

# The Role of High-Frequency Ventilation in Neonates: Evidence-Based Recommendations

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Respiratory failure in neonates, commonly defined as retention of carbon dioxide with a resultant decrease in the arterial blood pH and accompanied by hypoxemia, has multiple etiologies. It remains the most common complication of premature birth and the number one reason that neonates require assisted mechanical ventilation. Respiratory failure is a result of impaired pulmonary gas exchange mechanisms, such as can be seen with surfactant deficiency, atelectasis, or obstructive airway disease. Less common causes of respiratory failure may be a result of airway, musculature, or central nervous system abnormalities. The specific etiology of neonatal respiratory failure can, at times, be unclear and potentially multifactorial. Nonetheless, insights into the potential etiologies and pathophysiology of respiratory failure weigh heavily in the clinician's decisions regarding initiation of assisted mechanical ventilation.

Much progress has been made in the treatment of neonatal respiratory failure over the past few decades. In particular, antenatal steroids and exogenous surfactant replacement have decreased neonatal mortality and morbidity in premature infants [1–3]. However, lung injury and pulmonary morbidities secondary to mechanical ventilation remain an ongoing problem in the care of premature infants. Of most concern, chronic lung disease (CLD) develops in up to one third of preterm infants who have respiratory

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distress syndrome (RDS) who receive positive pressure mechanical ventilation [4]. Dilemmas still remain regarding optimization of both timing and mode of mechanical ventilation to decrease neonatal pulmonary morbidities.

High-frequency ventilation (HFV) is a form of mechanical ventilation that uses small tidal volumes and extremely rapid ventilator rates. It first came to the attention of the medical community during the 1970s, when a number of scattered reports appeared. Lunkenheimer and colleagues [5] reported the use of high-frequency oscillatory ventilation (HFOV) in apneic dogs, Sjöstrand [6] used high-frequency positive pressure ventilation in adults who have respiratory failure, and Carlon and colleagues [7] used a type of jet ventilation in adults who have bronchopleural fistula. Early reports of neonatal use came from Frantz and colleagues [8] in Boston, Massachusetts, and Pokora and colleagues [9] in St. Paul, Minnesota. In an attempt to clarify how it is possible to maintain pulmonary gas exchange when the tidal volumes used are often smaller than the anatomic dead space, Chang [10] described the multiple modes of gas transport that occur during HFV, including bulk convection, high-frequency “pendulluft,” convective dispersion, Taylor-type dispersion, and molecular diffusion. There are various high-frequency ventilator designs, including HFOV, high-frequency jet ventilation (HFJV), as well as “mixed” forms of HFV (eg, flow interrupters, high-frequency positive pressure ventilation). In the United States, the most commonly used high-frequency ventilators include the SensorMedics 3100A (SensorMedics Inc., Yorba Linda, California), which provides HFOV; the LifePulse high-frequency jet ventilator (Bunnell Inc., Salt Lake City, Utah), which provides HFJV; and the Infant Star ventilator (Infra-Sonics Inc., San Diego, California), which is a high-frequency flow interrupter (HFFI).

Potential advantages of HFV over conventional mechanical ventilation (CMV) include the use of small tidal volumes, the ability to independently manage ventilation and oxygenation, and the safer use of mean airway pressure that is higher than that generally used during CMV [11]. Animal studies suggest that HFV works at lower proximal airway pressures than CMV, reduces ventilator-related lung injury, improves gas exchange in the face of air leaks, and decreases oxygen requirements [12–17]. Most causes of neonatal respiratory insufficiency requiring mechanical ventilation are amenable to treatment with HFV or CMV. For either technique to be successful, lung volumes need to be optimized for the underlying condition, and pressure exposures must likewise be similarly regulated. Only by the careful application of the chosen technique can ventilator-induced lung injury be avoided. The question remains, however: is one form of ventilation better than the other?

