh breaths.

CO_2 Elimination

With conventional ventilation, which relies on bulk flow of gas to remove CO_2 from the alveoli, CO_2 removal is proportional to the product of respiratory frequency (rate) and tidal volume ($f \times V_T$). However, with HFV, CO_2 is removed largely by the extremely efficient mixing of gas in the airways (enhanced diffusion). With all HFV devices, CO_2 removal is roughly proportional to the product of frequency and the tidal volume squared ($f \times V_T^2$). In practical terms, this means that small adjustments in pressure amplitude or changes in lung compliance (and, hence, tidal volume) have a large effect on ventilation. Consequently, CO_2 elimination is relatively frequency-independent and is controlled primarily by adjusting HFV amplitude. With the HFOV device, amplitude is set directly. With the HFJV device, HFV amplitude is the difference between the independently adjusted PEEP and PIP.

Frequency

For each patient and device, it is important to choose a frequency that achieves optimal gas exchange without air trapping. Because of the inherent differences in the way gas is delivered, the optimal frequencies for HFJV are somewhat lower than those for HFOV. The optimal range of frequencies depends on both the body size and intrinsic lung mechanics of the patient. 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 (the product of compliance and resistance). In general, patients who have short time constants (low lung compliance and low airway resistance) can be ventilated effectively at higher frequencies than those who have longer time constants (high lung compliance or high airway resistance). Unfortunately, there is no simple method of calculating ideal frequencies for each of the HFV devices for an individual patient; clinical experience and trial-and-error adjustments are required.

Clinical Trials of HFV for Infants Who Have Respiratory Distress Syndrome (RDS)

Despite the well-documented advantages of HFV in animal models of RDS, data from controlled clinical trials in infants have yielded inconsistent results. This may reflect, in part, the evolution of conventional ventilation and the addition of antenatal steroids and exogenous surfactant to available therapies. It is useful to evaluate clinical trials of HFV in the context of these therapeutic advances. Individual trial results, with emphasis on their unique methodologic issues, are summarized briefly in this article, rather than presenting a meta-analysis, because important differences in devices used, strategies employed, and patient populations tend to be obscured by pooling studies performed with many different devices and strategies over a span of 2 decades.

Presurfactant Era

The initial prospective trials of HFV occurred in the 1980s during the presurfactant, presynchronized ventilation era (Table 1). The largest of these studies was the National Institutes of Health-funded HiFi trial. The study not only failed to show any improvement in pulmonary outcome for infants in the HFV arm, but it was stopped early because of adverse effects in the HFOV arm (safety issues are discussed in a later section). This trial used an HFOV device that never has been released for use in the United States and that provided a symmetric sinusoidal pressure waveform and a set inspiratory time of 50%. Patients received up to 12 hours of conventional ventilation prior to entry. HFV was a new technique in most study centers, and lung recruitment was not a consistent part of the HFOV ventilation strategy.

Table 1. Pulmonary Outcomes of Controlled Trials of HFV in the Presurfactant, Presynchronized Ventilation Era

Author and Year	Number of Patients	Characteristics of Study Group	Results
HiFi, 1989	673	Respiratory failure, 750 to 2,000 g (mean, 1,100 g)	HFOV did not decrease CLD
Carlo 1990	42	RDS, 1,000 to 2,000 g (mean, 1,420 g)	HFJV did not decrease CLD
Keszler, 1991	144	RDS complicated by PIE, ≥750 g (mean, 1,336 g)	HFJV accelerated resolution of PIE, improved survival
Clark, 1992	83	RDS, ≤1,750 g (mean, 1,100 g)	HFOV decreased CLD compared with conventional ventilation
HiFO, 1993	176	Severe RDS, ≥500 g, (mean, 1,700 g)	HFOV decreased rate of new air leak compared with conventional ventilation
Ogawa, 1993	92	Respiratory failure, 750 to 2,000 g (mean, 1,200 g)	HFOV did not improve outcome (outcome excellent in both HFOV and CV groups)

HFV=high-frequency ventilation, HFOV=high-frequency oscillatory ventilation, CLD=chronic lung disease, RDS=respiratory distress syndrome, HFJV=high-frequency jet ventilation, PIE=pulmonary interstitial emphysema, CV=conventional ventilation

In contrast, the Clark study, published in 1992, demonstrated for the first time a reduction in bronchopulmonary dysplasia (BPD) with early intervention without adverse effects using HFOV and a well-defined lung recruitment strategy. This study used an HFOV ventilator with a 1:2 inspiratory-to-expiratory ratio and was conducted at a center that had extensive HFOV experience. Although very encouraging, the study results were received with some skepticism because of the relatively high incidence of BPD in the control arm.

The small HFJV trial by Carlo, which used a device that never was commercially available, failed to show any reduction in BPD. However, this trial 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.

Two of the large clinical trials during this era were "rescue" trials designed to address the role of HFV in the treatment of infants who had severe, established RDS. The multicenter trial of HFJV focused on infants who had RDS complicated by pulmonary interstitial emphysema. Thus, the age at randomization was relatively high (44 h), and all of the infants had severe lung disease. HFJV led to faster and more frequent resolution of interstitial emphysema. When crossover for infants who failed conventional ventilation was accounted for, survival improved with the use of HFJV (65% versus 47%, $P<0.05$). Gas exchange also improved with HFJV, and there was a modest trend toward less CLD with HFJV (50% versus 67%, P=NS).

The HiFO study examined infants who had severe RDS to determine if HFOV would decrease the development or progression of air leaks. The 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 lung recruitment strategy validated in animal studies provided effective ventilation, improved oxygenation, and reduced the incidence of new air leak in infants who had severe RDS. However, there was no difference in the rate of progression or in resolution of existing air leak.

Ogawa and associates subsequently reported a smaller multicenter trial in preterm infants who had respiratory failure. Using the same ventilator as the HiFi trial but with a lung volume recruitment strategy, they found no difference in BPD between the HFOV and the tidal ventilation group, possibly due to the small sample size and low incidence of CLD in the control group (13%). Surfactant was used in many, but not all patients.

