Nitric Oxide Inhalation and High Frequency Oscillatory Ventilation for Hypoxemic Respiratory Failure in Infants*

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Abstract

Background: High frequency oscillatory ventilation has proved valuable in recruiting and sustaining lung volume; the combined treatment may augment nitric oxide delivery to target vessels. NO therapy lowers pulmonary resistance and improves oxygenation.

Objective: To retrospectively review data on changes in oxygenation – indicated by arterial/alveolar PO_2 ratio, oxygenation index, and outcome – in a cohort of 10 infants with hypoxemic respiratory failure in whom nitric oxide inhalation was instituted in a compassionate-use protocol after deteriorated oxygenation.

Methods: NO inhalation was administered at a range of 0.12–122 days of life using the SensorMedics system in 10 infants who developed hypoxemic respiratory failure associated with a variety of lung diseases while on HFOV.

Results: The infants' birthweight was 1,717 ± 1,167 g and their gestational age 31.1 ± 6.5 weeks. Mean exposure to NO inhalation was 14.2 days and ranged from 3–59 days. Oxygenation index decreased from 39.3 ± 13.2 to 12.7 ± 6.9 ($P < 0.0002$) after NO therapy. Despite an initial prompt response to NO inhalation, two patients died of progressive intractable respiratory failure and one term infant died of extrapulmonary complications (hypoxic ischemic encephalopathy grade III and multiorgan failure).

Conclusion: Our results indicate that the combined treatment of HFOV and NO inhalation is superior to HFOV alone for improving oxygenation in a selected cohort of infants ventilated for a variety of lung diseases.

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Previous reports have indicated that exogenous nitric oxide improves oxygenation in infants with severe hypoxemia and/or persistent pulmonary hypertension of the newborn [1–3]. Kinsella et al. [4] studied the response to nitric oxide inhalation in term and near-term infants with severe respiratory failure due to neonatal persistent pulmonary hypertension (meconium aspiration syndrome, diaphragmatic hernia) who met extracorporeal membrane oxygenation criteria. Prior to enrollment, infants in their study were ventilated with either conventional mechanical ventilation or high frequency oscillatory ventilation, depending on which modality provided optimal gas exchange. In most infants oxygenation improved and they subsequently recovered. In some cases, inhaled NO during HFOV improved oxygenation to a greater extent than HFOV alone or conventional mechanical ventilation with NO. Inhaled NO during HFOV may have potential advantages in the therapy of hypoxemic respiratory failure resulting from various parenchymal lung diseases. Since HFOV has proved valuable in recruiting and sustaining lung volumes, the combined treatment may augment NO delivery to target vessels. That being so, in infants with parenchymal lung disease resulting in hypoxemia, the HFOV plus NO inhalation may enhance ventilation/perfusion matching through redistribution of perfusion.

Since 1995, NO inhalation has been used in our neonatal intensive care unit for infants with hypoxemic respiratory failure whose lives were in jeopardy. We report our experience of this modality of treatment associated with HFOV.

Patients and Methods

We retrospectively reviewed the medical records of 10 infants who developed hypoxemic respiratory failure caused by acute or chronic lung disease while on HFOV, in whom NO inhalation was attempted in a compassionate-use protocol. All infants were admitted to the Neonatal Intensive Care Unit at Wolfson Medical Center from January 1996 to December 1998. All infants underwent echocardiography prior to the NO inhalation. Nitric oxide was administered after parental consent was obtained. This treatment was indicated if the oxygenation index was greater than 30. All infants were treated with high frequency oscillation using the InfantStar 950 (Nellcor Puritan Bennett Inc, Pleasanton, CA, USA) or Sensormedics 3100A oscillator (Sensormedics Inc, Yorba Linda, CA, USA) throughout their ventilatory course. All infants admitted to the NICU had continuous monitoring of heart rate, blood pressure, oxygen saturation and transcutaneous PCO_2 and PO_2 (Hewlett Packard monitoring component system, Adnover, MA, USA). An umbilical arterial catheter was inserted for monitoring blood gases in infants with acute lung diseases and arterial stab was used in infants with chronic lung disease.