Despite the wealth of laboratory and clinical research on HFV, there are no established guidelines for prioritizing the use of HFV versus CMV in neonatal respiratory failure. Since 1997, approximately 25% of infants

born at 1500 g or less reported to the Vermont–Oxford Network have been treated at some time with HFV [18]. Some clinicians choose to use HFV as the primary mode of mechanical ventilation for small infants. Others elect to only use HFV as a “rescue” method when CMV is failing. Most clinicians stand somewhere in the middle of this spectrum. This article is not a “how to” guide for the use of HFV. Rather, it reviews and evaluates the available literature to determine the evidence base for the use of HFV in neonatal respiratory failure.

### **Evidence review**

An evidence review was performed to answer the following questions:

1. In the presence of acute neonatal respiratory failure or respiratory distress syndrome, does elective use of HFV provide benefit over the use of CMV?
2. In the presence of ongoing, severe neonatal respiratory failure, does the use of HFV as a rescue mode of ventilation provide benefit over the continued use of CMV?
3. Are there specific etiologies to neonatal respiratory failure in which HFV has been superior to CMV?

An electronic search of Medline and the Cochrane Database of Systematic Reviews was performed to identify relevant studies to these questions. The key words used for the search regarding the first two questions were high frequency ventilation (including high frequency oscillatory ventilation and high frequency jet ventilation) and respiratory insufficiency. The time frame searched was from 1985 to 2006, with limitation of studies related to the age range “birth to 23 months.” The search produced the following number of citations: high frequency ventilation 657 articles, respiratory insufficiency 4090 articles, HFV and respiratory insufficiency 118 articles. Selected articles, in particular controlled clinical trials and meta-analyses, were reviewed and presented in this article regarding the current role of HFV in neonates.

### **Elective high-frequency ventilation**

#### *Literature review*

To date, there have been 15 randomized controlled clinical trials of elective use of HFV versus CMV for the treatment of premature neonates who have respiratory insufficiency or RDS. One additional study compares the use of HFV versus CMV in term and near-term infants. These trials and their pulmonary outcomes are summarized in Table 1 [19–34]. The data from these 16 randomized controlled trials of HFV have yielded conflicting results. Five of the 16 trials demonstrated that early elective use of HFV improved pulmonary outcomes, in particular, decreased the incidence of

Table 1  
Summary of randomized controlled trials of elective use of high-frequency ventilation versus conventional mechanical ventilation

References	Infants in trial	Eligibility criteria	Type of HFV	Pulmonary-related results
HiFi [19]	673	Respiratory failure, 750–2000 g	HFOV (Hummingbird, Senko Medical)	No difference in CLD or death. Increased air leaks in HFOV-treated group.
Carlo et al [20]	42	RDS, 1000–2000 g	HFJV (not stated)	No difference in death, air leaks, or CLD.
Clark et al [21]	83	RDS, <35 wk, ≤1750 g	HFOV (SensorMedics 3100A)	HFOV-only decreased CLD compared with CMV only. HFOV x 72 h followed by CMV did not decrease CLD.
Ogawa et al [22]	92	RDS, 750–2000 g	HFOV (Hummingbird, Senko Medical)	No difference in death, duration of mechanical ventilation, CLD, or air leaks.
Wiswell et al [23]	73	RDS, <33 wk, >500 g	HFJV (Bunnell Life Pulse)	No difference in air leaks, duration of mechanical ventilation, or CLD. Increased poor outcomes (grade 4 ICH, cystic PVL, or death) in HFJV group.
Gerstmann et al [24]	125	RDS, <35 wk	HFOV (SensorMedics 3100A)	HFOV decreased oxygen use, days on mechanical ventilation, and CLD. No difference in air leaks.
Keszler et al [25]	130	RDS, <36 wk, 700–1500 g	HFJV (Bunnell Life Pulse)	HFJV decreased oxygen use and CLD. No difference in air leaks.
Rettwitz-Volk et al [26]	96	RDS, <32 wk	HFOV (Stephan SHF 3000)	No difference in duration of mechanical ventilation, air leaks, CLD or death.
Plavka et al [27]	43	RDS, 500–1500 g	HFOV (SensorMedics 3100A)	HFOV reduced CLD. No difference in air leaks or duration of mechanical ventilation.

