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High-frequency Ventilation: Current Status

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OBJECTIVES

After completing this article, readers should be able to:

1. Define high-frequency ventilation and contrast this technique with conventional mechanical ventilation.
2. Describe three types of high-frequency ventilators.
3. Explain the basic mechanisms of gas exchange during high-frequency ventilation.
4. Describe potential adverse outcomes with high and low lung volume high-frequency ventilation strategies.

Introduction

Lung injury remains an important cause of morbidity among newborns who require assisted ventilation. Studies in immature animal models of respiratory distress syndrome (RDS) have shown that positive-pressure ventilation with large tidal volumes damages pulmonary capillary endothelium, alveolar and airway epithelium, and basement membranes. This mechanical damage results in leakage of fluid, protein, and blood into the airways, alveoli, and interstitial spaces, leading to inhibition of surfactant activity and further injury to the lung. Cyclic changes in lung volume appear to be more important than changes in airway pressure in causing this damage, suggesting that a ventilator strategy that avoids large changes in lung volume may reduce lung injury. Consequently, considerable interest has been generated over the past 15 years in the application of high-frequency ventilation (HFV) in newborns who have respiratory failure because this technique allows ventilation with very small tidal volumes.

Although studies using HFV in animal models of RDS have shown promising results in the prevention of lung injury, results of clinical studies of this ventilatory technique in newborns are not as promising. Despite many clinical trials, controversy continues to surround the indications for HFV in newborns,

whether HFV is more effective than other modes of ventilation for neonatal respiratory failure, whether HFV reduces adverse outcomes, or whether HFV is more likely to result in significant long-term complications than conventional mechanical ventilation (CMV).

This article provides an overview of HFV and reviews results of studies of its use for a variety of neonatal pulmonary disorders. We address its use as a primary mode of ventilation in infants who have RDS as well as its application as rescue therapy for severe respiratory failure and air leak syndromes in both preterm and term infants.

Definitions of HFV and Types of Ventilators

HFV has been defined in several ways. Most definitions include the following characteristics: 1) ventilation at a high rate, at least two to four times the natural breathing frequency, and 2) ventilation with small tidal volumes that are less than the anatomic dead space. In addition, gas transport during HFV cannot be explained by classic concepts of ventilation and lung mechanics. All high-frequency ventilators are capable of delivering extremely rapid rates (300 to 1,500 breaths/min, 5 to 25 Hz or cycles per second). They apply a continuous distending pressure to maintain lung volume, and small tidal volumes are superimposed at a rapid rate.

Three types of high-frequency ventilators are approved for use in newborns in the United States: a

high-frequency oscillatory ventilator (HFOV), a high-frequency flow interrupter (HFFI), and a high-frequency jet ventilator (HFJV). HFJVs are paired with a conventional pressure-limited device that is used to deliver positive end-expiratory pressure (PEEP) and intermittent "sigh" breaths to help prevent atelectasis. Expiration is passive (ie, dependent on chest wall and lung recoil) with HFJV and HFFI, and it is active with HFOV. Recently developed HFFI machines use a Venturi system to generate negative pressure swings during expiration that enhance lung emptying.

Although similar ventilatory strategies are used with the ventilators, the technical characteristics of these devices, including ranges of operational frequencies and control of airway pressure and amplitude, are substantially different.

HFOVs employ a piston or diaphragm to oscillate a bias flow of gas, resulting in both positive and negative pressure fluctuations (amplitude). The bias flow of gas leaves the ventilator circuit through a low-pass filter that acts as a resistor, generating the mean airway pressure. Operator-selected parameters include mean airway pressure, frequency, and piston amplitude. Frequency most commonly is set at 10 to 15 Hz, and inspiratory time at 33% of the oscillatory cycle, provid-

ABBREVIATIONS

CMV:	conventional mechanical ventilation
ECMO:	extracorporeal membrane oxygenation
HFFI:	high-frequency flow interrupter
HFJV:	high-frequency jet ventilator
HFV:	high-frequency ventilation
HFOV:	high-frequency oscillatory ventilator
NIH:	National Institutes of Health
PEEP:	positive end-expiratory pressure
PMA:	postmenstrual age
RDS:	respiratory distress syndrome

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ing an inspiratory:expiratory ratio of 1:2. During operation, mean airway pressure, through its effects on the degree of lung inflation, primarily influences oxygenation, while piston amplitude primarily affects ventilation. HFOVs are the only high-frequency ventilators in which expiration is active due to the negative pressure deflection during the expiratory cycle of the oscillated breaths.