Surfactant Era

The next group of studies took place after use of surfactant became routine, but before any advances in conventional ventilation equipment or techniques (Table 2)

Two large multicenter studies published in the mid-1990s suggested that both HFOV and HFJV, when initiated early and used with an appropriate ventilation strategy, can decrease the incidence of CLD. Gerstmann documented a survival rate without CLD at 30 days of 77% in the HFOV group and 56% in the conventionally ventilated group ($P<0.02$). He also reported a decreased need for exogenous surfactant and reduced overall hos-

Table 2. Pulmonary Outcomes of Controlled Trials of HFV During the Surfactant Era But Before Synchronized Ventilation

Author and Year	Number of Patients	Characteristics of Study Group	Results
Gerstmann, 1996	125	RDS, ≤35 wk (mean, 1,500 g)	HFOV improved survival without CLD, reduced surfactant needs, decreased hospital costs
Wiswell 1996	73	RDS, <33 wk, >500 g (mean, 945 g)	HFJV did not improve pulmonary outcome
Keszler 1997	130	RDS, ≤35 wk, 700 to 1,500 g (mean, 1,020 g)	HFJV reduced incidence of CLD at 36 wk corrected age and need for home oxygen

HFV=high-frequency ventilation, RDS=respiratory distress syndrome, HFOV=high-frequency oscillatory ventilation, CLD=chronic lung disease, HFJV=high-frequency jet ventilation

pital costs for the HFOV group. Duration of hospitalization did not differ between the groups, and 33% of infants in the HFOV group still required oxygen at the time of discharge. Similarly, we found 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 (Fig. 2). New air leaks occurred in 28% of HFJV patients compared with 35% of conventionally ventilated patients (*P*=NS). The infants in the HFJV trial were substantially smaller and less mature compared with the HFOV study (27.2 wk and 1,020 g versus 30.9 wk and 1,510 g). The incidence of CLD in the HFOV study was relatively high for such a relatively mature population, which possibly could be attributed to the higher altitude at which most of the infants were treated. The relevance of the HFOV study to the present population of micropreemies is unclear; most of such infants probably would be treated with continuous positive airway pressure today.

Disappointingly, a smaller HFJV study by Wiswell and colleagues not only failed to show any improvement in pulmonary outcomes, but it was stopped early because of adverse neurosonographic effects. These issues are discussed more fully in a subsequent section on safety of HFV.

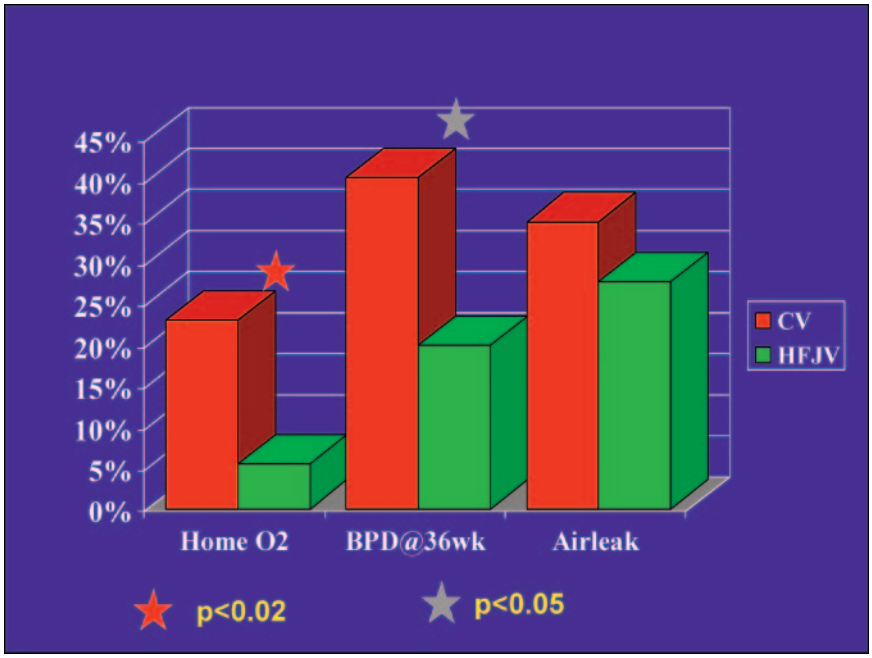


Figure 2. Major pulmonary outcomes of early intervention HFJV trial in preterm infants who had uncomplicated respiratory distress syndrome. CV=conventional ventilation, HFJV=high-frequency jet ventilation, BPD=bronchopulmonary dysplasia. Reprinted with permission from Keszler, et al. *Pediatrics*. 1997;100:593–599.

Modern Era (Routine Surfactant and Synchronized Ventilation)

The modern era of mechanical ventilation started in the late 1990s with widespread availability of synchronized mechanical ventilation and the introduction of more rapidly acting, possibly more effective surfactants. In more recent years, awareness of the possible value of a less aggressive approach to conventional mechanical ventilation has increased, although none of the published trials systematically employed what could truly be described as lung-protective strategies. With HFV now a maturing

Table 3. Pulmonary Outcomes of Controlled Trials of HFV During the Surfactant Era But Before Synchronized Ventilation

Author and Year	Number of Patients	Characteristics of Study Group	Results
Rettwitz-Volk, 1998	96	RDS, <32 wk (mean, 1,100 g)	HFOV did not improve outcome
Plavka 1999	43	RDS, 500 to 1,500 g (mean, 836 g)	HFOV reduced CLD at 28 d and 36 wk
Thome 1999	284	RDS, 24 to 30 wk (mean, 880 g)	HFFI did not improve outcome
Moriette 2001	273	RDS, 24 to 29 wk (mean, 986 g)	HFOV reduced need for surfactant, but did not improve pulmonary outcome
Courtney 2002 (NVSG)	498	RDS, 601 to 1,200 g (mean, 855 g), <4 h	HFOV decreased age at extubation, increased survival without CLD
Johnson 2002 (UKOS)	797	Needing ventilation, 23 to 28 wk, <1 h (mean, 853 g)	HFOV did not improve pulmonary outcome
Craft 2003	46	RDS, <1,000 g (mean, 726 g)	HFFI did not decrease CLD, trend to more air leak
Van Reempts 2003	300	RDS, GA <32 wk (mean, 1,195 g)	HFOV/HFFI did not improve pulmonary outcome

HFV=high-frequency ventilation, RDS=respiratory distress syndrome, HFOV=high-frequency oscillatory ventilation, CLD=chronic lung disease, HFFI=high-frequency flow interruptor, GA=gestational age

therapy, the hope was that definitive evidence of effectiveness could be established. Unfortunately, this has not been the case (Table 3).