Thome et al [28]	284	RDS, $\geq 24$ – $< 30$ wk	HFFI (Infant Star HFV)	HFFI was associated with more air leaks. No difference in duration of mechanical ventilation, death, or CLD.
Moriette et al [29]	273	RDS, 24–29 wk	HFOV (OHF1)	HFOV decreased need for surfactant. No difference in air leaks or CLD.
Courtney et al [30]	500	RDS, 601–1200 g, one dose of surfactant	HFOV (SensorMedics 3100A)	HFOV decreased age to extubation and CLD. No difference in death.
Johnson et al [31]	797	RDS, 23–28 wk	HFOV (Dräger Babylog 8000, SensorMedics 3100A, SLE 2000HFO)	No difference in CLD, air leaks, or death.
Van Reempts et al [32]	300	RDS, $< 32$ wk	HFOV (SensorMedics 3100A) or HFFI (Infant Star HFV)	No difference in CLD, air leaks, duration of mechanical ventilation, or death.
Craft et al [33]	46	Respiratory insufficiency, 23–34 wk, $< 1000$ g	HFFI (Infant Star HFV)	No difference in CLD, air leaks, duration of mechanical ventilation, or death.
Rojas et al [34]	119	Respiratory failure, $> 35$ wk CGA, $\geq 1750$ g	HFOV (SensorMedics 3100A)	No difference in CLD, air leaks, duration of mechanical ventilation, or death.

*Abbreviations:* CGA, corrected gestational age; ICH, intracranial hemorrhage; PVL, periventricular leukomalacia.

chronic lung disease, as compared with CMV [21,24,25,27,30]. The 11 remaining trials showed no difference in pulmonary outcomes when using HFV versus CMV [19,20,22,23,26,28,29,31–34]. Differences in high-frequency ventilators, ventilation strategies, definitions of chronic lung disease, study populations, and study center experiences over time, as well as the inability to blind the treatment intervention, may be the derivation of such incongruent results regarding early use of HFV versus CMV. Likewise, some of the studies were conducted before routine use of exogenous surfactant. Nonetheless, HFV is routinely used in many neonatal ICUs, and we need to glean as much knowledge as possible from the current body of evidence in the literature.

The HiFi trial [19], published in 1989, was the first controlled trial of HFV versus CMV in neonates and the second largest study of its kind to date. In the HFV group, the Hummingbird HFOV (Metran Co. Ltd., Saitama, Japan) was used at mean airway pressures comparable to those delivered by CMV. The study demonstrated no significant differences in the incidence of death (HFV, 18%; CMV, 17%) or chronic lung disease (HFV, 40%; CMV, 41%), defined as oxygen requirement and abnormal chest radiographic findings at 28 days between the two groups. Of concern, the study found significantly increased air leaks and severe intracranial pathology, including grade 3 and 4 intracranial hemorrhage and periventricular leukomalacia (PVL), in the HFV group. In a smaller study using the same Hummingbird HFOV and the same criteria for defining chronic lung disease but implementing a lung volume recruitment strategy, Ogawa and colleagues [22] demonstrated no significant differences in death or chronic lung disease in HFV- versus CMV-treated groups. In contrast to the HiFi study, however, this study did not show any significant difference in air leaks or severe intracranial pathology between the groups.

Although small in size, two studies by Carlo and colleagues [20] and Wiswell and colleagues [23] comparing HFV delivered by a HFJV versus CMV did not demonstrate any significant differences in pulmonary outcomes or mortality between each group. The studies did have conflicting results regarding intracranial pathology. Carlo and colleagues demonstrated no significant difference in the incidence of grade 2 through 4 intraventricular hemorrhage (IVH) between the two groups, whereas Wiswell and colleagues showed significantly more severe intracranial pathology (grade 3–4 IVH and PVL) in those treated with HFJV.