The only HFJV currently available for clinical use is a time-cycled, pressure-limited, constant gas flow interrupter that is used in parallel with a conventional ventilator. The conventional ventilator provides PEEP as well as intermittent "sigh" breaths, usually set at 2 to 10 breaths/min. The high-frequency jet breaths are delivered through a special triple-lumen endotracheal tube that has a distal airway pressure port, a jet side port, and a standard connection for the conventional ventilator. A special side port adapter for a standard endotracheal tube to deliver jet breaths is also available and avoids the need for reintubation. Operator-selected parameters include peak inspiratory pressure of both the jet and conventional breaths, PEEP, and frequency (usually set at 7 Hz). Peak inspiratory pressure, PEEP, and inspired oxygen concentration are adjusted as needed to maintain oxygenation. Carbon dioxide elimination is dependent on the peak inspiratory pressure-to-PEEP pressure difference. Because HFJVs require lower peak pressures to accomplish ventilation, PEEP may be increased to as high as 8 to 10 cm H₂O if needed to improve oxygenation.

HFFIs are adaptations of conventional mechanical ventilators that have both conventional and high-frequency options. They operate on a principle similar to jet ventilation. Gas from a high-pressure source is delivered into a standard ventilator circuit and endotracheal tube. To produce high-frequency breaths, the flow of gas is interrupted by a valve mechanism that may be controlled mechanically or by microprocessor. Operator-selected parameters include peak inspiratory pressure, PEEP, and frequency, which is usually set between 6 and 20 Hz. The high-frequency option often is used in

conjunction with the conventional ventilator to deliver intermittent "sigh" breaths. Oxygen delivery is dependent primarily on the PEEP delivered by the conventional part of the ventilator. Similar to HFJVs, carbon dioxide elimination is dependent on the peak inspiratory pressure-to-PEEP pressure difference.

Mechanisms of Gas Exchange

REMOVAL OF CARBON DIOXIDE

During CMV, gas exchange of both oxygen and carbon dioxide is accomplished by bulk convection (the bulk movement of fresh gas in and exhaled gas out of the lung), and minute ventilation is the product of frequency and tidal volume. If conventional mechanisms prevailed during HFV, one might predict that alveolar ventilation would not occur because the tidal volumes used are smaller than the anatomic dead space. Although the precise manner by which gas exchange occurs during HFV remains incompletely understood, a number of different mechanisms likely play a role within different segments of the lung. Similar to CMV, bulk convection may be an important mechanism during HFV in ventilating the most proximal alveolar units. Other proposed mechanisms for gas exchange during HFV include: *Pendelluft effect*, in which regional differences in time constants for inflation and deflation cause gas to recirculate among lung units and improve gas exchange; *asymmetric velocity profiles*, in which convective gas transport is enhanced by asymmetry between inspiratory and expiratory velocity profiles that occur at branch points in the airways; *Taylor dispersion*, in which augmented diffusion occurs because of turbulent air currents that result from interaction between axial velocity and the radial concentration gradient in the airways; and *molecular diffusion*, which, as in CMV, is the most important mechanism at the alveolar-capillary membrane.

In contrast to CMV in which ventilation is the product of frequency times tidal volume ($f \times V_t$), ventilation in HFV is defined by the equation $f^a \times V_t^b$, where a is esti-

mated as 0.75 to 1.24 and b is between 1.5 and 2.2, amplifying the effect of changes in V_t on ventilation. Thus, despite the extremely small tidal volumes generated, changes in delivered tidal volume during HFV may have a greater effect on carbon dioxide removal than during CMV. In addition, because of the characteristics of the device, delivered tidal volume is inversely related to frequency (ie, tidal volume decreases as frequency increases) during HFOV. Similar to all ventilators, as respiratory impedance increases, the delivered tidal volume decreases. As a result, changes in ventilator frequency or increased airway resistance resulting from secretions in the airway or a change in the diameter of the endotracheal tube can reduce delivered tidal volume markedly and have a large adverse effect on carbon dioxide removal during HFV.