Pre-ductal PaO_2 was maintained at 50–70 mmHg and oxygen saturation was kept between 85% and 95% in all infants. All infants with acute respiratory failure were also treated with exogenous surfactant (Curosurf, Chietti Inc, Parma, Italy) shortly after their admission to the NICU.

Blood methemoglobin was determined every 3 hours after initiation of NO inhalation on the first day of treatment, every 6 hours on the second day, and every 12 hours thereafter.

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NO = nitric oxide

HFOV = high frequency oscillatory ventilation

NICU = neonatal intensive care unit

Nitric oxide was supplied in 5,000 L cylinders (Linde Gas Inc, Manchester, UK) containing 600 parts per million. The gas was delivered via the InfantStar oscillator into the inspiratory limb of the patient's circuit approximately 15 cm from the endotracheal tube adapter. The measurement system of NO and NO_2 was placed on the expiratory limb close to the endotracheal tube adapter. In the SensorMedics 3100A oscillator, delivery and measurement lines were connected to the patient's limb according to the manufacturer's instructions. SensorMedics electronic flowmeter and gas analyzers were used for all infants.

The starting dose of inhaled NO was 10 ppm, which was increased stepwise by 5 ppm up to 40 ppm in infants with gestational age less than 34 weeks and up to 60 ppm in infants $\geqslant$ 35 weeks gestational age in order to attain a response. A response was defined as an increase in PaO_2 by more than 20 mmHg in the initial 10 minutes of NO administration. Ventilatory parameters remained unchanged during the initial 10 minutes. After an initial response NO dose was increased by 10 ppm. If the increased dose did not produce a further increase in PaO_2, it was decreased to the previous dosage. After a period of stabilization an attempt was made to reduce the NO dose by 3–5 ppm every 5 minutes until a decrease in oxygen saturation of 5% was reached. When this occurred, the NO was increased to the previous dose prior to the decrease in oxygenation. Weaning from NO was carried out in a reverse dose-response fashion. Endotracheal tube suctioning was performed, when necessary, through a swivel connector without disconnecting the infant from the breathing circuit, allowing continuous NO delivery.

In order to analyze the immediate results of the treatment with inhaled NO, we recorded blood gas and ventilatory data (pre-ductal PaO_2/PAO_2, $PaCO_2$, FiO_2, mean arterial pressure, oxygenation index and NO concentration) at 30 minute intervals before initiation of NO inhalation for 2 hours, and at 10–15 minute intervals thereafter for 4 hours. Oxygenation index was computed as: FiO_2*MAP*100/pre-ductal PaO_2. To further describe the outcome of infants treated with NO, the following variables were recorded and analyzed: age at onset of NO inhalation, peak NO concentration, duration of NO exposure, overall duration of ventilation, a/APO_2 ratio and oxygenation index 30 minutes prior to the initiation of NO inhalation, and a/APO_2 ratio and oxygenation index after 4 hours of NO inhalation.

Bronchopulmonary dysplasia was defined as persistent dependency on mechanical ventilation or supplemental oxygen after the 28th day of life. Chronic lung disease was defined as persistent dependency on mechanical ventilation or supplemental oxygen after a conceptional age of 36 weeks (conceptional age = gestational age + chronological age).

Statistical analysis

Pre- and post-treatment comparison between measured and calculated variables was carried out using a paired *t*-test, and significance was set at 0.05 (two-tailed). All data are presented as mean $\pm$ standard deviation

FiO_2 = fraction of inspired oxygen
MAP = mean arterial pressure
a/APO_2 = arterial/alveolar PO_2 ratio

Results

Clinical variables are presented in Table 1. The study population consisted of 10 infants, 7 males and 3 females. Four infants were born at term or near term and six were born prematurely. However, two infants who were born prematurely and developed chronic lung disease were started on NO inhalation when they reached term. Gestational age ranged from 25 to 42 weeks (31.1 $\pm$ 6.5 weeks) and birth weights ranged from 519 to 3,650g (1,717 $\pm$ 1,167g). Inhaled NO was required for the treatment of acute respiratory failure in seven infants (respiratory distress syndrome in three, and meconium aspiration syndrome in four), and was utilized as an adjuvant therapy for deteriorating bronchopulmonary dysplasia in one infant and for CLD in two. In one infant, the course of BPD was exacerbated by adenovirus pneumonitis.

