REVIEW

First intention high-frequency jet ventilation for periviable infants

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Purpose of review

Ventilation of periviable infants born at 22–23 weeks gestation remains a challenge in neonatology. This review highlights the evidence surrounding the use of first intention high-frequency jet ventilation (HFJV) in infants born near the limits of viability with a review of pulmonary fetal development and a focused overview of HFJV strategies including an in-depth analysis of the management strategies used in the initial randomized trials.

Recent findings

A paucity of recent trials exists, with no randomized control trials assessing the use of first intention HFJV performed in the last 25 years. A retrospective observational cohort trial of the use of HFJV for infants born at less than 750 g has been recently published demonstrating the efficacy of HFJV for this population even with 2.0-mm endotracheal tubes.

Summary

The lack of recent randomized trials contributes to the controversy surrounding the use of first intention HFJV. Although new research is needed in the area, this review includes the ventilation strategy of an experienced center with a focus on the use of first intention HFJV for the care of premature infants born less than 24 weeks gestation.

Keywords

high-frequency jet ventilation, neonatology, periviable infants

INTRODUCTION

Successful ventilation of periviable infants requires an understanding of fetal lung development and is optimized with a consistent approach. At the University of Iowa, we have utilized first intention high-frequency ventilation for all periviable infants born before 24 weeks gestation since 2006 and have offered resuscitation for infants born at 22 weeks gestation since 2008. Survival for infants born before 24 weeks gestation with this approach was 78%, with 64% of these infants demonstrating mild or no neurodevelopmental impairment at 18–22 months of corrected age [1▪▪]; 93% received high-frequency jet ventilation (HFJV) and 7% high-frequency flow interruption. The high survival rate of periviable infants at Iowa is the result of multidisciplinary management strategies refined over time with a focus on minimizing volutrauma with the use of first intention HFJV as a critical first step. This article will review fetal lung development, discuss the approach to using HFJV and examine the literature supporting this strategy.

DEVELOPMENTAL EMBRYOLOGY AND POSTNATAL LUNG DEVELOPMENT

Fetal lung maturation is divided into four periods: pseudoglandular, canalicular, terminal saccular, and alveolar [2]. Infants born at the limits of viability undergo much of their lung development after birth. In the pseudoglandular period, between 6 and 16 weeks, all the elements of the lung have formed except those involved with gas exchange, respiration is not possible and fetuses born during this period are unable to survive. Between 16 and 26 weeks, the lungs are in the canalicular period. During this period, the lumen of the bronchi and

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KEY POINTS

- HFJV ventilation has a strong physiologic rationale, and low tidal volume respiratory support strategies have been used successfully in periviable infants.
- Although controversy exists, randomized control trials evidence has demonstrated the effectiveness of HFJV in neonates.
- The paucity of recent studies suggests additional investigation into this field is needed.

terminal bronchioles become larger and the lung tissue becomes vascularized. By 24 weeks each terminal bronchus gives rise to respiratory bronchioles which divide into alveolar ducts. Respiration is possible toward the end of the canalicular period once thin-walled terminal saccules or primordial alveoli have developed at the ends of the respiratory bronchioles and the lung tissue is vascularized. Importantly the cranial segments of the fetal lung mature faster than the caudal segments resulting in segments of the lung that are mature enough for gas exchange as early as 22 weeks gestation as Type I pneumocytes begin to appear during this period. This allows for effective gas exchange to occur in these areas of the lung. During the terminal saccular period between 26 weeks and birth, an increasing number of terminal saccules develop, and the epithelium becomes very thin. Type I alveolar cells now fully line the terminal saccules and gas exchange readily occurs. Immature Type II alveolar cells which secrete pulmonary surfactant are scattered among the type I alveolar cells. The alveolar period takes place from 32 weeks to 8 years. Structures analogous to alveoli are present at 32 weeks, but the characteristic mature alveoli do not form until after birth; about 95% of alveoli develop postnatally. Lung development during the first few months after birth is characterized by an exponential increase in the surface area of the air blood barrier. About 50 million alveoli, one-sixth of the adult number, are present in the lungs of a term newborn infant, and by the 8th year, 300 million alveoli are present [3].