OXYGEN EXCHANGE

In all forms of mechanical ventilation, maintaining adequate lung volume helps to avoid atelectasis and preserve surfactant function, thereby enhancing oxygen exchange. Despite major differences in design and function of the devices used, the strategy of improving oxygenation during HFV and CMV is similar. In both circumstances, it is important to maximize ventilation-perfusion matching while avoiding impairment of cardiac output. With CMV, using relatively large tidal volume breaths recruits lung volume and using PEEP avoids atelectasis. With HFV, a high mean airway pressure (or PEEP) is used to recruit alveoli and maintain lung volume above functional residual capacity. Thus, in contrast to CMV, HFV maintains lung volume at a relatively constant level and uses small changes in tidal volume to accomplish ventilation. With both the HFFI and HFJV, intermittent sigh breaths or sustained inflations also may be used to recruit lung volume and avoid atelectasis.

HFV: Animal Studies

Several animal studies have examined the role of HFV in reducing

ventilator-induced lung injury. Early studies examining the use of HFOV in animals that had experimental RDS showed that using low mean airway pressures during HFV results in progressive atelectasis and hypoxemia. In contrast, when used with a strategy to optimize lung inflation with higher mean airway pressures, HFOV applied to baboons, monkeys, and rabbits reduced air leak, promoted uniform lung inflation, improved gas exchange and lung mechanics, and reduced the amount of inflammatory mediators. These effects are even greater when HFOV is used in concert with surfactant treatment. In one study of preterm baboons that had RDS in which ventilation was initiated immediately after delivery with a high mean airway pressure/lung volume strategy, HFOV prevented the deterioration in gas exchange and lung mechanics characteristically seen in animals treated with conventional ventilators. Early treatment with HFOV also prevented the morphologic changes of hyaline membrane disease seen in the conventionally treated animals.

HFOV is not as effective in reducing the pathologic findings of acute lung injury when initiated later in the course of RDS, after several hours of CMV. Studies in preterm lambs suggest that even a small number of large tidal volume breaths immediately after birth may be damaging to the surfactant-deficient lung and compromise the therapeutic benefit of surfactant replacement. These studies and others indicate that volutrauma, rather than barotrauma, is the primary cause of acute lung injury secondary to assisted ventilation and that HFOV that uses a relatively static lung volume and minimal cyclic volume changes may protect the surfactant-deficient lung from injury. Such data also led to an evolution in the clinical applications of HFV to recruitment of lung volume using high mean airway pressures.

Clinical Use of HFV

EARLY CLINICAL TRIALS

When HFV initially was developed and used clinically in newborns, its potential advantage over CMV was

believed to be the ability to provide adequate gas exchange using lower mean airway pressures, thereby limiting barotrauma. This was consistent with the role that barotrauma was thought to play in consequent lung injury. Several small studies performed in the early to mid-1980s confirmed that infants who had severe hyaline membrane disease and were failing CMV could achieve adequate gas exchange with either the HFJV or HFOV at mean airway pressures significantly lower than that required with CMV.

These preliminary findings prompted the National Institutes of Health (NIH) to conduct a multicenter randomized trial in the mid-1980s of preterm infants ($n=673$) requiring ventilatory assistance to test the hypothesis that the HFOV, as compared with CMV, would decrease the incidence of lung injury (ie, bronchopulmonary dysplasia and air leak) and be associated with fewer adverse effects, including neurologic sequelae. The strategy used for HFV during this trial stressed limitation of mean airway pressure in an effort to protect the lung from barotrauma.

Results of this large trial were disappointing. As used during the study, the HFOV did not reduce the incidence of bronchopulmonary dysplasia or death (the primary outcome), produce more effective gas exchange, or decrease the need for ventilatory support compared with CMV. An association was seen, however, between use of HFV and other adverse outcomes, including air leak and intracranial hemorrhage. Failure of the strategy of limiting mean airway pressure to reduce lung injury prompted a re-examination of the assumptions behind the clinical application of this technology in newborns. Rather than limiting mean airway pressure, subsequent studies incorporated a strategy more similar to that used in animal studies in which a higher mean airway pressure was used to help maintain a higher lung volume.

LATER CLINICAL TRIALS

Several clinical studies using the "high lung volume" approach to HFV have provided more promising

results than the original NIH trial. Clinical studies include trials of HFV as the initial mode of ventilation in preterm infants who have RDS (early intervention) and as rescue therapy in preterm and term infants who have severe lung disease or air leak syndromes.