The rather small HFOV study of Plavka and associates using an HFOV device in a group of extremely preterm infants who had a mean birthweight of 836 g documented a decreased incidence of CLD at 28 days and 36 weeks. As with the other successful HFOV studies, these investigators consistently used an optimal lung volume strategy and a 1:2 inspiratory-to-expiratory ratio.

The larger study by Rettwitz-Volk did not document an advantage of HFOV, despite relatively early institution of HFV, using a prototype piston oscillator that had a fixed 1:1 inspiratory-to-expiratory ratio. The oscillatory frequencies of 15 to 20 Hz were substantially higher than those typically used with HFOV today. Perhaps most importantly, in contrast to the Gerstmann and Plavka studies, the Rettwitz-Volk trial did not effectively recruit lung volume; 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 h and 6 cm H_2O by 24 h).

Thome and associates reported the results of the only large prospective trial using HFFI in 284 infants born at less than 30 weeks' gestation who had RDS (mean birthweight was 880 g). HFFI did not improve outcome, as measured by failure of assigned therapy, survival, and development of CLD, and, in fact, was associated with an increased incidence of air leak. It may not be a coincidence that the device has been withdrawn from production.

Another large multicenter trial using a unique HFOV device was published by Moriette and colleagues. A total of 273 infants, born at 24 to 29 weeks' gestation, were randomly assigned at approximately 2.5 hours after birth to receive HFOV or synchronized conventional ventilation. HFOV was provided by a piston oscillator that had a 1:1 inspiratory-to-expiratory ratio and a 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 improvement in pulmonary outcome (survival without supplemental oxygen at 28 d).

Two large multicenter trials designed to answer definitively the lingering questions of safety and efficacy were published simultaneously in the *New England Journal of Medicine* in 2002 and reached contrasting conclusions. In the Neonatal Ventilation Study Group (NVSG), 498 infants weighing 601 to 1,200 g were randomized by 4 hours after birth to HFOV and a lung recruitment strategy or to synchronized intermittent mandatory ventilation with 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. Infants in the HFOV arm were successfully extubated at an earlier age (13 versus 21 d, $P<0.001$) and were more likely to be alive and off all respiratory support by 36 weeks corrected age (56% versus 47%, $P<0.05$).

In contrast, the United Kingdom Oscillator Study (UKOS) did not demonstrate improved outcomes with HFOV, despite enrolling nearly 800 infants. A number of important differences between the two studies may explain the contrasting conclusions (Table 4). Although it is impossible to determine which of these differences may be primarily responsible for the discrepancy, it may be noteworthy that no published randomized trials have documented effectiveness of the HFOV device used in the UKOS study or any other oscillator that uses a fixed 50% inspiratory time. Additionally, the 1992 Clark study showed that the advantage of HFOV could be demonstrated only in the infants who remained on HFOV for 2 weeks or until extubation and not in those who were returned to conventional ventilation after 72 hours. Lack of extensive HFOV experience in some centers, absence of minimum severity of illness criteria, and lack of carefully defined weaning and extubation criteria are other important factors that differentiate the UKOS study from the NVSG trial.

Table 4. Comparison of the NVSG and UKOS Studies

	NVSG	UKOS
Study entry	<4 h after birth	<1 h after birth
Weight/age	601 to 1,200 g	23 to 28 wk
Severity of RDS	MAP >6, Fio_2 >0.25	All ventilated infants
HFOV strategy	Optimal volume	Optimal volume
CV strategy	Carefully defined	Not defined
Inspiratory-to-expiratory ratio	1:2	1:1
Weaning	On assigned mode for 2 wk or until extubation	Changed to CV at 3 to 4 d to wean

RDS=respiratory distress syndrome, MAP=mean airway pressure, HFOV=high-frequency oscillatory ventilation, CV=conventional ventilation

The most recent large trial was a single-center Belgian study published in 2003 by Van Reempts and associates. A total of 300 infants of less than 32 weeks' gestation were randomly assigned to receive HFV with HFOV (122 infants), HFFI (25 infants), or conventional mechanical ventilation. The mean birthweight was 1,195 g, and the mean gestational age was 28.7 weeks, indicating that these infants were much larger and more mature than those in all other recent studies. The investigators did not appear to use an effective volume recruitment strategy. Unlike with other trials in which volume recruitment was pursued aggressively, these investigators did not see any difference in Fio_2 between the HFV and conventional ventilation groups (both approximately 0.50 on day 1). The control group received synchronized ventilation with rapid rates, and attempts were made to minimize lung injury. This study also did not show any apparent benefit of HFV and may, despite its shortcomings, be the last large trial of elective HFV in preterm infants.

Clinical Trials Supporting Other Indications for HFV

In most newborn intensive care units, HFV commonly is used to treat diseases other than RDS. Despite its general acceptance for rescue treatment of a variety of conditions, few large trials of HFV unequivocally support these indications. Understandably, clinicians typically do not require as high a level of evidence for rescue interventions where current therapy is failing as they do for prophylactic use in infants who are likely to do well with conventional therapy.

Rescue of Potential Extracorporeal Membrane Oxygenation (ECMO) Candidates

In a multicenter randomized trial of 94 term infants who were meeting or nearing criteria for rescue treatment with ECMO, Clark and associates compared HFOV and best available conventional ventilation. Sixty percent of patients initially assigned to conventional ventilation met treatment failure criteria compared with 44% of those assigned to HFOV. Of the 24 patients in whom conventional ventilation failed, 15 (63%) responded to HFOV. In contrast, only 23% of patients who failed on HFOV responded to conventional ventilation (P=0.03). Interpretation of this study is made somewhat difficult by baseline differences in disease severity, its crossover design, and its relatively small size.