CLINICAL APPLICATION OF DEVELOPMENTAL PHYSIOLOGY

Accelerating fetal lung development is critical for the survival of periviable infants, and thus respiratory management of these infants begins before birth. Administration of antenatal corticosteroids (ANS) for impending preterm delivery at 22–23 weeks gestation is needed for the improvement of survival by enhancing maturation of type II alveolar cells and thinning the mesenchyme to allow for more effective gas exchange [4]. ANS administration reduces severe interventricular hemorrhage, death and decreases neurodevelopmental impairment at 18–22 months in infants born at 22–25 weeks gestation [5–8]. Ehret *et al.* [9] showed that concordant receipt of ANS and postnatal life support was alone; infants born at 22 weeks gestation who received both ANS and postnatal life support had higher survival, 38.5%, as compared with 17.7% in those who did not receive ANS. At Iowa, between 2006 and 2015, 91% of 22 and 23 week infants received antenatal steroids [1■■]. Antenatal corticosteroids are administered at Iowa at 21 5/7 weeks when there is concern for potential early birth, such as in cases of preterm premature rupture of membranes, labor, or incompetent cervix before 22 weeks. This approach highlights the collaborative and supportive relationship our division has with our obstetric and maternal fetal medicine colleagues and plays a crucial role in our outcomes.

At the canalicular stage of lung development it is important to avoid shear force injury from volutrauma, since the incidence of pneumothorax and pulmonary interstitial emphysema (PIE) have an inverse association with gestational age [10,11]. First intention HFJV provides a lung protective strategy, which when combined with ANS, increases the potential for safer ventilation. HFJV allows for low tidal volume gas exchange minimizing volutrauma and shear force injury. The Model 203 Life Pulse High Frequency Ventilator (Jet), (Bunnell, INC. Salt Lake City, Utah, USA) was granted premarket approval by the FDA for the reduction of barotrauma (Federal Register Vol. 53, No. 154, 30101, 1988). The Bunnell Jet utilizes a microprocessor controlled pinch valve to generate a stream of high-frequency pulses of fresh gas, from which the tidal volume is derived by regulating the desired peak pressure. Rapid rates, 240–660 breath per minute (BPM) allow for tidal volumes smaller than physiologic dead space to be utilized. Ventilation occurs primarily from convective flow streaming (Taylor dispersion), as the gas is injected into the airways at a very high-velocity resulting in the gas molecules traveling by laminar and transitional flow down the core of the bronchial tree minimizing the impact of dead space [12]. Exhalation on HFJV is passive from elastic recoil. A special endotracheal tube (ETT) adapter is used, which has a separate port through which the HFJV pulses are introduced and a monitoring port to measure pressures. HFJV has been shown to decrease gas flow through a pneumothorax and decrease exposure of the developing lung to high ventilator mean airway pressures [13,14].

INDICATIONS FOR FIRST INTENTION HIGH-FREQUENCY JET VENTILATION

The first randomized control trial (RCT) of HFJV was carried out by Carlo *et al.* [15] demonstrating that HFJV provided gas exchange at lower mean airway pressures than conventional ventilation. Clear support for the initial use of the HFJV in premature infants with respiratory distress syndrome (RDS) was seen in a multicenter randomized clinical trial by Keszler *et al.* [16], which found a significant reduction in bronchopulmonary dysplasia (BPD) in infants with RDS who received surfactant without any increase in nonpulmonary morbidities compared with controls (HFJV $n=65$, conventional ventilation $n=65$). This built upon previous work that concluded that infants with PIE were exposed to less mean airway pressure and improved at a more rapid rate when rescued with HFJV than infants managed with conventional ventilation [17]. PIE is one of the most serious complications of RDS in premature infants since PIE significantly increases morbidity and mortality especially for infants with birth weights less than 1500 g exposed to peak inspiratory pressures (PIPs) more than 25 cmH_2O during the first 2 weeks of life [18]. In a RCT of term infants with hypoxemic respiratory failure and pulmonary hypertension, Engle *et al.* [19] found that infants receiving HFJV compared with conventional ventilation had improved oxygenation and ventilation (HFJV $n=11$, conventional ventilation $n=13$) with no increase in mortality. In addition, Davis *et al.* demonstrated an improvement in severe hypoxemic respiratory failure in 28 late preterm infants treated with surfactant and optimized conventional ventilation after conversion to HFJV and given repeat surfactant [19,20].