Table 2 shows data related to NO treatment. In four infants in whom MAS caused hypoxemic respiratory failure, NO inhalation

CLD = chronic lung disease
BPD = bronchopulmonary dysplasia
MAS = meconium aspiration syndrome

Table 1. Clinical characteristics of the 10 infants studied

Patient	Gender	GA (wk)	BW (g)	Apgar score 5 mn	Lung disease at NO inhalation
1	M	40	3,120	5	MAS
2	M	42	3,650	6	MAS
3	M	39	3,110	8	MAS*
4	M	36	2,540	8	MAS
5	F	26	740	2	RDS
6	F	27	940	2	RDS
7	M	26	1,010	7	RDS
8	F	25	519	9	CLD
9	M	26	840	5	CLD
10	M	26	700	10	Pneumonitis

GA = gestational age, BD = body weight
* Associated with hypoxic ischemic encephalopathy

Table2. Data on nitric oxide inhalation

Patient	Age at onset (days)	Peak dose (ppm)	Duration of No therapy (day)	Days on ventilator
1	0.3	21	6	7
2	0.25	47	7	16
3	0.44	12	28	44
4	0.12	52	3	4
5	18	50	59	84
6	1.5	40	7	30
7	5	36	4.5	13
8	122	60	18	157
9	63	49	3	144
10	30	38	6.5	90

Table 3. Ultrasonographic and echocardiographic findings and outcome

		Brain ultrasonography		
Patient	**Echo**	**Prior to NO**	**After NO**	**Outcome**
1	PH	Normal	Normal	Alive
2	Normal	Normal	Normal	Alive
3	PH	Normal	Normal	Alive
4	Normal	Edema	Edema	Dead
5	PH	IVH III	IVH III	Dead
6	Normal	Normal	Normal	Alive
7	PH	IVH III	PHH	Alive
8	Normal	IVH I	Normal	Dead
9	PH	Microcephaly	Microcephaly	Alive
10	Normal	Cystic PVL	Cystic PVL	Alive

PH = pulmonary hypertension
IVH = intraventricular hemorrhage
PVL = periventricular leukomalacia
PHH = post-hemorrhagic hydrocephalus.

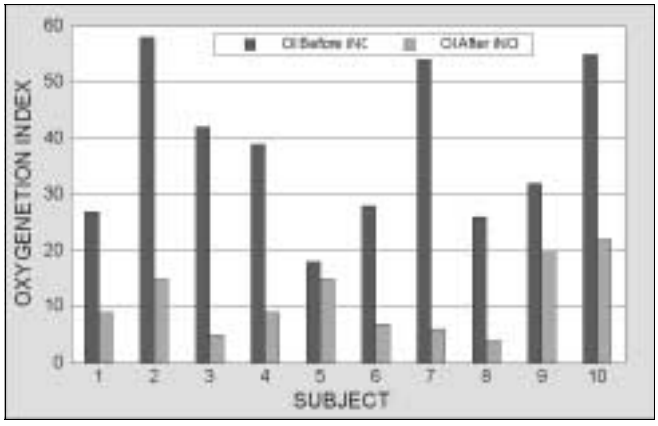

Figure 1. Changes in oxygenation index before and after initiation of NO inhalation

was initiated shortly after birth (within a few hours). Most preterm infants with RDS were started on NO inhalation after their 2nd day of life and those with BPD or CLD after 30 days of life. Peak inhaled NO dose, defined as the highest dose inhaled throughout the course of NO exposure, varied between 12 and 67 ppm (40.5 $\pm$ 13.9 ppm). The highest peak dose, above 50 ppm, was used in two infants during resuscitation – one infant with MAS and one with CLD. These two infants subsequently died. Table 3 presents the outcome and echocardiographic and ultrasonographic findings before and after NO inhalation. Figure 1 illustrates the mean changes in oxygenation index. In seven infants it was greater than 30 prior to the initiation of inhaled NO. Oxygenation index decreased from a mean of 39.3 $\pm$ 13.2 to 12.7 $\pm$ 6.9 after exposure to NO ($P < 0.0002$).

