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ORIGINAL ARTICLE

Neonatal pulmonary hypertension treated with inhaled nitric oxide and high-frequency ventilation

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Term and near-term infants with pulmonary hypertension are frequently treated with inhaled nitric oxide. This therapy can be delivered with high-frequency ventilation, but there has been limited study of the relative effectiveness of high-frequency jet ventilation and high-frequency oscillatory ventilation.

Objective: To compare short-term clinical outcomes of neonates with pulmonary hypertension treated with inhaled nitric oxide plus either high-frequency jet ventilation or high-frequency oscillatory ventilation.

Study Design: Study infants met the following criteria: $\geqslant 35$ weeks gestation, respiratory failure with pulmonary hypertension, no congenital malformations and treatment in the first week of life with inhaled nitric oxide plus either high-frequency jet ventilation ($n = 22$) or high-frequency oscillatory ventilation ($n = 43$). Data were collected from medical records.

Result: The jet ventilation and oscillatory ventilation groups were similar in terms of gestational age, but the jet ventilation group had less severe respiratory illness (that is, lower oxygenation index) just prior to initiation of the combination of nitric oxide and high-frequency ventilation. The jet ventilation group spent more hours on inhaled nitric oxide (71.4 versus 40.8; $P = 0.004$) but was less likely to require extracorporeal membrane oxygenation (2(9%) versus 19(44%); $P = 0.004$). No difference was found in the ages at which oxygen and high-frequency ventilation were discontinued.

Conclusion: Term and near-term neonates with pulmonary hypertension who require nitric oxide have similar short-term outcomes regardless of whether nitric oxide is delivered by high-frequency jet ventilation or high-frequency oscillatory ventilation.
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Introduction

Persistent pulmonary hypertension of the newborn (PPHN) refers to a lack of normal cardiopulmonary adaptation following delivery,[1] including persistence of the elevated pulmonary vascular resistance that is characteristic of fetuses. [2] Most often PPHN occurs in infants with meconium aspiration syndrome (34 to 51%), pneumonia/sepsis (20 to 23%), idiopathic PPHN (17 to 25%), congenital diaphragmatic hernia (10 to 15%) or respiratory distress syndrome (9 to 12%).[3,4] Prior to the introduction, in the late 1990s, of inhaled nitric oxide (iNO), therapies for PPHN included induced alkalosis, supplemental oxygen, mechanical ventilation and neuromuscular blockade; and patients who failed to respond to these measures were treated with extracorporeal membrane oxygenation (ECMO).[5] iNO has been shown to reduce the need for ECMO in term and near-term neonates with pulmonary hypertension.[3,4,6,7]

High-frequency ventilation (HFV) has been used with increasing frequency for PPHN,[8] and when combined with iNO results in an acute rise in arterial oxygen saturation,[9] and reduces the likelihood of ECMO treatment.[10] Studies of iNO delivered by HFV have, to date, utilized high-frequency oscillatory ventilation (HFOV). However, since patients treated with high-frequency jet ventilation (HFJV), as compared to conventional ventilation, require lower peak pressures to achieve the same level of oxygenation,[11,12] HFJV might offer an advantage over HFOV for patients with PPHN who require iNO. *In vitro* study indicates that iNO can be delivered with HFJV,[13] and in a small series of preterm neonates with hypoxic respiratory failure unresponsive to HFOV and iNO, HFJV plus iNO resulted in improvement.[14] In the current study we compared the short-term clinical outcomes for a series of term and near-term infants with PPHN who were treated with iNO in combination with either HFOV or HFJV. Our objective was to assess whether short-term outcomes of those treated with HJFV and iNO were at least as good as those treated with HFOV and iNO.

Methods

This study was approved by the Institutional Review Board of Wake Forest University Baptist Medical Center.