A similar single-center study by Engle and colleagues compared HFJV and conventional ventilation for 24 near-ECMO patients. HFJV significantly improved gas exchange and showed a trend toward less frequent need for ECMO. None of the nine HFJV survivors had CLD compared with four of 10 receiving conventional ventilation. These differences were not statistically significant, but the study was extremely small and, thus, susceptible to type II statistical error.

Pulmonary Interstitial Emphysema

The initial focus of intervention with HFJV was treatment of pulmonary interstitial emphysema. Consequently, the strategy developed for its use emphasized the lowest possible peak and mean airway pressures. The multicenter randomized trial of HFJV for the treatment of pulmonary interstitial emphysema (Keszler, et al, 1991) remains the best available evidence for the use of HFV in the treatment of existing air leak. No comparable HFOV study is available, although uncontrolled data suggest some effectiveness in this condition.

Bronchopleural and Tracheoesophageal Fistula

Gonzales and associates demonstrated a substantial decrease in leak through chest tubes in a group of infants who had bronchopleural fistula when they were switched from conventional ventilation to HFJV. Similarly, improved gas exchange and reduced flow through tracheoesophageal fistula was demonstrated by Goldberg and by Donn. Other case reports and small series, particularly from the early days of HFV, demonstrate the advantages of HFJV in patients who have gross air leak. It is widely believed that the advantage of HFJV in such patients may be in the ability to ventilate them with extremely short inspiratory times.

Abdominal Distention/Decreased Chest Wall Compliance

Increased intra-abdominal pressure results in upward pressure on the diaphragm, reduces diaphragmatic excursion, and decreases compliance of the respiratory system in newborns who have acute intra-abdominal disease such as necrotizing enterocolitis or postoperatively in infants who have gastroschisis, omphalocele, or diaphragmatic hernia. Large tidal volume ventilation exacerbates the hemodynamic compromise normally caused by positive pressure ventilation. Fok documented improved gas exchange with HFOV in eight such infants who were failing conventional ventilation. We also reported improved ventilation and hemodynamic variables in 20 similar patients using HFJV. The role of HFV in supporting patients who have increased intra-abdominal pressure is supported further by a study in which we demonstrated improved gas exchange and better hemodynamics with HFJV in an animal model of increased intra-abdominal pressure.

Combined Therapy

Kinsella was the first to recognize the potential of HFV for optimizing delivery of inhaled agents such as nitric oxide because of its ability to optimize lung inflation. In a large multicenter trial, he demonstrated that in infants who had significant parenchymal lung disease, HFOV in combination with inhaled nitric oxide was more effective than inhaled nitric oxide delivered with conventional ventilation.

Chronic Lung Disease

Several recent uncontrolled reports suggest a possible role for HFJV in very preterm infants who have CLD and are doing poorly on HFOV or conventional ventilation. These infants have very poorly supported, dilated small airways that are prone to collapse and air-trapping. Overinflation, expiratory flow limitation at low lung volume, and heterogeneity of lung aeration are characteristic of such lungs, making effective and gentle mechanical ventilation very difficult. The possible benefit of HFJV is that it allows effective ventilation with very short bursts of gas flow that stream down the center of the airway, while maintaining the airways splinted open with adequate distending airway pressure and allowing for effective passive exhalation around the periphery. This is in contrast to HFOV, which is likely to exacerbate air trapping in this situation because of the active exhalation that tends to collapse the airways. The effectiveness of this approach is being tested in a prospective randomized trial. No specific recommendation can be made at this time.

Safety of HFV

A major continuing HFV controversy centers on its possible role in increasing the risk of severe intracranial hemorrhage (ICH) or periventricular leukomalacia (PVL). Potential mechanisms for such a relationship include pulmonary overexpansion and high intrathoracic pressure leading to cerebral venous congestion as well as hypocapnia resulting from the ease with which HFV typically eliminates CO_2.

Animal studies have provided limited information on the possible impact of HFV on the central nervous system, primarily because few good animal models of ICH/PVL exist. A study of the effects of HFOV on intracranial pressure in healthy adult cats concluded that intracranial pressure dynamics were not affected. In another study, no significant differences in intracranial pressures or cerebral perfusion pressures during both HFOV and tidal ventilation were seen in newborn lambs while incrementally increasing mean airway pressure.

The conclusions of published controlled clinical trials of HFV in human infants regarding this question are summarized in Table 5. Of the four HFJV trials, one was too small, the two large studies showed no increase in

Table 5. Neurologic Outcomes of Controlled Trials of HFV

Author and Year	Number of Patients	Ventilator Type	Results
HiFi, 1989	673	HFOV	Increased severe ICH and PVL
Carlo 1990	42	HFJV	No difference in ICH
Keszler, 1991	144	HFJV	No difference in ICH
Clark, 1992	83	HFOV	No difference in ICH
HiFO 1993	176	HFOV	Borderline increase in severe ICH
Ogawa, 1993	92	HFOV	No difference in ICH
Gerstmann, 1996	125	HFOV	No difference in ICH and PVL
Wiswell 1996	73	HFJV	Increased severe ICH and cystic PVL
Keszler 1997	130	HFJV	No difference in ICH and PVL
Plavka 1997	43	HFOV	No difference in ICH and PVL
Rettwitz-Volk 1998	96	HFOV	No difference in ICH
Thome 1999	284	HFFI	No difference in ICH
Moriette 2001	273	HFOV	Possible increase in severe ICH
Courtney 2002	498	HFOV	No difference in severe ICH and/or PVL
Johnson 2002	797	HFOV	No difference in ICH and/or PVL
Craft 2003	46	HFFI	No difference in severe ICH and/or PVL
Van Reempts 2003	300	HFOV/HFFI	No difference in severe ICH and/or PVL

HFV=high-frequency ventilation, HFOV=high-frequency oscillatory ventilation, HFJV=high-frequency jet ventilation, HFFI=high-frequency flow interruptor, ICH=intracranial hemorrage, PVL=periventricular leukomalacia

ICH, and the trial by Wiswell found a substantial increase in the incidence of both ICH and PVL. Severe ICH occurred in 22% of the conventionally ventilated infants and 41% of HFJV infants; cystic PVL occurred in 6% of tidal ventilation infants and 31% of HFJV infants. Unlike previous trials, a pediatric ultrasonographer masked to study group independently evaluated the cerebral ultrasonography scans. The Data Monitoring and Safety Committee stopped the study early because of the high incidence of ICH/PVL in the HFV patients. In contrast, we found no difference in ICH in our rescue study of very sick infants who had pulmonary interstitial emphysema or in the more recent trial of infants who had uncomplicated RDS. The latter study occurred concurrently and under a similar protocol to the Wiswell trial, with one key difference: our multicenter trial specified an HFJV strategy aimed at optimizing lung volume.