The highest methemoglobin levels observed in the study group throughout the period of NO exposure reached 3%.

RDS = respiratory distress syndrome

Discussion

These patients represent the most severely ill term and preterm infants derived from a total population of about 10,000 born at the Wolfson Medical Center during the study period. Nitric oxide inhalation treatment was attempted in a compassionate-use protocol after deteriorated oxygenation in spite of HFOV. Of the 10 infants who showed early improvement of oxygenation index, 3 died and 3 of the survivors, who were born prematurely, developed severe neurologic sequelae. The outcome of infants with lung disease complicated by hypoxemic respiratory failure may be related to various factors. Progressive hypoxemia may account for the adverse outcome in these infants, however it is possible that a neurotoxic effect of the NO doses used in our severely ill infants may have been a contributing factor.

All infants in this study improved on NO inhalation while on HFOV. The above results are consistent with those reported by previous studies [4,5]. Those investigators showed that both term and preterm infants ventilated with HFOV responded better to NO inhalation when compared with infants on conventional ventilation [4,5]. A plausible explanation could be that more alveoli are kept open during HFOV when an optimal lung volume policy is adopted. Optimized lung volume an augments NO delivery to target vessels, allowing better perfusion and better lung volume/perfusion matching.

The ability of inhaled NO to relax constricted airways has been documented in laboratory studies of animals with induced bronchoconstriction [6]. However, this was less pronounced than airway relaxation produced by beta-sympathomimetic drugs in asthmatic adult patients [7]. The effect of inhaled NO on constricted airways has not been investigated in infants. Bronchodilation induced by inhaled NO could also account for the improved gas exchange observed in infants with BPD or CLD in the present study.

Our cohort of infants consisted of four term infants and six preterm infants treated with NO inhalation in the context of a compassionate-use protocol. In preterm infants, hypoxemia often results from ventilation/perfusion mismatching with low lung volume due to surfactant deficiency. Current therapeutic approaches to RDS include the administration of exogenous surfactant and ventilator strategies aimed at recruiting lung volume. Hypoxemia may also result from associated neonatal persistent pulmonary hypertension, as demonstrated by Subhedar and Shaw [8] who showed that none of the preterm infants with RDS in their trial had echocardiographic evidence of extrapulmonary shunting. This stands in contrast to the findings in term and near-term infants where a higher proportion had an intracardiac shunt [9]. These authors found pulmonary hypertension and reduced pulmonary blood flow in infants with RDS. Laboratory studies in the premature lamb with severe RDS demonstrated that NO inhalation improved gas exchange and caused sustained reduction in pulmonary vascular resistance without increasing vascular leak [10]. These laboratory studies provided the rationale for clinical use of NO inhalation in preterm infants [11,12].

Little is known about the role of NO in the preterm newborn. Given the lack of convincing benefits associated with NO treatment

in term and near-term infants, there are concerns about extending these investigations to small preterm infants. Moreover, there appears to be no information suggesting that NO inhalation may be of benefit in preterm infants.

Potential hazards of NO inhalation include the build up of toxic NO_2, methemoglobinemia, hemorrhagic complications related to altered platelet-endothelial interaction [13,14], and the development of CLD. None of the infants in our study had significant methemoglobinemia. Van Meurs et al. [12] reported on 11 preterm infants treated with NO inhalation as the preliminary part of a large study. Despite the improvement in oxygenation, four infants experienced intracranial hemorrhage after exposure to NO. Exposure to NO did not affect the severity of brain ultrasonographic findings in our infants. This concurs with the recently reported results of a randomized controlled study of NO inhalation in premature newborns with severe hypoxemic respiratory failure. This study found no difference in adverse outcome between NO-treated preterm infants and their controls [15]. Surfactant inactivation by inhaled NO is a potential hazard that can aggravate lung damage and enhance the development of CLD. Interestingly, Kavanagh et al. [16] investigated the effect of NO on rabbit lungs and found that it may act as a superoxide scavenger, suggesting that this mechanism could account for NO protection against lung injury. Inhaled NO may also attenuate the pathogenesis of neutrophil/oxidant-mediated lung injury. Moreover, in a mechanically ventilated premature lamb with RDS the inhalation of NO decreased inflammation (lung neutrophil accumulation) [17].

