Use of Noninvasive High-Frequency Ventilation in the Neonatal Intensive Care Unit: A Retrospective Review

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Abstract

Objective The aim of the article is to review the effectiveness of neonatal noninvasive high-frequency ventilation (NIHFV) in preventing endotracheal mechanical ventilation.

Study Design Retrospective case series including all 79 instances of NIHFV use at four participating centers between July 2010 and September 2012.

Results In 73% of cases, NIHFV was used as rescue after another noninvasive mode, and prophylactically (postextubation) in the remainder. In 58% of cases, infants transitioned to another noninvasive mode, without requiring intubation. There were significant reductions in the mean (SD) number of apneas, bradycardias, or desaturations (over 6 hours) (3.2 [0.4] vs. 1.2 [0.3]; $p < 0.001$), $\text{FiO}_2$ (48 [3] vs. 40 [2]%; $p < 0.001$) and $\text{CO}_2$ levels (74 [6] vs. 62 [4] mm Hg; $p = 0.025$) with NIHFV. No NIHFV-related complications were noted.

Conclusions NIHFV is a promising NIV mode that may help prevent or delay intubation and deserves further clinical research.

Keywords
- noninvasive ventilation
- ventilator-induced lung injury
- bronchopulmonary dysplasia
- intubation

Endotracheal mechanical ventilation (EMV) in preterm infants has been linked with various forms of lung injury including bronchopulmonary dysplasia, infections, and air leak syndromes—collectively termed ventilator-induced lung injury (VILI). As such, there has been a trend of increasing use of noninvasive ventilation (NIV) modes in neonatal intensive care units (NICUs) over the last decade in an attempt to reduce VILI, with recent reports demonstrating equal effectiveness of NIV when compared with EMV in preterm infants. Many studies comparing these different modes of NIV have yielded inconsistent results with regards to effectiveness in preventing reintubation, and the choice of the mode of NIV used is largely based on local practices and comfort. In recent years, NIPPV is gaining wider acceptance but a recently completed large multicenter trial by Kirpalani et al failed to demonstrate superiority over NCPAP. However, in this study the NIPPV arm included a wide range of pressures and inspiratory times, some of which could be considered as BP-NCPAP.

Despite efforts to minimize EMV, many patients fail to sustain on NIV modes and require intubation. Stefanescu et al...
reported a failure rate of approximately 40% within 1 week of extubation in a cohort of infants less than 1,000 g.\textsuperscript{14} Similarly, Barrington et al reported a failure rate of 44% within 72 hours in a cohort of infants less than 1,251 g.\textsuperscript{9} As such, to minimize the risk of EMV and VILI, a relatively newer form of NIV that is emerging is noninvasive high-frequency ventilation (NIHFV). In this modality, high-frequency ventilation is delivered via nasopharyngeal tubes, short nasal prongs or masks. While this modality holds promise, there are only a limited number of clinical studies evaluating it in the neonatal population, as described later.\textsuperscript{15–18}

To date, the clinical use of NIHFV has only been evaluated in four studies. Two small case series studies on 21 and 14 infants reported a decrease in carbon dioxide (CO\textsubscript{2}) with NIHFV use.\textsuperscript{15,16} A randomized controlled trial involving 46 term infants with transient tachypnea of the newborn (TTN) demonstrated faster clinical recovery with the use of NIHFV compared with NCPAP.\textsuperscript{17} Lastly, a recent case series reporting NIHFV use after extubation in a group of high-risk infants demonstrated sustained extubation in 14 of the 20 infants.\textsuperscript{18} All of these studies have been relatively small in sample size, and some with a heterogeneous population. With the exception of the study on term neonates with TTN, all were performed without control groups. However, despite some limitations, these studies have demonstrated the feasibility of the use of NIHFV, with no reports of any associated adverse events.