Controversy exists regarding the primary use of HFJV for premature infants with RDS receiving surfactant therapy. Wiswell *et al.* [21] in a RCT published in 1996, assessed the effects of elective HFJV on premature infants with RDS treated with surfactant (HFJV $n=37$, conventional ventilation $n=36$) and found that the HFJV group exhibited more adverse outcomes including death and/or cystic periventricular leukomalacia (PVL). However, there were differences in the ventilator management strategies employed compared with Keszler's study including the use of an initial peak end expiratory pressure (PEEP) setting of 4–5 vs. 6–8 cmH_2O, as well as different approaches to the management of improved ventilation with decreasing levels of $PaCO_2$. In the Keszler study, as PIP was weaned in response to improving ventilation, the PEEP was increased to maintain the mean airway pressure (MAP) at the level required to maintain oxygenation. In the Wiswell study a different approach to adjusting PIP may have contributed to significant differences found in $PaCO_2$ levels between the HFJV and conventional ventilation groups with mean $PaCO_2$ levels after 4 h of randomization (as well as the lowest $PaCO_2$ levels seen during the first 3 days of life) significantly lower in the HFJV group compared with the conventional ventilation group (HFJV 16.9 ± 6.5, conventional ventilation 22.2 ± 6.6). In Keszler's study there were no significant differences between the two modes of ventilation ($PaCO_2$ levels 40.3 ± 8.8 on HFJV and 41.4 ± 8.5 on conventional ventilation). Furthermore, there were differences in the crossover rates from HFJV to conventional ventilation between the studies with 4.6% of the HFJV patients crossing over in the Keszler study compared with 19% in the Wiswell study. The different outcomes in these two well designed studies demonstrates the challenge in comparing RCTs involving complex devices as the implementation of different management strategies within individual studies can impact the outcomes [22].

A 2000 Cochrane review comparing HFJV vs. conventional ventilation across three trials, (Carlo, Wiswell, and Keszler) found a reduction in chronic lung disease at 36 weeks post menstral age in survivors [23]. There were no significant differences in mortality or intraventricular hemorrhage. The presence of PVL, though significant in Wiswell's trial, when taken in aggregate with Keszler's trial was no longer significant. A 2006 Cochrane review assessed the role of HFJV as a rescue therapy compared with conventional ventilation, only included a single trial (Keszler) [24] and when updated in 2015, still only included that same trial [25]. Plavka *et al.* [26] assessed the effect of switching from conventional ventilation to HFJV in 11 extremely premature infants with severe respiratory failure and chorioamnionitis finding that HFJV improved gas exchange. A final Cochrane review attempted to compare HFJV vs. HFOV in preterm infants, but found no studies that met their criteria [27].

THE USE OF FIRST INTENTION HIGH-FREQUENCY JET VENTILATION AT IOWA FOR PREMATURE INFANTS BORN AT 22–23 WEEKS GESTATION

Our strategy is based on fetal lung development and focuses on minimizing mechanical injury from volutrauma and reducing the effects of hyperinflation on both lung injury and cardiac output. At Iowa, all periviable infants born at 22–23 weeks are intubated in the delivery room with either a 2.0 or 2.5 mm ETT and within 10 min of life placed on first intention HFJV for lung protection to reduce the risks of volutrauma. We have recently shown that infants (median gestation age 23 weeks, interquartile range (IQR) 22–24 weeks, birthweight median 545 g, IQR