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Study population
Potential study participants were identified from a prospectively collected database of all patients treated with iNO in the neonatal intensive care unit at Brenner Children's Hospital (BCH). All neonatal patients admitted to BCH are born at other hospitals and are transferred to BCH for subsequent care. We reviewed the medical records of all infants treated with iNO between 1 April 2000 and 31 August 2005, and identified those who met the following inclusion criteria for the current study: $\geqslant$35 weeks gestation, respiratory failure with clinical evidence of pulmonary hypertension, no major congenital malformations, treatment with iNO in the first week of life and receipt of iNO in conjunction with either HFJV or HFOV. No prespecified criteria were used to define persistent pulmonary hypertension among the infants we studied; treating physicians used a variety of diagnostic tests, including hyperoxia test, comparison of preductal and postductal arterial oxygen saturations and echocardiography.[15] A total of 65 patients were identified who met the inclusion criteria; 43 were treated with iNO and HFOV and 22 with iNO and HFJV. The mode of ventilator support was chosen by the attending neonatologist, with input from respiratory therapists. In first several years of the study period, HFOV was used almost exclusively. However, because of increasing familiarity with HFJV over time, this mode was used almost exclusively at the end of the study interval.

Data
A research nurse, blinded to the study hypothesis, reviewed medical records and collected data about risk factors, severity of illness and clinical outcomes. Data about gestational age and respiratory diagnoses (for example, meconium aspiration, pneumothorax) were taken from admission summaries. The time at which therapies were initiated and ventilator settings were found in nurses' bedside flow sheet. Blood gases were collected from laboratory reports.

Data analysis
Group were compared using the Wilcoxon's rank sum test for continuous variables and χ^2-tests or Fisher's exact tests for categorical variables. Logistic regression was used to obtain an estimate of the strength of association between treatment (HFOV plus iNO or HFJV plus iNO) and requirement for ECMO, adjusting for baseline group differences.

Results

Baseline characteristics
There were no differences between the two groups in gestational age, gender, birth weight, race, diagnosis or mode of delivery (Table 1). At the time of admission to BCH there were no differences in prior use of cardiovascular pressor support or HFV at the referral hospital, or prior occurrence of air leak (pulmonary interstitial emphysema or pneumothorax). The HFJV group, however, arrived at BCH at a later age than the HFOV group (23.9 versus 9.2 h; $P = 0.02$), was more likely to have received iNO at the referral hospital (13(59%) versus 8(19%); $P = 0.001$), and was more likely to have received the combination of HFV with iNO at the referral hospital (10(45%) versus 5(12%); $P = 0.002$).

Table 2 displays respiratory and ventilator data recorded just prior to the initiation of the combination of HFV and iNO (that is, when both were being administered). At that point in time, the HFOV patients had a greater oxygenation index (37 versus 19; $P = 0.04$), lower alveolar/arterial (a/A) oxygen ratio (0.059 versus 0.089; $P = 0.05$), and lower PaO_2 (41 versus 60; $P = 0.04$) when compared to the HFJV group. There was no difference in the mean airway pressure between the two groups. Multiple data points are missing for patients in each group for PaO_2 and mean airway pressure, and therefore, oxygenation index and a/A oxygen ratios. The a/A oxygen ratio was calculated for 42 of 43 HFOV patients and 17 of 22 HFJV patients, compared to the oxygenation index for which only 27 of 43 HFOV patients and 13 of 22 HFJV patients had calculated values. These missing values are the result of either unavailable arterial blood gas values at referral hospitals, or unrecorded mean airway pressures.

Short-term clinical outcomes
No differences were found in the proportions who were discharged on supplemental oxygen, age at which oxygen was discontinued, or the age at extubation. The HFJV group, however, was older when HFV was discontinued (5.7 versus 2.9 days; $P = 0.03$) and spent more hours on iNO (71.4 versus 40.8; $P = 0.004$). The HFOV group was significantly more likely to require ECMO (19(44%) versus 2(9%); $P = 0.004$; Table 3).

Patients who required ECMO had a greater oxygenation index (67 versus 22; $P = 0.0005$), lower PaO_2 (28 versus 58; $P = 0.0001$), and a lower a/A oxygen ratio (0.042 versus 0.089; $P = 0.0001$) than those who did not require ECMO. The association between HFJV plus iNO and a lower risk of ECMO persisted when logistic regression was used to adjust for the baseline difference in a/A oxygen ratio just prior to initiation of the HFV/iNO combination.