Over the last few years, with the goal of minimizing EMV, NIHFV has gained acceptance for use in a select group of high-risk patients at our centers based on positive experience at one European institution in Cologne, Germany (Dr. André Oberthür, MD; written communication, September 16, 2010). However, there is still very limited data on its effectiveness, indications for use, and safety profile. We conducted a retrospective review of the experience with the use of NIHFV at our centers, with the goal of addressing these specific questions. We hypothesized that the use of NIHFV will be associated with successful sustained extubation in a significant proportion of high-risk patients placed on this mode, while reducing the number of apneas, bradycardias, and desaturations as well as improving both oxygenation and ventilation.

**Methods**

**Research Design**

This was a retrospective case series study conducted at four large Canadian tertiary care NICUs. All infants who were placed on NIHFV at these centers between July 2010 (time when NIHFV use was adopted) and September 2012 were included.

**Data Collection**

Data were collected from health records of all patients on NIHFV by two authors (A.M. and B.S.) using a standardized data collection form. At each site, log files kept by respiratory therapists for all patients trialed on NIHFV were reviewed. Data were collected on baseline characteristics of each “instance” including sex, birth gestational age and weight, as well as age (in days), postmenstrual age (PMA), and weight at time of NIHFV use. Each instance refers to a unique NIHFV trial. If NIHFV was utilized on one patient on three separate occasions, this patient contributed on three instances to all data, including baseline characteristics. Other parameters such as mode of delivery, maternal chorioamnionitis, surfactant administration, use of antenatal steroids (complete defined as two doses, incomplete defined as one dose before delivery), chronic lung disease (defined as supplemental oxygen or respiratory support requirement at 36 weeks’ PMA) were also documented. Data collected for NIHFV use included indications and duration of use, all recorded settings, (including mean airway pressure [MAP], amplitude, and frequency) and the mode of ventilation immediately preceding and following NIHFV initiation. Indication of NIHFV use was divided into “rescue” (when transitioned from another NIV mode) or “prophylactic” (when extubated directly to NIHFV).

Other outcome data collected included number of apneic, bradycardic (heart rate < 100 bpm) or desaturation (oxygen saturation < 85%) episodes denoted collectively as “spells” as per nursing chart records, fraction of inspired oxygen (FiO\textsubscript{2}), and CO\textsubscript{2} levels as measured transcutaneously (or from a blood gas sample where available) preceding and following NIHFV initiation. Because of the retrospective nature of this study, there were some instances where one or more of these data were not available for analysis. Any documented adverse outcomes attributed to NIHFV use were searched for in each patient’s chart. Furthermore, all cranial ultrasonography results preceding and following NIHFV initiation were documented, and intraventricular hemorrhage (IVH) was reported according to the Papile classification.\textsuperscript{19}

**Instruments and Devices**

NIHFV was administered using either short nasal prongs or masks (BC series, Fisher and Paykel Healthcare, Laval, Québec, Canada) at each participating site. If required due to pressure leak, chinstraps were used at the discretion of the attending medical team. Two sites used the Babylog 8000 (Drager, Lubeck, Germany), one of which also used the Leoni Plus (Heinen + Lowenstein, Deutschland, Germany) and the remaining two sites used the VNS500 (Drager, Lubeck, Germany) to deliver NIHFV. The ventilators were connected to the nasal interface using nonrigid circuits (RT series, Fisher and Paykel Healthcare, Laval, Québec, Canada).

**Noninvasive Ventilation Use**

The use of NIHFV at each institution was based on locally developed guidelines that provided indications for NIHFV use, initial settings of various parameters and weaning/adjustment strategies. These guidelines were used in addition to clinical judgment of the attending medical team. Supplementary file number 1 (available online only) summarizes the guidelines from each institution. Similarly, each unit also had guidelines for CPAP, BP-NCPAP and NIPPV use—provided as supplementary file number 2 (available online only).

**Outcomes**

The primary outcome was the rate of successful transition to another mode of NIV without the need for intubation on
NIHFV. The decision to intubate a patient was based on the medical team’s discretion at each site, with no specific predefined guidelines. Secondary outcomes included a comparison of the mean of the number of spells 6 hours before and 6 hours after NIHFV use. FiO₂ and transcutaneous CO₂ (TcCO₂), or PaCO₂ where available, levels immediately before and 1 hour after NIHFV use were also comparatively analyzed. The data for spells was collected for rescue NIHFV use only, as in instances of prophylactic use, the patient was intubated before NIHFV use. Any adverse outcomes attributed to the use of NIHFV were reported, as well as grades of IVH before and after NIHFV use.