It is not possible to draw definite conclusions about the relationship of HFJV to ICH/PVL from these HFJV trials, but inadvertent hyperventilation in infants treated with the low-pressure strategy is the most likely explanation for the development of ICH/PVL. Although the incidence of hypocapnia was not statistically different between the two groups, a larger sample size might have demonstrated a role for this known risk factor. In fact, a subsequent publication that included patients from the randomized trial as well as other patients treated with HFJV at the same institution clearly demonstrated that prolonged exposure to hypocapnia was an independent predictor for neuroimaging abnormalities in patients receiving HFJV. Earlier published data from the same institution described a dramatically increased incidence of periventricular hemorrhage and cerebral palsy in conventionally ventilated preterm infants exposed to marked hypocapnia, findings that have been documented in a number of other studies.

Although our 1991 rescue trial showed no difference in the incidence of ICH, it is important to point out that some infants did not have pre-enrollment cerebral ultrasonography, and the average age at enrollment was nearly 48 hours. Because ICH is most likely to occur within the first 48 to 72 hours after birth, the late entry may have obscured any possible difference. In the more recent early intervention trial, we showed no overall increase in IVH 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, a substantial proportion of the HFJV patients were ventilated using the traditional low-pressure strategy of HFJV, similar to that used in the Wiswell study. Although this protocol deviation detracted from the quality of our 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 IVH/PVL in the optimal volume subgroup (9% versus 33% in the low pressure group; conventional group incidence was 28%) (Fig. 3) and no difference in pulmonary outcome. Interestingly, once again, the low-pressure subgroup of HFJV had significantly lower $PaCO_2$ values compared with both the conventional ventilation and the optimal volume HFJV subgroups (Fig. 4).

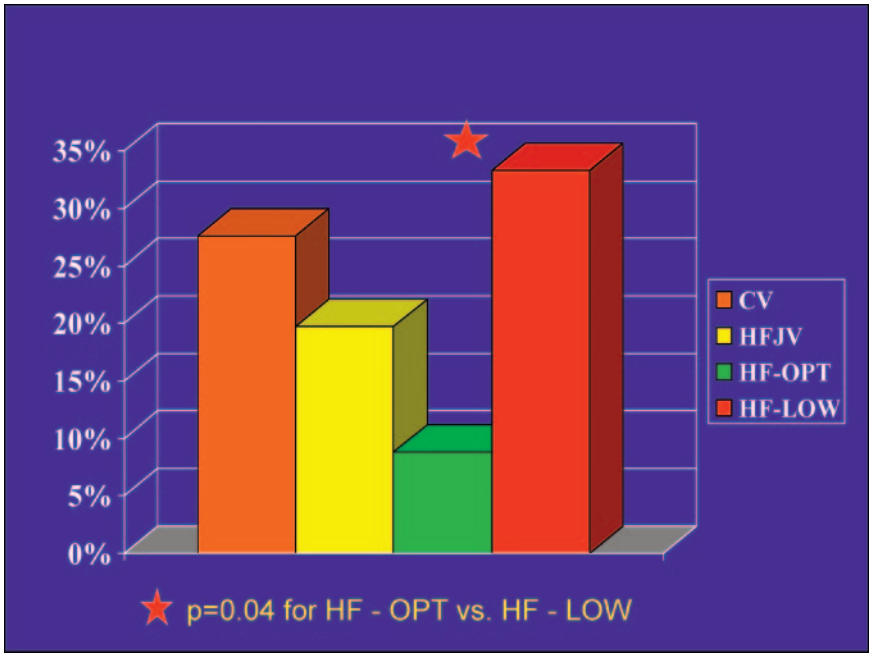


Figure 3. Incidence of severe intraventricular hemorrhage or periventricular leukomalacia with subgroup analysis by high-frequency jet ventilation (HFJV) strategy. CV=conventional ventilation, HF-OPT=optimal volume strategy of HFJV, HF-LOW=low-pressure strategy of HFJV. Reprinted with permission from Keszler, et al. *Pediatrics.* 1997;100:593–599.

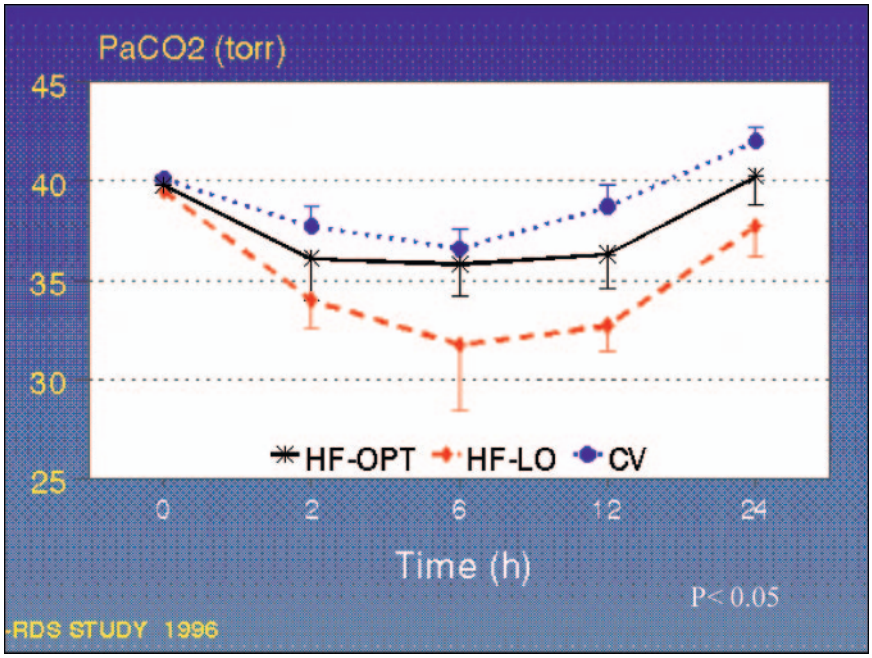


Figure 4. $Paco_2$ values in patients ventilated with conventional ventilation (CV), optimal volume HFJV strategy (HF-OPT), and low-pressure strategy (HF-LOW). The extent and duration of hypocapnia was significantly greater in the HF-LOW than the two other groups.