Ventilation with high-frequency flow interrupters versus CMV has been looked at in a large trial of 284 patients by Thome and colleagues [28] in 1999, and in a smaller, more recent study, the Sy-Fi study, by Craft and colleagues [33]. Thome's study included babies 24 to 30 weeks, whereas the Sy-Fi study included similarly aged babies but added a weight criterion of less than 1000 g. Both studies demonstrated no difference in chronic lung disease, mortality, or severe IVH. Both demonstrated increased air leaks in the HFFI-treated groups. In the Sy-Fi study, however, it was a select group

of infants, those treated with HFFI and weighing more (751–1000 g), that had a higher incidence of air leaks.

The vast majority of controlled trials of HFV versus CMV have employed HFOVs. However, the types of oscillator, some of which are not commercially available in the United States, varied from study to study, and one must be cognizant of this variable when comparing studies. In the largest trial of HFV versus CMV to date, Johnson and colleagues [31] included 797 preterm infants and used multiple different types of HFOV in the HFV arm. This trial demonstrated no difference in air leaks, CLD, or death in the HFV-treated group compared with the CMV-treated group. Unlike the concerning findings of the initial large HiFi study, Johnson and colleagues did not demonstrate any differences in severe IVH or PVL between the two treatment groups. Similarly, trials conducted by Rettwitz-Volk and colleagues [26] and Moriette and colleagues [29], using oscillators that are not commercially available in the United States, did not document an advantage of HFOV over CMV, with the exception of decreased exogenous surfactant requirements in the HFOV arm of the Moriette trial. Lastly, a recent prospective controlled trial of HFV versus CMV by Van Reempts and colleagues [32] revealed information on short-term endpoints as well as long-term follow-up results. They employed either HFOV or HFFI to provide HFV. The trial demonstrated no difference in duration of ventilation, air leaks, CLD, or mortality between the HFV and CMV groups. Looking at short- and long-term neurologic findings, they found no differences in the incidence of severe intracranial hemorrhage, PVL, or in the scores of more long-term assessment of motor and cognitive function at approximately 1 year of age.

To date, five controlled trials of HFV versus CMV have shown a benefit in pulmonary outcomes in the HFV groups. Favorable pulmonary results in the HFV-treated groups have occurred in less than one third of the total number of controlled trials of HFV versus CMV, and it is worth noting that most of these “positive” trials used HFOV (SensorMedics 3100A) as the means to provide HFV. Clark and colleagues [21] published the first positive trial in 1992. This single center study had three arms: HFOV only, HFOV for 72 hours followed by CMV, and CMV only. Babies in the HFOV-only arm had a decreased incidence of CLD. None of the three groups differed significantly in the incidence of air leaks, IVH, or death. Subsequently, Gerstmann and colleagues [24], in a multicenter controlled trial, demonstrated similar results of beneficial pulmonary outcomes with HFV, including a decreased need for multiple doses of surfactant and decreased incidence of CLD. Plavka and colleagues [27], in a smaller, single-center study, concluded similar results of decreased need for exogenous surfactant and decreased CLD in HFOV-treated babies. By far the most notable of the positive trials comes from Courtney and colleagues [30] and the Neonatal Ventilation Study Group. They published the largest controlled trial to date that demonstrates a benefit of HFV in pulmonary outcomes. This study included 500 preterm neonates who received at least

one dose of surfactant. The neonates randomized to the HFOV arm had significantly fewer days of mechanical ventilation as well as a decreased incidence of CLD compared with those treated with CMV. There was no difference in mortality, IVH, or PVL between the groups.

There is only one controlled trial of HFJV versus CMV that has ever demonstrated a beneficial pulmonary effect from using early, elective HFJV. Keszler and colleagues [25], in a multicenter controlled trial of 130 babies who had RDS, demonstrated a decreased incidence of CLD at 36 weeks corrected gestational age, as well as a decreased need for home oxygen therapy in the HFJV-treated group. Furthermore, there were no differences in air leaks, IVH, or death between the two groups.