Pulmonary hypertension can be reduced and arterial oxygenation improved with NO of up to 20 ppm [9,18,19]. However, in some infants improved oxygenation was attained using NO of 80 ppm [3]. Similarly, in our group of infants, the peak dose of inhaled NO varied from 12 ppm to 60 ppm. It seems that in the neonatal lung the degree of improvement with NO depends also upon the presence of mature surfactant and the severity of primary lung disease [5].

The exposure to NO in the present study ranged from 3 to 59 days (mean 14.2 days). Long-term NO inhalation in neonates was reported by Abman et al. [20] who treated infants with low dose NO (3–10 ppm) for up to 24 days, and by Kitayama and colleagues [21] who administered NO in the incubator of an infant for 61 days. The short duration of action of inhaled NO may be a disadvantage to clinical therapy because patients with chronic pulmonary hypertension may require continuous and long-term treatment. Discontinuation of NO inhalation can lead to dramatic decreases in oxygenation and increases in pulmonary vascular resistance that may be severe and may require restarting. The "rebound" effect could increase with prolonged treatment. The mechanisms accounting for failure of weaning from long-term treatment include a long-range effect on pulmonary structure and function and endogenous NO synthesis.

Our results indicate that the combined treatment of HFOV and NO inhalation is superior to HFOV alone for improving oxygenation in infants with a variety of lung diseases. We speculate that the high rate of adverse outcome in our infants, whose lives were in jeopardy prior to the institution of NO, may be attributed to the extent of their initial hypoxemia rather than to NO toxicity.

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APPENDIX

High Frequency Oscillatory Ventilation

- **Principles of operation**

There are three distinguishing characteristics of HFOV: the frequencies range from 5 to 30 Hertz (300–1,800 cycles per minute), active inspiration and active expiration, and tidal volume about the size of the dead space. The management of a patient with HFOV is based on a few simple principles:

1. Oxygenation is decoupled from ventilation in that changes made to alter oxygenation have little effect on CO_2 elimination from the lungs, and conversely, changes made to effect $PaCO_2$ change have little effect on oxygenation.
2. To change oxygenation, lung volume has to be adjusted, as there is a close relationship between lung volume and surface area for gas exchange. Because during HFOV, lung volume is established with MAP, the MAP adjustment will have a profound effect on oxygenation.
3. Manipulating the oscillatory tidal volume attains control over CO_2 clearance from the lungs. In HFOV, $PaCO_2$ is closely related to the delivered oscillatory volume (expressed as peak to peak pressure = amplitude of oscillation = delta pressure).

There are two types of oscillators commercially available for use in neonates. The InfantStar is designed around microprocessor-controlled solenoid valves that open and close at high frequencies. The opening and closing of these valves generate a pulse of high velocity gas, which is transmitted down the airways. The pulse of gas also leads to small recoil in the ventilator circuit, which results in an active expiratory phase. The SensorMedics 3100A generates pressure waves with a diaphragm driven by an electromagnet. The sinusoidal pressure wave that is generated by the diaphragm is transmitted to the airways and alveoli.

Neonatal Intensive Care Unit Guidelines for HFOV

In our neonatal intensive care unit high frequency oscillation is a primary mode of ventilation for infants who require ventilatory support irrespective of their underlying lung disease. Oscillatory frequency is kept unchanged at 15 Hz (900 cycles/minute) throughout the ventilatory treatment. The frequency of 15 Hz is used for reasons of convenience and practicality, since it allows shaking to be used as a clinically detectable index of transmission of oscillations to the lungs. Since a fixed frequency of 15 Hz is used, changes in oscillatory tidal volume (amplitude of oscillation) determine changes in $PaCO_2$.

Immediately after intubation, MAP is set at 10 cm H_20 and increased stepwise by 1–2 cmH_2O until the FiO_2 decreases below 0.30 (high lung volume strategy). Thereafter, MAP is decreased in a stepwise fashion by 1–2 cmH_2O, as long as oxygenation does not deteriorate.

Arterial PCO_2 is maintained between 35 and 45 mmHg in infants with RDS or MAS and between 45 and 55 mm Hg in infants with BPD or CLD.