It is important to understand how inadvertent hypocapnia occurs when the low-pressure strategy is used with HFJV. Because HFJV is very good at lowering $PaCO_2$, pressure amplitude needs to be lowered in response. However, if PEEP is maintained at a low value of 4 to 5 cm H_2O while lowering the PIP, a significant drop in mean airway pressure occurs, leading to a fall in oxygenation. If the user is unwilling to increase the PEEP to maintain mean airway pressure, a point comes when further drop in PIP is precluded by poor oxygenation. Thus, the clinician tolerates some hypocapnia as a compromise. The appropriate response, of course, is to increase PEEP proportionally, thus narrowing the pressure amplitude while maintaining mean airway pressure unchanged.

Interpretation of the results from the trials evaluating HFOV and HFFI also suggest a causative role for hypocapnia. The HiFi trial suggested that HFOV is associated with an increased incidence of ICH or PVL. 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 the results. Possible inadvertent hyperventilation also could explain some of these findings, but the blood gas data were not reported. Finally, the constellation of complications observed in the HFOV patients (more air leak, ICH, hypotension, and poor gas exchange leading to crossover) is consistent with inadvertent air-trapping and increased intrathoracic pressure, which has been shown to occur under certain circumstances when using a 1:1 inspiratory-to-expiratory ratio and a frequency of 15 Hz, as was done

in the HiFi study. This problem would not be detected easily because pressure is not measured distal to the endotracheal tube.

In the HiFO study, the infants had severe lung disease and entered the study at an average age of nearly 24 hours. Pre-enrollment cranial ultrasonography studies were obtained in nearly all infants. Although infants in the HFOV groups had a borderline significant increase in the incidence of severe ICH, the actual numbers were small (6/81 HFOV versus 2/84 tidal ventilation), making this finding subject to a type I statistical error. It is of interest, however, that $PaCO_2$ was lower in the HFOV patients.

In contrast, the early study of Clark and more recent studies of Gerstmann, Rettwitz-Volk, Plavka, and Thome all found no increase in the incidence of ICH or PVL in the HFV group. Based on the experiences from earlier trials, hyperventilation was carefully avoided.

These reassuring results were thrown into question by the study of Moriette and associates. Despite using an optimum volume strategy of HFOV, they documented an apparent increase in severe IVH (14% for conventional ventilation versus 24% for HFOV; odds ratio 1.94; confidence interval 1.05 to 3.60, $P<0.05$). The difference was no longer significant when adjustment was made for baseline variation in maternal hypertension. On the other hand, when infants who received only conventional ventilation were compared with those who received HFOV by primary assignment or as a result of crossover, severe IVH was significantly more common in the latter group (24.9% versus 9.5%, $P<0.002$). The mean $PaCO_2$ in the control group remained in the range of 40 to 44 torr during the study, whereas in the HFOV group, $PaCO_2$ fell from a mean of 47 torr at baseline to a low of 35 torr 6 hours after randomization ($P<0.001$). Although a causative relationship cannot be clearly established in the individual studies, the hypocapnia theme recurs in all studies that showed adverse neuroimaging effects of HFV and is consistent with known physiologic mechanisms.

Consistent with this hypothesis, the most recent NVSG, UKOS, and Van Reempts studies, which together included more than 1,500 infants, found no difference in the incidence of severe ICH or cystic PVL after carefully avoiding hypocapnia. These findings suggest that neurologic injury is not an inherent problem with HFV, although it must be emphasized that most HFV devices are powerful ventilators, capable of rapidly lowering $PaCO_2$. It is equally critical to recognize that with optimization of lung volume, lung compliance improves rapidly. Consequently, it is incumbent on users of HFV to monitor CO_2 carefully, preferably continuously, and be prepared to make rapid adjustments to pressure amplitude to avoid exposure to dangerously low $PaCO_2$ levels.

Another concern raised in several recent meta-analyses is the apparent overall increase in the risk of air leak with HFOV. On closer inspection, it becomes apparent that this difference is largely attributable to the now discredited HiFi trial and the two HFFI trials that used ventilators that no longer are marketed. Furthermore, the difference only existed with respect to radiographic findings of pulmonary interstitial emphysema; the incidence of gross air leak showed no overall difference. None of the HFJV trials reported an increase in air leak in the treated group.

Choice of HFV

Despite their mechanical and physiologic differences, HFJV and HFOV share many similarities. Both devices use extremely small tidal volumes to avoid the larger cyclic volume changes required with conventional ventilation. Both can (and usually should) be used with a strategy aimed at optimizing lung volume. The erroneous 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 in the 1980s. This strategy was appropriate for the treatment of air leak, which was the predominant use of HFJV at that time, but is not an inherent feature of HFJV. HFJV can achieve excellent volume recruitment when an appropriate ventilator strategy in employed and consequently achieves excellent oxygenation and ventilation. In fact, recruitment is facilitated by the background sighs provided by the conventional ventilator.

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 probably is more important than the differences between the devices for most patients. Both jets and oscillators have been shown to be safe and effective in randomized clinical trials, and both can be used to treat patients who have uncomplicated RDS with a similar degree of success.

Available data from published randomized trials do not support the use of other types of HFV devices. Although lack of sufficient evidence of effectiveness is not the same as clear evidence of ineffectiveness, it would seem prudent to limit clinical use to devices that have been adequately studied and, when used optimally, shown to be both safe and effective in prospective randomized trials.