#### *Evidence-based recommendations*

There is no evidence from the authors' current review of the literature or other meta-analyses that elective use of HFV, in the form of HFOV or HFFI, provides any greater benefit to premature infants who have RDS than CMV [35]. The data are limited and the results are mixed as to whether HFJV may reduce the incidence of CLD [36]. At this time, preferential use of HFV as the initial mode of ventilation to treat premature infants who have RDS is not supported.

#### *Gaps in knowledge*

Ventilation strategies play a potentially significant role in pulmonary outcomes. There are no standardized criteria for the optimal use of HFV, nor are there sufficient data to determine the best techniques for lung recruitment. Similarly, though recruitment and maintenance of lung volume is an important component of treatment for many conditions, there are no easy-to-use techniques for accurate clinical measurement of lung volumes at the bedside. Finally, the use of so-called "high-volume ventilation strategies" versus "low-volume ventilation strategies" is incompletely defined, and the issue of which ventilator to use to provide HFV is unknown. In the same light, standardized strategies have not been defined for the optimal use of CMV, which today has many different ventilation modes and modalities available for clinical use. Lastly, and perhaps most important, long-term neurodevelopmental outcomes are of particular interest to physicians treating premature infants; these are lacking in most published studies.

### **Rescue high-frequency ventilation**

#### *Literature review*

The body of literature regarding the use of HFV as a rescue technique is small and incomplete. In particular, there are only two controlled trials to date that explore this issue in premature infants who have severe respiratory distress. If controlled trials comparing rescue HFV versus CMV in term and



near-term infants are included, the total number of studies only increases to four. These trials and their pulmonary outcomes are summarized in Table 2 [37–40].

The HIFO trial investigated whether the use of rescue HFOV provides any benefit over continued CMV in preterm infants who have severe respiratory insufficiency, in particular with regard to pulmonary air leaks [38]. The HIFO trial randomized 176 preterm infants (<35 weeks, >500 g) who had severe respiratory distress, and had or were at increased risk of developing pulmonary air leak to HFOV versus continued CMV. This trial demonstrated a reduction in new pulmonary air leaks in the HFOV arm; however, there was no significant difference in the incidence of ongoing pulmonary interstitial emphysema, pneumomediastinum, or pneumothorax overall. There was also no difference in duration of mechanical ventilation or death between the two groups. IVH rates were increased in the HFOV-treated group compared with the CMV-treated group. This is a potentially worrisome finding, and unfortunately, there is no long-term neurologic or developmental follow-up described in this study.

In a more select population, Keszler and colleagues [37] randomized 144 preterm infants (<35 weeks,  $\geq 750$  g and <2000 g) who had severe respiratory failure and pulmonary interstitial emphysema to ventilation with the Bunnell HFJV device versus continued CMV at high rates. The study did allow for crossover if an infant met criteria for failure of the initially allocated ventilation mode. A significant number of patients in both groups met failure criteria (39% HFJV, 63% CMV) and crossed over to the alternate ventilation strategy. This being said, the patients treated with HFJV had more rapid improvement of their pulmonary interstitial emphysema. However, there were no differences in chronic lung disease, new air leaks, severe IVH, or mortality between the two groups. When the crossover population was excluded, the study demonstrated a lower mortality rate in the HFJV-treated group compared with the CMV-treated group.

The two aforementioned controlled studies of rescue HFV versus CMV in preterm infants were completed at a time when exogenous surfactant and antenatal steroids were not necessarily administered on a routine basis. Therefore, the generalization of specific results to today's neonatal ICU population can potentially be called into question. The controlled studies of rescue HFV versus CMV in term or near-term infants by Clark and colleagues [39] and Engle and colleagues [40] are somewhat more applicable because they were performed more recently, and the infants studied are of a gestational age that antenatal steroids and exogenous surfactant are not obligatory. Nonetheless, since the time of their publication, exogenous surfactant and other interventions, such as inhaled nitric oxide (iNO), are used with increasing frequency and are not accounted for in these studies.