Discussion

Inhaled nitric oxide decreases the need for ECMO in patients with PPHN,[3,4,6,7] and following its approval for clinical use, the number of patients entered in the national registry of ECMO patients with a diagnosis of sepsis, idiopathic PPHN or meconium aspiration declined by about 50%. [16] In a randomized trial, improvement in oxygenation occurred more frequently in infants with PPHN treated with HFOV plus iNO as compared to infants treated with either HFOV or iNO alone.[9] In another trial, HFJV resulted in improved oxygenation at lower mean airway pressures than required with

Table 1 Baseline attributes and at the time of admission to Brenner Children's Hospital

Attribute	*HFOV and iNO (n = 43)*	*HFJV % iNO (n = 22)*	P-*value*
Gestational age (weeks)	39 (36–41)	39 (36–42)	0.8
Gender			
Male	20 (47)	15 (68)	0.1
Female	23 (53)	7 (32)	
Birth weight (g)	3423 (2340–5600)	3516 (2697–4224)	1.0
Race			
White	25 (58)	11 (50)	0.5
African American	13 (30)	6 (27)	
Hispanic	4 (9)	5 (23)	
Other	1 (2)	0	
Diagnosis			
Meconium aspiration syndrome	24 (56)	13 (59)	0.9
Sepsis	16 (37)	8 (36)	
Idiopathic PPHN	3 (7)	1 (5)	
Delivery mode			
Vaginal	21 (49)	9 (41)	0.8
C-section, elective	8 (19)	4 (18)	
C-section, emergent	14 (33)	9 (41)	
Age at admission (h)	9.2 (3.7–102)	23.9 (3.9–76)	0.02
Pulmonary interstitial emphysema[a]	2/41 (5)	0	0.3
Pneumothorax	8 (19)	4 (18)	1.0
Pressors	36 (84)	21 (95)	0.4
HFV	21 (49)	15 (68)	0.1
Inhaled nitric oxide	8 (19)	13 (59)	0.001
Inhaled nitric oxide and HFV	5 (12)	10 (45)	0.002

Abbreviations: HFOV, high-frequency oscillatory ventilation; HFJV, high-frequency jet ventilation; HFV, high-frequency ventilation; NO, nitric oxide; PPHN, persistent pulmonary hypertension.
Data are medians (range) or number of infants (percent).
[a]Patient with pulmonary interstitial emphysema, timing unknown.

Table 2 Respiratory illness indicators just prior to HFV/iNO combination

Indicator	*HFOV and iNO*	*HFJV and iNO*	P-*value*
Oxygenation index[a]	37 (7–94)	19 (6–58)	0.04
PaO_2[a]	41 (8–284)	60 (23–220)	0.04
Mean airway pressure	16 (10–28)	13 (9–24)	0.2
a/A ratio[a]	0.059 (0.013–0.43)	0.089 (0.035–0.32)	0.05

Abbreviations: a/A, alveolar/arterial; HFOV, high-frequency oscillatory ventilation; HFJV, high-frequency jet ventilation; iNO, inhaled nitric oxide; MAP, mean airway pressure; OI, oxygen index.
Data are medians (range).
[a]Not all patients with available data: HFOV with iNO: 27/43 with OI and MAP, 43/43 with PaO_2 42/43 with a/A ratio; HFJV with iNO: 13/22 with OI and MAP, 20/22 with PaO_2, 17/22 with a/A ratio; ECMO: 9/21 with OI and MAP, 20/21 with PaO_2 and a/A ratio; no ECMO: 31/44 with OI and MAP, 43/44 with PaO_2, 39/44 with a/A ratio.

conventional ventilation.[17] The current study is the first to compare two modes of HFV with respect to short-term outcomes in term and near-term infants treated with iNO for PPHN. To the extent that we were successful in adjusting for baseline differences in illness severity, our analysis suggests that term and near-term neonates with pulmonary hypertension who require nitric oxide have similar outcomes irrespective of whether nitric oxide is delivered by HFJV or HFOV.