Possible benefits of HFJV over HFOV in certain specific circumstances may be based on the difference between the devices in their inspiratory-to-expiratory ratio and the nature of gas movement in the large airways. Some evidence suggests that one of the key elements in treating pulmonary interstitial emphysema is a short inspiratory time. In this area, the jet ventilator, with its approximately 1:6 to as much as 1:10 inspiratory-to-expiratory ratio, may have an advantage over the HFOV device, with its 1:2 inspiratory-to-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 appears to be more suitable for ventilation of infants who have disruptions of the large airways. Most centers where both HFJV and HFOV are available use HFJV preferentially for treatment of severe air leak. Also, although active exhalation (negative pressure applied at the airway opening) during HFOV is seen as an advantage in some situations, it probably is counterproductive in extremely preterm infants who have CLD.

Indications for HFV

Clearly, the early comparisons between HFV and the relatively crude conventional ventilation techniques of the 1980s and 1990s no longer can be considered directly relevant today. The widespread use of surfactant replacement therapy and increased use of antenatal steroids have greatly changed the population characteristics of infants who are mechanically ventilated today. For example, although the Gerstmann study was conducted in the 1990s during the era of routine surfactant therapy, enrolled infants had a mean birthweight of 1,500 g and were born at almost 31 weeks' gestation. Few of these infants would be ventilated today, and they would not be considered at risk for CLD.

Recent meta-analyses have suggested that surfactant, antenatal steroids, and improvements in conventional mechanical ventilation with the use of lung-protective strategies have eliminated any advantages of HFV as a primary mode of ventilation. However, this argument is not consistent with the positive findings of the NVSG trial, which sought to use the best available conventional ventilation strategy, and the negative findings of the UKOS trial, which did not even define conventional ventilatory strategies. More likely, the difference in these studies hinged on inclusion of a large number of infants who had little or no lung disease in the UKOS study and the other differences noted in Table 4. It is likely that with reasonably gentle conventional ventilation strategies, any benefit of HFV will be demonstrable only in infants who have significant lung pathology. The lack of effect in the most recent trial by Van Reempts is as likely due to the ineffective lung volume recruitment strategy with HFOV as to improved conventional ventilation. Unfortunately, because of the large number of patients, the latter two trials have a large impact on the meta-analysis.

Subanalyses within the overall meta-analysis sought to validate the message that apparent benefits of HFV shown in earlier studies were due to injurious conventional ventilation. Clearly, the judgments regarding ventilatory strategies, both conventional and high-frequency, are somewhat subjective and open to interpretation. For example, none of the published trials classified as using a "lung-protective strategy" in the meta-analysis specifically defined a lung-protective strategy of conventional ventilation that followed the principles of the open lung concept. Yet, indisputably, the more recent large, "real world" studies do not suggest a clear advantage of HFOV. Nonetheless, most experienced users of HFOV remain convinced that, *when used in appropriately selected patients with the optimal volume recruitment strategy and careful attention to avoiding hypocapnia*, HFOV is capable of reducing the incidence of CLD.

Proposed Indications for HFV

Treatment of air leak syndromes, such as pulmonary interstitial emphysema and bronchopleural or tracheoesophageal fistula, is one of the best-documented indications for HFV and appears to be nearly universally accepted. Data from several animal studies, numerous anecdotal reports, and our randomized clinical trial in infants who had pulmonary interstitial emphysema all support this conclusion. Patients who have air leak should be treated with HFV until at least 24 hours after the air leak has resolved. When available, there may be advantages to using HFJV rather than HFOV for this indication.

HFV may be preferable to conventional ventilation for patients who have severe uniform lung disease, such as RDS. The data from numerous animal studies and from the clinical trials that used HFOV and a volume recruitment strategy support the argument that the use of small tidal volumes at high frequencies facilitates more uniform lung inflation and may cause less damage to severely noncompliant lungs than do the larger tidal volumes of conventional ventilation. No objective data are available to establish specific threshold criteria for initiation of this "early rescue" application, but as a rough guideline, most clinicians consider the require-

ment for inspiratory pressures above 25 cm H_2O or FiO_2 above 0.4 to 0.6 sufficient to consider a trial of HFV.

HFV may be an effective rescue therapy for patients who have severe nonuniform disease such as aspiration syndromes. The studies by Wiswell using the piglet model of meconium aspiration syndrome (MAS) and by our group using a canine model suggest that HFV improves gas exchange and causes less damage to these lungs than does conventional ventilation. It is important to recognize that MAS is a heterogeneous syndrome that evolves over time. Airway obstruction usually predominates in the early stages. Although HFJV may facilitate mobilization of secretions, the presence of debris in the airways may interfere with efficient ventilation. Some affected infants develop significant air-trapping on HFV and actually do better on conventional ventilation. For infants in whom the surfactant-inhibitory effect of meconium predominates and in the subsequent inflammatory stages of MAS, HFV is often effective. There are no controlled trials of HFV in infants who have mild aspiration syndromes. Based on the controlled trial of Clark, and to a lesser degree that of Engle, as well as extensive anecdotal experiences from most centers offering ECMO, a trial of HFV is appropriate in term infants who have severe respiratory failure and are candidates for ECMO. When HFV is used in these infants, slower frequencies must be employed because of the longer time constants to minimize the chance of air-trapping.

Patients who have significant parenchymal lung disease and 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. This indication is based on the randomized trial of Kinsella as well as subsequent clinical observations.

HFV may have a role in the treatment of patients who have pulmonary hypoplasia, such as is seen with diaphragmatic hernia or oligohydramnios sequence. Although this indication has not been well studied, substantial anecdotal evidence suggests 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 achieves adequate gas exchange while using extremely small tidal volumes. However, limited data from clinical trials in these patients do not support the presumed advantage of this approach.

HFV is a preferred mode of ventilation when severe chest wall restriction or upward pressure on the diaphragm due to abdominal distention interfere with tidal ventilation and cause CO_2 retention or hemodynamic embarrassment.