Clark and colleagues [39] randomized 79 term or near-term infants (>34 weeks,  $\geq 2000$  g) who had severe respiratory failure from various etiologies (meconium aspiration, RDS, pneumonia, congenital diaphragmatic hernia,

Table 2  
Summary of randomized controlled trials of rescue use of high-frequency ventilation versus conventional mechanical ventilation

References	Infants in trial	Eligibility criteria	Type of HFV	Pulmonary-related results
Keszler et al [37]	144	Pulmonary interstitial emphysema on CMV, $\geq 750$ g	HFJV (Bunnell Life Pulse)	Increased treatment success in HFJV group. Decreased mortality in HFJV group is crossover excluded. No difference in CLD, new air leaks, airway obstruction, or necrotizing tracheobronchitis.
HIFO Study Group [38]	176	Severe RDS, $\geq 500$ g, $< 48$ h old	HFOV (SensorMedics 3100A)	Decreased new air leaks in HFOV group. No difference in ongoing air leak syndrome, duration of mechanical ventilation, or death.
Clark et al [39]	79	Severe respiratory failure, $> 34$ wk, $\geq 2000$ g, $< 14$ d old	HFOV (SensorMedics 3100A)	Improved gas exchange and increased treatment success in HFOV group. No difference in CLD, air leaks, duration of mechanical ventilation, need for ECMO, or death.
Engle et al [40]	24	Severe respiratory failure and pulmonary hypertension, $\geq 35$ wk, $> 2000$ g	HFJV (Bunnell Life Pulse)	Improved gas exchange in HFJV group. No difference in CLD, air leaks, duration of mechanical ventilation, need for ECMO, or death.

*Abbreviation:* ECMO, extracorporeal membrane oxygenation.

other) to HFOV versus continued CMV. The average age at randomization was 37 to 40 hours, and crossover to the alternate form of ventilation was allowed if preset criteria for treatment failure were achieved. The study demonstrated improved gas exchange and less treatment failure with HFOV, both in the patients initially allocated to rescue HFOV as well as in those that failed continued CMV and crossed over to HFOV. There was no difference in the incidence of chronic lung disease, IVH, or death between the two groups.

Engle and colleagues [40] randomized a more specific population of term and near-term infants ( $\geq 35$  weeks,  $>2000$  g) who had severe persistent pulmonary hypertension to HFJV versus CMV. The average age at randomization was 22 to 25 hours and crossover for treatment failure was not allowed in this study, because those who failed their allocated form of ventilation were referred for extracorporeal membrane oxygenation (ECMO). In this study, the HFJV-treated patients had improved oxygenation and ventilation versus the CMV-treated group; however, there were no long-term differences in the duration of mechanical ventilation or the incidence of chronic lung disease, air leaks, IVH, patients requiring ECMO, or death.

#### *Evidence-based recommendations*

Although limited in nature, there is no evidence from the authors' current review of the randomized controlled trials or other meta-analyses that use of rescue HFV provides any long-term benefit over continued CMV in the preterm, near-term, or term patient who has respiratory failure [41–43].

#### *Gaps in knowledge*

Although there is a significant amount of data from nonrandomized uncontrolled trials regarding the use of rescue HFV in babies who have an inadequate response to CMV, such as that by Davis and colleagues [44], few randomized controlled trials of HFV versus CMV in conditions other than acute RDS in the preterm infant exist. Similarly, the few randomized trials that have been published regarding rescue HFV were performed when the administration of exogenous surfactant and antenatal steroids were not the norm. Current randomized clinical trials of rescue HFV are necessary.

### **High-frequency ventilation for conditions other than respiratory distress syndrome—management of bronchopleural or tracheoesophageal fistula, and high-frequency ventilation plus inhaled nitric oxide**

#### *Literature review*

Because of the low occurrence rates of bronchopleural and tracheoesophageal fistulas in neonates, there are no randomized controlled trials

evaluating their management with HFV versus CMV. However, a few studies have formally evaluated the amount of air leak through these types of fistulas using HFV versus CMV. In the management of infants who had bronchopleural fistula, Gonzales and colleagues [45] showed a decrease in chest tube air leak when using HFJV versus CMV. Goldberg and colleagues [46] and Donn and colleagues [47] reported similar experiences in managing infants who had tracheoesophageal fistulas with HFJV. Furthermore, case reports, such as that by Bloom and colleagues [48], and animal studies, such as that by Orlando and colleagues [49], relay findings of an observed benefit to the use of HFV in the ventilatory stabilization of patients who have tracheoesophageal or bronchopleural fistula.