450–615 g) can be successfully managed on HFJV with a 2.0 mm ETT with a survival rate of 77% [28▪▪]. Infants born at less than 24 weeks gestation are started on a jet rate of 300 BPM with an inspiratory time of 0.02 s for an inspiratory to expiratory (I : E) ratio of 1 : 9. We begin with an initial PEEP of 5 cmH_2O and adjust based on aeration as needed to improve oxygenation using the initial dose of surfactant, gently bagged in, as the primary lung recruitment maneuver. Our initial PEEP is lower than the PEEP used in Keszler's trial, but reflects the increases use of ANS as well as the improved efficacy of the newer surfactants (Curosurf/Infasurf vs. Exosurf/Survanta) and is focused on the avoidance of hyperinflation and overdistention to prevent altered hemodynamics and compromised cerebral blood flow secondary to impaired venous return to the heart as a neuroprotective strategy. Hypocarbia is rigorously avoided, with a $PaCO_2$ goal of 45–55 mmHg in the first 7 days of life. If signs of PIE develop the jet rate is lowered and a higher $PaCO_2$ is tolerated (60 mmHg). Initial PIP is started to elicit 'good chest wall shake' between 20 and 24 cmH_2O. Initially no conventional sigh breaths are added to minimize exposure to tidal volumes beyond those used with HFJV. However, if scattered atelectasis develops or the neonate begins to exhibit significant desaturation episodes from an inadequate respiratory drive that is unresponsive to methylxanthines, four conventional breaths are added and increased as needed. Over the next several weeks, the baseline jet rate and PEEP may be increased to treat microatelectasis through an increase in MAP before increasing the Jet PIP which is increased when needed to maintain pCO_2 goals. Infants requiring definitive intervention for a significant patent ductus arteriosus do so while remaining on the HFJV [29]. Periviable infants are typically extubated directly from the HFJV to noninvasive ventilation (NIV) using NIV Neurally Adjusted Ventilatory Assist once they exhibit a sustained respiratory drive without requiring prior conversion to conventional ventilation. Infants who fail extubation due to central apnea will be placed on conventional ventilation whereas infants who fail extubation due to worsening lung disease will be placed back on HFJV. With this approach the incidence of Grade 3 BPD, which is associated with twofold higher rates of late death, serious respiratory morbidity and moderate-to-severe neurodevelopmental impairment was 6% [1▪▪,30].

CONCLUSION

There is no RCT assessing the role of first intention HFJV in infants born at less than 24 weeks gestation; the mean gestational age of the HFJV cohort in the Wiswell study was 26.9 ± 2.9 weeks and in the Keszler study, 27.3 ± 2.1 weeks. Furthermore, no first intention HFJV RCT has been conducted in almost 25 years leading to continued controversy regarding the use of first intention HFJV for the periviable population. Many retrospective studies have found positive outcomes when utilizing HFJV with a first intention approach however, controversy exists surrounding the use of HFJV due to the different mortality and morbidity outcomes from the two major RCTs. It is important to remember that, as with any machine, variation in results may occur based on variation in practice rather than due to the mechanics of the device. As Dr A Charles Bryan wrote 'The RCT is ideal for evaluating things like drugs, as randomization practically eliminates further medical input. It is far less effective in testing technologies, where the whim of the physician controls the way in which the technology is applied [22].'

First intention HFJV has a strong physiologic rationale, and it is possible that HFJV rescue studies which found limited benefit reflect a degree of lung injury that exceeded the ability of healing from minimizing further volutrauma. This is the reason that periviable infants at Iowa, following resuscitation and intubation in the delivery room, are started on HFJV within 10 min of life and maintained on HFJV until they have matured to the point of successful extubation. The goals of first intention HFJV for periviable infants are to minimize mechanical injury to the immature fetal lung (PIE and pneumothorax), to reduce mortality due to lethal BPD [31] and morbidity due to Grade 3 BPD [30] and most importantly to optimize neurodevelopmental outcomes.

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Conflicts of interest

There are no conflicts of interest.

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▪ of special interest
▪▪ of outstanding interest

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