In patients with PPHN, the elevated pulmonary vascular resistance causes right to left shunting of blood across the ductus arteriosus or the foramen ovale.[2] Disturbances of cardiac performance, hypovolemia and decreased systemic vascular resistance may further compromise pulmonary blood flow in PPHN.[18] It is plausible that because of differential effects on cardiac

Table 3 Short-term clinical outcomes

Outcome	*HFOV and iNO (n = 43)*	*HFJV and iNO (n = 22)*	P-*value*
Death	0	0	—
ECMO	19 (44%)	2 (9%)	0.004
Home oxygen[a]	2 (5%)	2 (10%)	0.5
Age oxygen discontinued (days)	12.2 (5.6–43.1)	10.9 (6.0–21.3)	0.3
Age when extubated (days)	7.9 (2.4–28.5)	7.5 (1.8–11.7)	0.2
Age when HFV discontinued (days)	2.9 (0.3–11.2)	5.7 (1.5–11.7)	0.03
Hours of iNO after transfer	40.8 (0.7–149.8)	71.4 (5.1–248.9)	0.004

Abbreviations: HFOV, high-frequency oscillatory ventilation; HFJV, high-frequency jet ventilation; HFV, high-frequency ventilation; iNO, inhaled nitric oxide; ECMO, extracorporeal membrane oxygenation.
Data are medians (range) or number of infants (percent).
[a]Excludes two patients in HFOV with iNO group and one patient in HFJV with iNO group who were transferred back to the referring hospital.

output, the effectiveness of HFJV and HFOV differs in patients with PPHN. In small animals, impairment in cardiac function relates primarily to increasing mean airway pressure and is independent of the mode of ventilation.[19–22] In a cat model, HFOV and HFJV have similar effects on cardiac output as mean airway pressure is increased.[23] However, at similar proximal airway pressures, the HFJV produces a higher PaO_2, higher pH and lower $PaCO_2$.[24] If HFJV does improve gas exchange at lower airway pressures than HFOV, it may in fact produce less impairment of cardiac function. Thus, one potential benefit of HFJV may be improved cardiac output.

HFOV is a safe and effective rescue therapy for neonates with PPHN who fail conventional ventilation, and HFOV combined with iNO, as compared to HFOV alone or iNO combined with conventional ventilation, resulted in a greater improvement in arterial oxygenation and reduced need for ECMO.[9,10] Likewise, HFJV improves oxygenation and ventilation of infants with PPHN, as compared to conventional ventilation.[17] However, the relative effectiveness of HFOV and HFJV in the treatment of PPHN has not been well studied. In a group of preterm neonates with chronic lung disease and hypoxemia refractory to the HFOV,[14] the oxygenation index decreased within 3 h after the initiation of HFJV. The current study indicates that HFJV might also be an appropriate means of delivering iNO to in term and near-term infants with PPHN.

Several limitations in our study should be noted. We report on a relatively small sample size from a single institution. Furthermore, the data were collected retrospectively, and thus multiple data points were unavailable. Most importantly, treatment was not randomly assigned, and the two groups differed on important characteristics at baseline. These differences, as well as differences in unmeasured confounders, could explain the lower frequency of ECMO in patients treated with HFJV and iNO. The majority of the patients in the HFOV group were treated prior to April 2004, and all of the HFJV study patients were treated after March 2004. It is therefore likely that changes in practices over time, including increased familiarity with, and effectiveness of, nitric oxide, contributed to the group differences we observed.

Despite these limitations, our analysis suggests that the short-term outcomes of near-term neonates with pulmonary hypertension treated with HFJV and iNO are no worse than those treated with HFOV and iNO. Although our results do not provide evidence that is sufficient to warrant changes in clinical care, if the findings reported here are replicated, a randomized controlled trial comparing HFOV and HFJV would be warranted.

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