An argument can be made that, in experienced hands and with an optimal ventilator strategy, HFV may be the preferred mode of ventilation for all preterm infants who have significant RDS. Despite the inconsistent results of clinical trials, a number of centers continue to use HFV as a primary mode of ventilation for high-risk infants who have RDS. However, the enthusiasm for the routine use of HFV as a primary mode of ventilation has been tempered by the recent negative trials and continues to be tempered by the lingering concerns about the ease with which inadvertent hyperventilation can occur and the possibility of neurologic injury. For this reason, in most circumstances and in most nurseries today, it is unlikely that routine use of HFV in

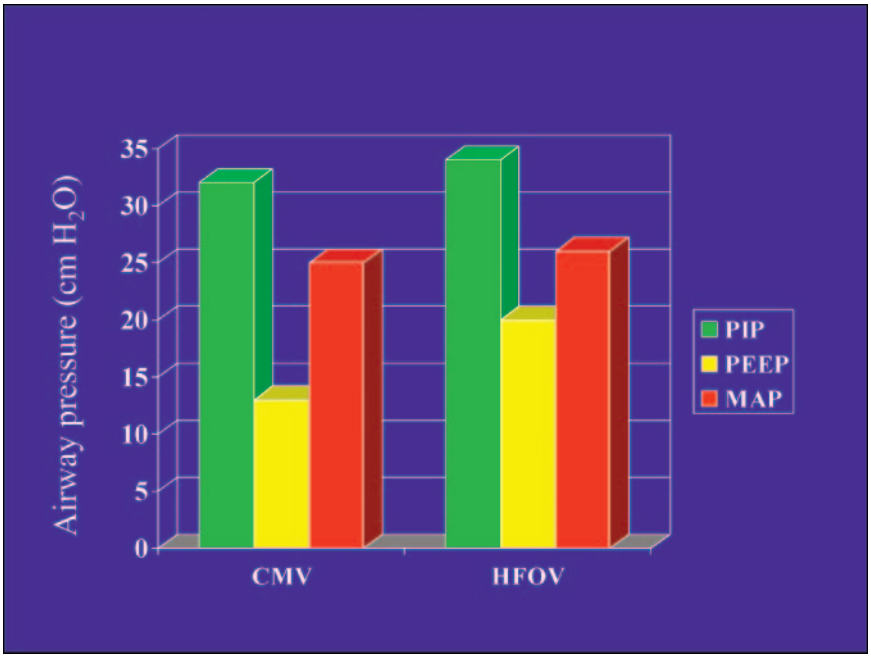


Figure 5. Airway pressures with conventional ventilation (CMV) using the open-lung concept approximated those used with HFOV in this short-term animal study. Gas exchange, lung mechanics and lung histology were identical in both groups. From Vazquez de Anda, et al. *Intensive Care Med.* 1999;25:990–996. PIP=peak inspiratory pressure, PEEP=positive end-expiratory pressure, MAP=mean airway pressure

preterm infants offers a substantial benefit over state-of-the-art conventional ventilation.

Conclusion

HFV is an effective treatment modality in a variety of clinical situations. Neonatologists have gained important insights into the factors involved in lung injury and the potential for damage to distant organs, such as the brain, that may result from suboptimal use of mechanical ventilation. The laboratory and clinical investigations of these techniques have contributed tremendously to our understanding of the pathophysiology of respiratory failure and the critically important concept of recruiting and maintaining adequate lung volume.

The logical result of this improved understanding of respiratory pathophysiology is a substantial convergence of HFV and tidal ventilation. In general, we now use smaller tidal volumes, faster respiratory rates, and higher levels of PEEP with conventional ventilation. In fact, several recent studies in animals have demonstrated that many, if not all, of the benefits of HFV appear to be a function of the optimization of lung volume, rather than the ventilatory rate (Fig. 5). This is consistent with the data from the multicenter clinical trials. The only studies that showed benefit of HFV were those that used an optimum lung volume strategy. Thus, it can be argued that the HFV trials compared optimal lung volume strategies of HFV to low lung volume strategies of conventional ventilation.

Perhaps the most important contribution of HFOV is that it helped clinicians overcome the fear of using adequate distending airway pressure. Arguably, the key advantage of HFV may be that in patients who have severe disease, it is probably easier and safer to achieve lung recruitment with the rapid rate and smaller pressure amplitude/tidal volume of HFV. At the same time, the advent of advanced modes of fully synchronized and volume-targeted conventional mechanical ventilatory modes has made conventional ventilation far more sophisticated and more attractive. The ability to control delivered tidal volume effectively and to monitor ventilatory variables accurately makes it much easier to avoid inadvertent hypocapnia. For this reason, it is our practice to use pressure support and volume guarantee mode as the first line treatment for most preterm infants requiring mechanical ventilation, reserving HFV for those who have more severe respiratory failure or specific indications for HFV previously described.

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NeoReviews Quiz

4. Three modes of high-frequency ventilation are currently available in the United States: high-frequency oscillatory ventilation, high-frequency jet ventilation, and high-frequency flow interruption. The ratio of inspiratory time to expiratory time with each breath varies, depending on the mode of high-frequency ventilation. Of the following, the *most* typical inspiratory-to-expiratory time used with high-frequency jet ventilation is:

   A. 1:2.
   B. 1:3.
   C. 1:4.
   D. 1:5.
   E. 1:6.

5. The gas exchange with high-frequency ventilation occurs, in part, by enhanced molecular diffusion resulting from increased mixing of gases in the airways. Of the following, the high-frequency ventilator variable *most* likely to influence oxygenation is:

   A. Amplitude.
   B. Frequency.
   C. Inspiratory-to-expiratory time ratio.
   D. Mean airway pressure.
   E. Tidal volume.

6. A major continuing controversy regarding high-frequency ventilation centers on its possible role in increasing the risk of severe intracranial hemorrhage (ICH) or periventricular leukomalacia (PVL). Of the following, the *most* likely explanation for the development of ICH/PVL in relation to high-frequency ventilation is:

   A. Enhanced lung volume.
   B. Excessive intrathoracic pressure.
   C. Persistent acidemia.
   D. Prolonged hypocapnia.
   E. Refractory hypoxemia.

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