**Statistical Analysis**
All statistical analyses were performed using SAS version 9.3 (SAS Institute, Cary, NC). Baseline characteristics were described using descriptive statistics. When comparing outcomes data, t-test, Wilcoxon rank sum test, chi-squared test, or Fisher exact test were used as appropriate. All data are reported as median (range) when describing the baseline characteristics and duration of NIHFV use, or mean (standard deviation [SD]) when describing the secondary outcomes such as spells, oxygenation, and ventilation.

**Ethics Review**
This study was approved by the research ethics boards of each participating institution.

**Results**

**Patient Characteristics**
Over the study period, 52 infants underwent NIHFV at the four study sites and contributed to a total of 79 instances of its use. Table 1 depicts the baseline characteristics of all instances of NIHFV use based on the primary outcome. Only the mode of delivery was significantly different between the two groups (p = 0.0170).

**Indications and Settings of Noninvasive High-Frequency Ventilation Use**
NIHFV was used as a rescue mode in 58 of the 79 instances (73% of all use) and as a prophylactic mode in the remainder.

### Table 1 Baseline characteristics

<table>
<thead>
<tr>
<th>Variables</th>
<th>All instances of NIHFV use (n = 79)</th>
<th>Instances of NIHFV transitioned to NIV (n = 46)</th>
<th>Instances of NIHFV requiring intubation (n = 33)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Birth weighta (g)</td>
<td>740 (500–2,860)</td>
<td>765 (510–1,430)</td>
<td>720 (500–2,860)</td>
<td>0.2666</td>
</tr>
<tr>
<td>Gestational agea (wk)</td>
<td>25 (23–35)</td>
<td>25 (23–28)</td>
<td>24 (23–35)</td>
<td>0.1237</td>
</tr>
<tr>
<td>Weighta (g) at study entry</td>
<td>830 (480–3,600)</td>
<td>865 (500–3,600)</td>
<td>770 (480–2,703)</td>
<td>0.2840</td>
</tr>
<tr>
<td>Small for gestational age, %</td>
<td>11.4</td>
<td>10.9</td>
<td>12.1</td>
<td>0.8629</td>
</tr>
<tr>
<td>Postmenstrual age at study entrya (wk)</td>
<td>28 (24–46)</td>
<td>28 (24–26)</td>
<td>27 (24–38)</td>
<td>0.2522</td>
</tr>
<tr>
<td>Age at the time of initiation of NIHFVa (d)</td>
<td>20 (2–147)</td>
<td>21 (3–147)</td>
<td>15 (2–94)</td>
<td>0.2838</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Male, %</td>
<td>51</td>
<td>50</td>
<td>48</td>
<td>0.8963</td>
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<tr>
<td>Female, %</td>
<td>49</td>
<td>50</td>
<td>52</td>
<td></td>
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<tr>
<td>Antenatal steroids</td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>Complete, %</td>
<td>50</td>
<td>42</td>
<td>60</td>
<td>0.2218</td>
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<tr>
<td>Incomplete, %</td>
<td>18</td>
<td>22</td>
<td>12</td>
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<tr>
<td>None, %</td>
<td>23</td>
<td>29</td>
<td>15</td>
<td></td>
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<tr>
<td>Unknown, %</td>
<td>9</td>
<td>7</td>
<td>9</td>
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<td>Surfactant therapy, %</td>
<td>92</td>
<td>88</td>
<td>97</td>
<td>0.2163</td>
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<td>Mode of delivery</td>
<td></td>
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<td></td>
<td></td>
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<tr>
<td>Vaginal, %</td>
<td>45</td>
<td>33</td>
<td>59</td>
<td>0.0170b</td>
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<td>Cesarean section, %</td>
<td>54</td>
<td>67</td>
<td>38</td>
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<tr>
<td>Unknown, %</td>
<td>1</td>
<td>0</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Presence of chorioamnionitis, %</td>
<td>11.5</td>
<td>13.3</td>
<td>9.1</td>
<td>0.7259</td>
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<tr>
<td>Chronic lung disease, %</td>
<td>70.8</td>
<td>60.6</td>
<td>81.3</td>
<td>0.0673</td>
</tr>
</tbody>
</table>