Early Intervention for RDS

Several prospective, randomized trials have compared the HFOV, HFJV, and HFFI as the initial mode of ventilator therapy with CMV in preterm infants who have RDS (Table), although the most data are available for the HFOV. Study designs for these trials have stressed early randomization to the primary mode of ventilation (usually <12 h) and specific HFV strategies to optimize lung volume recruitment. It is important to note that although HFV strategies were specified by study protocols, the CMV strategies used in all but one study were not standardized. The primary endpoint for most of these studies was the incidence of death or chronic lung disease, variably defined as oxygen requirement at 28 to 30 days or at 36 weeks postmenstrual age (PMA).

Results of these trials have been contradictory, with some showing a potential benefit of HFV and others documenting no difference compared with CMV. A recent trial compared the HFJV to CMV in 130 preterm infants, all of whom received surfactant for RDS. This study demonstrated a decrease in the incidence of chronic lung disease at 36 weeks PMA in infants randomized to HFV. No differences in other adverse outcomes, including air leak and intraventricular hemorrhage, were observed between the two groups. Two earlier trials using the HFOV showed similar results. These trials included a very small number of patients whose birthweights were less than 1,000 g (a total of 55 infants in both studies combined) and reported a surprisingly high incidence of chronic lung disease in the infants receiving CMV despite their relatively heavy birthweights (65% and 44% at 30 days of age, respectively). Thus, these results may not be applicable to extremely low-birthweight infants, the group at

TABLE. Randomized Early Intervention Trials of HFV for Uncomplicated Respiratory Distress Syndrome

REFERENCE	DEVICE	N	BODY WEIGHT (KG) MEAN	CLD RATE (HFV VERSUS CMV)
Carlo (1987)	HFJV	41	1.48	No difference
NIH HIFI (1989)	HFOV	673	1.10	No difference
Carlo (1990)	HFJV	42	1.42	No difference
Clark (1992)	HFOV	83	1.10	30% versus 65% at 30 d 10% versus 38% at 36 wk PMA
Ogawa (1992)	HFOV	92	1.20	No difference
Pardou (1993)	HFFI	24	1.30	No difference
Gerstmann (1996)	HFOV	125	1.50	24% versus 44% at 30 d*
Wiswell (1996)	HFJV	73	0.90	No difference
Keszler (1997)	HFJV	130	1.00	67% versus 71% at 30 d 20% versus 40% at 36 wk*
Rettwitz-Volk (1998)	HFOV	96	1.10	No difference
Thome (1999)	HFFI (Venturi)	284	0.88	No difference

* $P < 0.05$; CLD = chronic lung disease, CMV = conventional mechanical ventilation, HFV = high-frequency ventilation, HFFI = high-frequency flow interrupter, HFJV = high-frequency jet ventilator, HFOV = high-frequency oscillatory ventilator, PMA = post-menstrual age

highest risk for developing chronic lung disease.

Other prospective, randomized studies using HFV compared with CMV have not demonstrated any benefit of one mode of ventilation over the other. The most recently published study included the largest number of infants (n=284) in any trial of HFV since the NIH study and is the only one to date that compares HFV to a standardized protocol for CMV. Similar to the animal studies of HFV, this investigation examined very early initiation of HFV using a high lung volume strategy. Investigators randomized infants who had a gestational age of less than 30 weeks and were diagnosed with RDS to either the HFFI with a Venturi system or to low tidal volume, high-rate CMV. Criteria for surfactant treatment were also standardized in the protocol, and HFV was initiated within 1 hour after birth in almost all randomized patients. The mean birthweights of the HFV and CMV groups were 888 and 870 g, respectively, which was substantially lower than in previous trials. The primary outcome

variable was the incidence of “treatment failures” on the randomized mode of ventilator therapy, defined as air leaks within the first 10 days, reaching a threshold oxygenation index stratified by gestational age at birth, death, or chronic lung disease. There was a trend toward a higher incidence of “treatment failures” in the HFV group, but no difference in the incidence of chronic lung disease between the two groups. The higher treatment failure rate in the HFV group was due to a higher incidence of air leaks compared with those receiving CMV.

