Nasal high-frequency jet ventilation (nHFJV) following extubation in preterm infants

Short title: Nasal high-frequency jet ventilation (nHFJV)

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Jessica Davidson, Bradley A Yoder

Division of Neonatology

University of Utah School of Medicine

A. Abstract

This prospective, randomized trial involves extubating preterm infants from mechanical ventilation to nasal high-frequency jet ventilation (nHFJV) to assess whether this decreases the rates of reintubation compared to nasal intermittent positive pressure ventilation (NIPPV), which is currently a common practice. With this study, we aim to decrease the rates of reintubation and days requiring mechanical ventilation, which are both risk factors for bronchopulmonary dysplasia (BPD). Additionally, nHFJV may decrease rates of severe BPD, diagnosed at 36 weeks corrected gestation age (CGA).

B. Background

Premature infants often experience respiratory insufficiency requiring increasing respiratory support, including endotracheal intubation and mechanical ventilation. The need for invasive mechanical ventilation as well as the duration of intubation are risk factors for BPD (Dumpa et al, 2011). Increasing efforts for early extubation to a non-invasive mode of support, such as continuous positive pressure ventilation (CPAP) or NIPPV, have been made. However, in these high risk preterm infants there remains a considerable rate of respiratory failure on CPAP requiring escalation in support, including reintubation (Barrington et al, 2001). Additionally, infants who have failed extubation experience higher rates of BPD and/or death (Manley et al, 2016; Chawla et al, 2017).

Use of non-invasive high frequency ventilation (HFV) has been described as a rescue method following failure of other non-invasive ventilator modes or as a means to increase the success post-extubation. When used as invasive high frequency ventilation, high frequency oscillatory ventilation (HFOV) or high frequency jet ventilation (HFJV) utilize supraphysiologic respiratory rates and small tidal volumes which has been show to inflict less lung injury than conventional modes of ventilation (Cotton et al, 2001).

Using a mechanical newborn lung model, nasal HFV has improved CO2 removal when compared to conventional NIPPV (Mukerji et al, 2013; Mukerji et al, 2015). Animal studies in the lab of Kurt Albertine have shown improved ventilation and oxygenation in the high frequency nasal ventilation group versus the mechanical ventilation group in a preterm lamb model leading towards better alveolar formation noted histologically (Reyburn et al, 2008; Null et al, 2014).

Few small clinical studies have looked at the use of nasal HFV however many were for short periods of time. Preterm infants on CPAP showed a significant decrease in pCO2 after being switched to nHFV for a two hour period (Colaizy et al, 2008). In a pilot trial investigating the use of nasal HFV immediately after extubation in high-risk preterm infants, it was noted that pCO2 levels significantly decrease, although returned to pre-extubation values after discontinuing nasal HFV (Czernik et al, 2012). In a recent randomized controlled trial, 81 infants were randomized to nasal HFV or nasal CPAP following surfactant administration (Zhu et al, 2017). Infants in the nasal HFV group had a significantly decreased need for invasive mechanical ventilation compared to the nasal CPAP group, however their cohort had a mean gestation age of ~32 weeks (Zhu et al, 2017). None of these clinical studies noted any negative impact from using nasal HFV.

C. Significance and Purpose

Very low birth weight infants are at increased risk of requiring prolonged duration of mechanical ventilation and multiple intubations, both of which are risk factors for ventilator-induced lung injury and BPD. Thus, it is important to investigate respiratory support methods that are able to effectively oxygenate and ventilate these high risk preterm infants while reducing their risk of lung injury. Nasal high-frequency ventilation is one potential intervention that may decrease the risk of respiratory failure in very low birth weight infants. Small studies have shown effective respiratory support over short time periods in infants, however these studies use nasal high-

frequency oscillatory ventilation. To our knowledge there are no published studies looking at the use of nasal high-frequency jet ventilation in this high risk population.

D. Hypothesis and Specific Aims

We hypothesize that extubation of very preterm infants to nHFJV will significant decrease the rates of reintubation compared to those infants extubated to NIPPV.