*aResults presented as median (range) and p values calculated using Wilcoxon rank sum test.

b*p Value < 0.05.
The most common indication for its use was spells in 31 cases, accounting for 39% of all NIHFV use. Among the 58 instances of rescue use, the patient was either on BP-NCPAP (at one site where NIPPV is not routinely used) or NIPPV in 49 cases (84%) preceding the use of NIHFV, whereas in the remaining nine cases, patients were on NCPAP. The mean peak inspiratory pressure (PIP) on NIPPV, the mean airway pressure (MAP) on BP-NCPAP and MAP on NCPAP before NIHFV initiation were 19.2 (3.1) cm H2O, 7.5 (0.9) cm H2O, and 9.3 (1.5) cm H2O, respectively. The median duration of NIHFV use was 57 hours (range, 1.3–415 hours).

Lab 1 depicts the distributions of the prevalence of each indication (panel A) and duration (panel B) of NIHFV use.

Outcomes

Of all instances of NIHFV use, 46 (58%) patients were successfully transitioned to another NIV mode, precluding the need for intubation. In the remaining 33 instances (42%), patients required intubation. When all NIHFV instances were stratified by weight at NIHFV initiation (< 1,000 g vs. > 1,000 g) or by indication (prophylactic vs. rescue), the rate of successful transition to another NIV remained greater than 50% for all subgroups, as shown in Table 2. Amongst those intubated after NIHFV use, the two most common indications were spells (52%) and ventilation failure (42%), as defined by CO2 retention.

Data for number of spells were available for 49 instances, and the number of spells over 6 hours decreased from 3.2 (0.4) to 1.2 (0.3) per hour (p < 0.001). The oxygenation (n = 53) and ventilation (n = 19) comparisons showed a decrease in FiO2 from 48 (3) to 40 (2)% (p < 0.001) and decrease in CO2 from 74 (6) to 62 (4) mm Hg (p = 0.025) before and after the use of NIHFV. These results are depicted in Fig. 2.

No adverse events attributable to NIHFV were reported. Cranial ultrasonography results preceding and following NIHFV initiation were available in 73 instances. There was progression of IVH in two patients—no IVH to unilateral grade II IVH in one, and unilateral grade I to bilateral grade II IVH in the other. In the remaining instances, there was either no change (n = 68) or regression of IVH grades (n = 3). There were no reports of nasal septum injury, necrotizing enterocolitis, or bowel perforations attributed specifically to NIHFV use.

Discussion

In this retrospective analysis of our experience, NIHFV was utilized in 79 instances, and in the majority of cases its use was as a rescue mode. About 58% of all NIHFV instances (rescue or prophylactic) resulted in a successful transition to another NIV mode, thus preventing intubation in the majority of this high-risk patient group. The use of NIHFV was associated with a decrease in the number of “spells”, as well as an improvement in oxygenation and ventilation. No adverse events were reported as a result of NIHFV use.

To our knowledge, this is the largest reported case series of patients on NIHFV, and the first to report its use on such a large group of patients at high risk of requiring intubation from North America. These results confirm the feasibility and add to the growing body of literature supporting the use of NIHFV as an effective modality in preventing intubation. Arguably, in many of the cases in our study, patients would have been intubated had it not been for the use of NIHFV. This is particularly evident given that the majority of these patients were already on what is perceived to be maximum NIV support with either BP-NCPAP or NIPPV preceding rescue.
NIHFV use. It also demonstrates that patients may have fewer spells, and have improved oxygenation and ventilation on NIHFV.