In addition to disappointing pulmonary outcomes, the NIH trial raised concerns that HFV might result in a higher incidence of air leak and neurologic injury. Subsequent trials using a high lung volume approach to HFV have not borne out these concerns, with no significant differences seen in the incidence of air leak, intraventricular hemorrhage, or periventricular white matter injury. However, recent data suggest that using HFV as the primary mode of ventilation with a low mean airway pressure strategy may

increase the risk of neurologic injury. In one trial that compared early use of the HFJV with a low lung volume strategy to CMV, the incidence of neurosonographic abnormalities (periventricular white matter injury or grade 4 intraventricular hemorrhage) was significantly greater in the HFJV group. An earlier study from the same investigators concluded that lower carbon dioxide tensions seen in patients treated with the HFJV were associated with a higher incidence of periventricular white matter injury. In the subsequent study, however, only randomization to the HFJV was independently associated with development of neurologic abnormalities. Another study of early use of the HFJV employing a high lung volume approach did not find this relationship. These results suggest that the strategy used for gas exchange with HFV may influence both pulmonary and neurologic adverse outcomes.

To account for the relatively small number of infants included in most studies and the contradictory results, a meta-analysis of random-

ized trials of HFOVs recently was performed using the guidelines of the Cochrane Collaboration. Four trials of elective HFOV versus CMV were included in the analysis. A trend toward a decreased incidence of chronic lung disease in the HFOV-treated infants was observed. When the NIH trial, the only one to use a low mean airway pressure strategy, was excluded from the meta-analysis, a significant reduction in the incidence of death or chronic lung disease in the HFOV group was observed. No increase in the incidence of neurosonographic abnormalities was observed in the HFOV-treated infants when the NIH trial was excluded from the meta-analysis. Even when data from the three studies that used a high lung volume HFV strategy are combined, however, the meta-analysis includes very few infants whose birthweights are less than 1,000 g.

Despite the results from animal studies and the meta-analysis, in our opinion the contradictory results of the clinical trials do not support the use of HFV as a primary mode of ventilation for infants who have RDS for several reasons. Most of these trials have been performed by investigators who have extensive experience in HFV, so results may not be duplicated by those who have less experience in the technique. In addition, by the nature of the intervention, masking of investigators is not possible, which also might affect some outcomes. In some studies, differences in outcome may have less to do with the mode of ventilation than with the use of a standardized approach for one mode of ventilation (HFV) by experienced investigators and a nonstandardized approach for the other mode of ventilation (CMV). When both modes of ventilation are "optimized," differences in pulmonary or other outcomes may no longer be evident. Indeed, only studies in which there is a relatively high rate of chronic lung disease in the CMV-treated infants have demonstrated a lower incidence of chronic lung disease in the HFV-treated infants.

However, the data do support the conclusion that HFV is at least comparable to CMV in uncomplicated RDS in terms of short-term out-

comes when used by experienced clinicians. Clinical trials of HFV in which a low lung volume strategy was used are cautionary. Furthermore, as with any mode of ventilation, HFV may be associated with a higher incidence of complications when employed by those who are less experienced with its use. In addition, long-term follow-up studies that investigate postneonatal survival, lung function, and neurodevelopment of infants treated with HFV have yet to be performed.

Rescue Therapy With HFV

PRETERM INFANTS

HFV frequently is used to treat infants who have pulmonary interstitial emphysema or other air leak syndromes and as a rescue therapy in infants who continue to require high levels of CMV support after surfactant therapy. Few trials of HFV as a rescue therapy for preterm infants who have severe pulmonary dysfunction or air leak have been performed, and none have been undertaken since the routine availability of exogenous surfactant therapy. The largest randomized trial to date ($n=176$) examined whether use of the HFOV compared with CMV would decrease the development or progression of air leak syndrome in infants younger than 48 hours of age who had severe RDS. A high lung volume HFV strategy was used, and the protocol included management guidelines for infants randomized to CMV. During the first 24 hours after randomization, infants in the HFOV group required lower inspired oxygen concentration and had lower arterial carbon dioxide tension compared with the infants who received CMV. Fewer infants randomized to HFOV developed air leak among those who did not have any leak prior to study. No differences between the groups were observed in the progression of air leak in those who already had leaks. Of concern, the incidence of severe intraventricular hemorrhage was significantly higher in infants treated with HFV. Neither the number of infants who weighed less than 1,000 g nor outcome data by birth-weight categories were reported.