Our specific aims are:

1. To examine the rate of respiratory failure requiring reintubation and invasive mechanical ventilation (IMV) within 72 hours of initiating study intervention.
2. To examine the rate of respiratory failure requiring reintubation and IMV within 7 days of transitioning off of non-invasive study intervention
3. To compare the total number of days requiring intubation with mechanical ventilation
4. To compare the rates of moderate to severe BPD with and without altitude correction at 36 weeks CGA per criteria defined by 2001 NICHD Consensus Conference

E. Methods

1. **Trial design**: This is a prospective, randomized trial.

2. **Study site**: The study site will be the University of Utah Medical Center, a Level III neonatal intensive care unit with 52 beds.

3. **Population**: Infants born $24^{0/7}$ to $28^{6/7}$ weeks gestational age (GA) requiring invasive mechanical ventilation (IMV) and meet extubation criteria within the first 7 days of life
    a. **Inclusion criteria**:

i. $24^{0/7}$ to $28^{6/7}$ weeks GA

ii. Intubated within 24 hours of life to synchronized intermittent mandatory ventilation (SIMV) or high frequency ventilation (HFV, includes HFOV or HFJV)

iii. Meets unit guidelines for extubation within 7 days of life

1. See Table 1 for outline of criteria

iv. Infants intubated for surfactant replacement therapy via INSURE method (Intubation-Surfactant-Extubation) are eligible

v. Initiation of treatment arm must occur within 6 hours of extubation

1. If randomization occurs after the time of extubation, infants are eligible if FiO2 requirements are >30%

vi. Consent obtained from parent/legal guardian

b. **Exclusion criteria**:

i. Major congenital and/or chromosomal anomalies

ii. Upper oropharyngeal anomalies

4. **Randomization**:

a. Infants stratified by GA ($24^{0/7}$ – $25^{6/7}$ weeks, $26^{0/7}$ – $28^{6/7}$ weeks) and randomized in blocks of 4 to nHFJV or NIPPV group

b. Randomization and initiation of treatment arm must occur within 6 hours of extubation

c. Randomization will occur via sealed opaque envelopes

5. **Intervention**: Subjects will be randomized to be extubated to nasal HFJV (nHFJV) via the Bunnell Life Pulse high-frequency JET ventilator through a latex free PVC nasopharyngeal airway.

a. Initial settings for nHFJV:
    i. PEEP = 8
    ii. HFJV PIP = 25
    iii. On-time = 0.034 second
    iv. Rate = 360 breaths per minute
    v. Conventional rate = 10 breaths per minute
    vi. I-time = 1 second
    vii. Conventional PIP = 24
    viii. FiO2 adjusted to maintain target saturations per unit guidelines
b. Available sizes of nasopharyngeal airway are 12 Fr and 14 Fr with an internal diameter of 3.0 mm and 3.5 mm, respectively, which will be attached to a 3.0 mm LifePort endotracheal tube adapter

6. **Control group**: Randomized subjects will be extubated to non-invasive positive pressure (NIPPV) via Hudson prongs.
    a. Initial settings
    b. PIP = 25
    c. PEEP = 6
    d. Ti = 0.6 sec
    e. Rate = 20 breaths per minute
    f. FiO2 adjusted to maintain target saturations per unit guidelines
    g. Infants in the control group must remain on the Hudson prong interface for a minimum of 72 hours. At that time, can be transitioned to another interface to deliver NIPPV at the discretion of the medical team.

7. **Data to be collected**:

a. **Specific Aim 1**: To examine the rate of respiratory failure requiring reintubation and IMV within 72 hours of initiating study intervention.
    i. Reintubation criteria:
        1. Respiratory acidosis with pH <7.2 and $PaCO_2$ >60 mmHg on 2 successive blood gases on optimal ventilatory settings
        2. FiO_2 >0.6 to maintain SpO_2 >88% for >1 hour
        3. Impending respiratory failure noted by Silverman score >6
            1. Silverman, W. and Anderson, D.: *Pediatrics* 17:1, 1956.
            2. Depiction of scoring system noted in Figure 1.
        4. Severe/worsening apnea and bradycardia
            1. >3 episodes per hour requiring stimulation OR
            2. >1 episode of apnea requiring bag-mask ventilation in 24 hours
b. **Specific Aim 2**: To examine the rate of respiratory failure requiring reintubation and IMV within 7 days of transitioning off of non-invasive study intervention.
c. **Specific Aim 3**: To compare the total number of days of intubation with mechanical ventilation in the two study arms
d. **Specific Aim 4**: To compare rates of moderate to severe BPD with and without altitude correction at 36 weeks CGA per criteria defined by 2001 NICHD Consensus Conference