Another common use for HFV in the neonatal population is in conjunction with iNO for severe hypoxemic respiratory failure, often as a result of persistent pulmonary hypertension. In a randomized controlled trial, Kinsella and colleagues [50] looked at the effects of combining HFOV with iNO compared with either therapy used alone in infants who have persistent pulmonary hypertension. This study enrolled 205 neonates who had pulmonary hypertension from various underlying etiologies and demonstrated maximal treatment success (better arterial oxygenation) with the simultaneous use of HFOV and iNO. When looking at the premature population, Schreiber and colleagues [51] did not find such a benefit from ventilation modality. They enrolled 207 infants born at less than 34 weeks gestation into a randomized, double-blind, controlled study of iNO and differing ventilation strategies with CMV versus HFOV. There was no difference in pulmonary outcomes or death directly related to ventilation mode. In a randomized study of pediatric patients who had hypoxemic respiratory failure, Dobyns and colleagues [52] found similar results to Kinsella's study with maximally improved oxygenation when using the combination of HFOV plus iNO as compared with HFOV alone, CMV plus iNO, or CMV alone. Although iNO is a new therapy and its potential synergy with HFV is similarly rather new, bench research further confirmed adequate and accurate delivery of iNO with both the HFOV and HFJV systems [53,54].

### *Evidence-based recommendations*

Review of the literature supports the use of HFV with iNO to maximize oxygenation and treatment effects in hypoxemic respiratory failure, in particular in babies who have pulmonary hypertension. The current literature lacks any randomized trials to support the use of HFV over CMV in the treatment bronchopleural or tracheoesophageal fistula. That being said, the data do merit consideration, as the use of HFV in this population appears to diminish the amount of continuous air leak and improve patient stabilization.

### *Gaps in knowledge*

Ideally, randomized trials are needed to elucidate the optimal ventilatory strategy in infants who have bronchopleural or tracheoesophageal fistula. However, because of the small number of patients who have these problems, it is unlikely that a randomized controlled trial will ever be feasible.

### **Summary**

High-frequency ventilation is a form of mechanical ventilation that uses small tidal volumes and extremely rapid ventilator rates. It allows for pulmonary gas exchange at lower mean airway pressures than conventional mechanical ventilation. When HFV was first introduced on the menu of respiratory therapies for sick babies, hope abounded that HFV would be the universal remedy for most forms of neonatal respiratory insufficiency. In particular, clinicians were optimistic that HFV could be particularly useful in decreasing the incidence of chronic lung disease of prematurity. After almost 20 years of data gathering, this does not appear to be the case. When looked at as a whole, the currently available randomized controlled trials comparing HFV versus CMV have not demonstrated any clear benefit of HFV either as a primary mode or as a rescue mode of ventilation in neonates who have respiratory insufficiency. However, the current literature does support the preferential use of HFV over CMV in conjunction with iNO to maximize oxygenation in hypoxemic respiratory failure, in particular, as a result of persistent pulmonary hypertension.

Clearly, HFV has become a reliable and useful addition to the various modes of mechanical ventilation in neonates. Nonetheless, as most causes of neonatal respiratory insufficiency requiring mechanical ventilation are amenable to treatment with HFV or CMV, clinical judgment still dictates the choice of one form or the other, because the high-quality evidence currently available is still inconclusive. Ongoing studies will ideally elucidate the optimal lung volume and ventilatory strategy for specific disease states as well as provide clinicians with long-term follow-up data regarding neurologic and developmental outcomes of children treated with the various forms of ventilation.

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