Use of the HFJV was shown to be superior to CMV in a large randomized trial of infants who had pulmonary interstitial emphysema ($n=144$). Infants randomized to the HFJV had a lower mortality rate and a more rapid radiographic improvement. No differences in the incidence of chronic lung disease or intraventricular hemorrhage were observed. Randomized trials with other modes of HFV for therapy of preterm infants who have pulmonary interstitial emphysema or other forms of air leak have not been performed. It remains unclear whether the different types of HFV are equally effective in management of air leak syndromes. Caution should be exercised, however, given the lack of comparative trials of different types of HFV, the significant design differences between the available devices, and the potential for complications in this very sick population of infants.

TERM INFANTS

Limited data also are available for the use of HFV in near-term and term infants as a rescue therapy for severe respiratory failure or persistent pulmonary hypertension. Most studies have included infants who had severe respiratory failure associated with a high risk of mortality, thereby making them potential candidates for extracorporeal membrane oxygenation (ECMO). The causes of respiratory failure in these infants are heterogeneous, including respiratory distress syndrome, congenital pneumonia, meconium aspiration pneumonia, pulmonary hypoplasia, and congenital diaphragmatic hernia.

Only one prospective randomized trial of HFV in near-term and term infants who had respiratory failure has been performed. In this study, 79 infants who had gestational ages of at least 34 weeks referred for ECMO were randomized to HFOV or CMV. In the crossover design, those who failed the initial treatment were switched to the alternative ventilator mode. The proportion of infants who failed their initial treatment assignment was comparable between the HFOV and CMV groups. However, of those who failed conventional ventilation, 63%

responded to the HFOV, significantly more than the 23% who responded to CMV after failing therapy with the HFOV. No significant differences in mortality or morbidity (chronic lung disease, air leak, intracranial hemorrhage) were observed.

Retrospective studies also suggest that HFV improves gas exchange in infants who have severe respiratory failure and may reduce the need for ECMO. The response rate appears to be disease-specific, with infants who have homogeneous lung diseases such as respiratory distress syndrome or pneumonia more likely to respond to HFV than those who have more heterogeneous lung disease, such as meconium aspiration pneumonia. Limited follow-up studies suggest that the incidence of chronic lung disease may be greater in ECMO candidates rescued with HFV than in those treated with ECMO, although long-term neurologic outcomes have not been compared.

Other studies suggest that lung volume recruitment with HFOV may enhance the response to inhaled nitric oxide, a selective pulmonary vasodilator, in infants who have persistent pulmonary hypertension complicated by parenchymal lung disease. A recent prospective, randomized trial compared CMV with inhaled nitric oxide to HFOV alone in 203 infants who had severe pulmonary hypertension. Treatment failure resulted in crossover to the alternative treatment, which led to combination treatment with an HFOV plus inhaled nitric oxide. In this study, the response rate (defined as a sustained $\text{PaO}_2 > 60$ mm Hg) for the HFOV plus nitric oxide was significantly higher than for either therapy alone in infants who had respiratory distress or meconium aspiration pneumonia. Several animal studies also support the synergistic effects of HFV and inhaled nitric oxide.

Conclusion

HFV is an important adjunct to CMV in the management of preterm and term newborns who have respiratory failure. Clinical trials demonstrate that HFV used with a high lung volume strategy is a safe alter-

native to CMV and may be particularly effective as a rescue therapy in infants who have severe respiratory failure.

Several questions remain about the use of HFV, however. The different types of HFV devices available have not been compared with each other in the clinical setting, nor have they been compared with newer modes of CMV, such as synchronized intermittent mandatory ventilation. Therefore, it remains unclear whether HFOV, HFJV, and HFFI are interchangeable. In addition, there is a striking paucity of data about the potential benefit (or harm) of HFV in the extremely low-birthweight population in the post-surfactant era. Compared with larger birthweight infants, this group is at the greatest risk for developing chronic lung disease as well as other significant long-term complications.

Despite animal data suggesting that early application of HFV modifies the sequence of lung injury that can be initiated by CMV, results of clinical trials of HFV to prevent chronic lung disease in preterm infants have been much less compelling. This is likely due to the complex, multifactorial etiology of chronic lung disease in extremely preterm infants. The mode of mechanical ventilation used may be less important than other perinatal and neonatal factors that can contribute to lung injury and consequent chronic lung disease in these infants. Questions also remain about the risk-benefit ratio for HFV, such as whether ventilatory strategy influences the risk of neurologic complications. Answers to these questions await further research into the uses of HFV within the context of other evolving therapies for the care of sick newborns.

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