8. Procedure/Protocol

a. Identify infants meeting inclusion criteria within the first 24 hours of life

i. If infant meets extubation criteria within the first 7 days of life, approach care provider for permission to obtain consent from parents/legal guardian

1. Record patient and maternal demographic information.

b. Ensure standard of care transcutaneous monitor (TCM) is placed prior to initiation of study intervention

i. Blood gases ordered per clinical practice

c. Randomized infants extubated to nHFJV or NIPPV

i. Nasopharyngeal airway to be replaced in alternating nares every 48 hours to decrease risk of skin breakdown

d. Respiratory settings adjusted to maintain target blood gas and/or TCM values

i. Goal: pH >7.2, PaCO2 45-60 mmHg, PaO2 60-80 mmHg

ii. Adjustment of nHFJV support as indicated in Table 2

iii. Adjustment of NIPPV support as indicated in Table 3

e. Record vital signs (heart rate, respiratory rate, blood pressure) and ventilator support, including FiO2, TCM/PaCO2 and Silverman score for the first 24 hours of study support as follows: every 1 hour for three recordings then every 3 hours for three recordings and then every 6 hours for two recordings. Subsequently we will record this data every 12 hours until 48 hours and then every 24 hours for the remaining 7 days of the study period.

f. Infant can be transitioned to CPAP via binasal prongs and/or mask when on minimal settings of the respiratory intervention for $\geq$ 24 hours with acceptable oxygen saturations and TCM

i. Minimal nHFJV settings

1. PEEP of 6, IMV rate of 0, HFJV PIP of 15, HFJV rate of 360 breaths per min, FiO2 $\leq$ 0.3

2. Transition to CPAP of 6 cm H2O

ii. Minimal NIPPV settings

1. PEEP of 5, PIP of 15, rate of 5 breaths per minute
2. Transition to CPAP of 6 cm H2O

iii. At the discretion of the attending physician, infant can be placed on bubble CPAP (bCPAP) or ventilator-interface CPAP.

g. Criteria for termination of non-invasive study mode:

i. Respiratory failure meeting reintubation criteria as noted above

ii. At the request of the attending physician and/or parent/legal guardian

iii. Upon transfer of infant to Primary Children's Hospital for non-respiratory medical/surgical care

h. Continue study respiratory intervention for 7 days, after which the respiratory support will be transitioned from nHFJV to another respiratory support modality of the attending physicians choosing.

9. **Statistical Analysis**: Data will be de-identified and analyzed on an intent to treat basis. Statistical analysis will be performed using SPSS (version 25, IBM, Armonk, NY). The primary outcome and other categorical measures will be analyzed by Chi-square or Fisher's Exact test. Student's *t* test will be used for analysis of normally distributed continuous data and Mann-Whitney *U* test will be applied for ordinal data or continuous data that is not normally distributed. Two-sided P values of less than 0.05 will be considered to indicate statistical significance, and no adjustments will be made for multiple comparisons

10. **Population and Recruitment Time:**

a. Approximately 60 infants born 24 0/7 to 28 6/7 weeks GA are born at the UUMC NICU each year

    i. Estimated sample size is 40 infants (n=20 per group)This is a pilot study designed to test feasibility and safety of the nHFJV. However, the sample size proposed may allow identification of possible significant benefits. Based on historical failure rates in this patient population, including a recent study from Zhu et al, the estimated failure approaches 50% with the current standard. If we were able to show a reduction in that failure rate by 50% (from 50% to 25%, as shown in the Zhu, et al study) we would approach a P value of 0.05 by Chi-squared analysis.

        1. Zhu X-W, et al. Pediatric Pulmonology, 2017; 52(8)

b. Expected time to complete study from initiation through closeout is approximately 2 years.

F. Risks and Benefits

NIPPV is a routine and well known mode of respiratory support with a few known risks, including air leaks, gaseous distension/discomfort and skin breakdown at the site of the prongs/mask. Effort is made to decrease the gaseous distension by allowing the enteric tube placed for enteral feeds to vent periodically throughout the day. We do not anticipate higher risk in the patients randomized to the nHFJV group. The nasopharyngeal airway will be replaced in alternating nares in the nHFJV group every 48 hours to decrease the risk of skin breakdown.