Previously, a study by van der Hoeven et al demonstrated the use of NIHFV in a heterogeneous patient population (21 preterm and term infants) with NCPAP failure based on either higher PaCO2 levels, acidosis, or higher FiO2 requirements and reported a decrease in PaCO2 levels. NIHFV was used for a median of 35 hours and demonstrated a decrease in the CO2 levels from 8.3 to 7.2 kPa, with no adverse effects. Although many of the patients remained extubated, many of these infants were term and were unlikely to require intubation in the first place. Colaizy et al studied a group of infants who were stable on NCPAP after putting them on NIHFV for 2 hours, and showed a decrease in TcCO2 levels in this group of 14 infants. However, it is difficult extrapolate these results to high-risk patient population. Neither of these two studies examined extubation failure rates or change in number of spells.

A randomized controlled trial comparing NIHFV with NCPAP in 46 term infants showed a reduction in time to clinical improvement of TTN from 377 to 105 minutes. However, it can be argued that many of these infants did not require NIHFV (or NCPAP) in the first place, and were unlikely to be at high risk of requiring intubation. Furthermore, the unblinded nature of the study inherently introduces biases, and the reported benefit of NIHFV over NCPAP in this context must be interpreted with caution. Czernik et al have reported the prophylactic use of NIHFV in 20 infants after extubation. Of the 20 infants, 14 remained extubated and were transitioned to another NIV mode, after remaining on NIHFV for a minimum of 32 hours. However, although these infants were deemed to be at a high risk of extubation failure, without a control group, it is difficult to predict as to how many infants would have remained extubated even without the use of NIHFV.

NIHFV holds promise as a mode of NIV that might help reduce the risk of intubation in a select group of high-risk patients. It may help reduce the number of spells, and improve ventilation as well as oxygenation. An additional advantage conferred by NIHFV may be the lack of the need for synchronization, something that remains a challenge with current use of NIPPV. Even though NIHFV was used successfully in preterm infants less than 1,000 g without any reported adverse effects, the safety profile remains unknown, particularly in the extremely preterm infants. To our knowledge, no study has been planned or powered appropriately to address the safety profile specifically. Further work needs to be done to elucidate the group of patients most likely to benefit from this modality, and to adequately address its safety profile.

Yet another area of uncertainty is the parameters for use in NIHFV. As noted earlier, there is a significant range of MAPs used, which raises the possibility that it may be the higher recruitment pressure, rather than the oscillatory effect that leads to these improved outcomes. The use of this large range of MAPs also raises the question of what should the appropriate limit be. On the one hand, positive end expiratory pressures with the use of NCPAP rarely exceed 8 to 10 cm H2O, whereas similar MAP ranges as reported here in NIHFV are routinely used in intubated patients on high-frequency ventilation. Therefore, while seemingly acceptable for intubated patients, it is unclear whether there is an increased risk of harm when such MAPs are administered via noninvasive interfaces. The ventilation tubing and leak at the level of the nasopharynx leads to a much lower delivered MAP and amplitude than that set at the ventilator—however the quantification of this dampening effect is currently unknown and requires further research. Although no cases were identified in the present review, the risk of abdominal distension and associated complications including perforation need to be carefully considered. These questions remain unanswered but with rigorously planned prospective studies to help address them and with further experience with its use, NIHFV has the potential to minimize the long-term morbidities associated with EMV.

One of the limitations of the study is the lack of a control group. However, given that the majority of NIHFV use was as a rescue mode in patients at high risk of being intubated, our
conclusions are promising. Another limitation is the retrospective nature of the study that inherently leads to the risk of missed data, evident by the lack of proper documentation of oxygenation requirements and CO₂ levels in many of the instances of NIFHV use. Also, there remains a risk of selection bias in that more unstable patients may have been tried on NIFHV, and the benefit of NIFHV may be overestimated. Lastly, the lack of a control group meant study was not powered to look specifically at complications that may have arisen from NIFHV, or may not have been adequately documented. Despite some limitations, this retrospective review demonstrates that NIFHV can prevent intubation in a significant proportion of high-risk patients after other noninvasive modes of ventilation have failed. To provide definitive answers regarding the role of NIFHV in neonatal intensive care including indications, parameters of settings and its safety profile, rigorously planned prospective trials are warranted.

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Conflicts of Interest
None.

References