Potential benefits to study participants assigned to the nHFJV group may include decreased risk of reintubation and decreased days requiring mechanical ventilation. This improvement may translate to decreased severity of BPD at 36 weeks CGA. Benefits to society include increased

knowledge in a novel mode of respiratory support that may aid in quicker extubation and as a rescue mode of respiratory support to prevent intubation and mechanical ventilation. This potential for reduced severity of BPD could shorten hospital stays and decrease subsequent medical costs associated with care for severe BPD.

G. References

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Table 1. Unit guidelines for extubation criteria

WEIGHT (grams)

	< 1000	1000-2000	2000-3000	> 3000
MAP	8	9-10	10-12	12
Amp	16	18	20	22
FiO2	< 0.4			

HFOV

WEIGHT (grams)

	< 1000	1000-2000	2000-3000	> 3000
PIP	< 16	16-20		20
PEEP	< 6	< 7		< 8
PS	< 6 – 8			
FiO2	< 0.4			
Rate	16 – 20			

PC-SIMV and PC-PSV

WEIGHT (grams)

	< 1000	1000-2000	2000-3000	> 3000
PIP	< 16	16-20		20
PEEP	< 6	< 7		< 8
VT	4 – 5 ml/kg			
PS	< 6 – 8			
FiO2	< 0.4			
Rate	16 – 20			

SIMV + VG and PSV + VG

Table 2a. Adjustment of nHFJV support

	In order of preference:
Improving PaO2	1. Wean FiO2 until ≤ 0.3 2. Wean PEEP by 1 cm H20 to a minimum of 6
Improving PaCO2	1. Wean IMV PIP by 1-2 every 3-4 hours to a minimum of 15 cm H2O 2. Wean IMV rate by 2 every 3-4 hours to off 3. Wean HFJV PIP by 1-2 every 3-4 hours to minimum of 15 cm H2O
Worsening PaO2 and FiO2 > 0.4	1. Increase PEEP by 1-2 cm H2O every 15 minutes to maximum of 12 cm H2O 2. If no chest rise with IMV breaths, increase IMV PIP by 1-2 cm H2O to a maximum of 30 cm H2O
Worsening PaCO2	1. Increase HFJV PIP by 2-3 cm H2O until visible chest wiggle to maximum of 30 cm H2O 2. If no effect, increase HFJV rate by 60 bpm to maximum of 480 bpm 3. If no effect, increase IMV PIP by 1-2 cm H2O every 30-60 minutes to maximum of 30 cm H2O 4. If no effect, increase IMV rate by 1-2 bpm to maximum of 20 bpm

Table 2b. Caveats of care with nHFJV support

1) IMV PIP should remain at least 1-2 below the nHFJV PIP so conventional breaths do not interrupt HFJV. Listen to infants' breaths and adjust as needed.
2) If receiving "cannot meet ready conditions" alarm, decrease the IMV breaths until the alarm stops and then increase IMV breaths to goal
3) Set/keep "slope" on Drager IMV breaths to 0.0
4) If increasing stomach gas, can consider weaning nHFJV PIP by 1-2 to minimum of 16 cmH2O
5) Can increase nHFJV PIP by 1-2 if lower levels activate "low PIP" alarm
6) If PAW reaches 12 cm H2O, recommend obtaining chest x-ray
7) Air trapping related to inadequate high frequency expiratory time or excessive nHFJV PIP should not occur due to the non-invasive approach

Table 3. Adjustment of NIPPV support

	In order of preference:
Improving PaO2	1. Wean FiO2 until ≤ 0.3 2. Wean PEEP by 1 to a minimum of 5 cm H20
Improving PaCO2	1. Wean PIP by 1-2 every 3-4 hours to a minimum of 15 cm H2O 2. Wean rate by 5 every 3-4 hours to minimum of 5 bpm
Worsening PaO2 and FiO2 > 0.4	1. Increase PEEP by 1-2 cm H2O every 15 minutes to maximum of 10 cm H2O
Worsening PaCO2	1. Increase PIP by 2-3 cm H2O to maximum of 30 cm H2O 2. Increase rate by 5 to maximum of 30 bpm

Figure 1. Silverman Scoring system for respiratory failure