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ORIGINAL ARTICLE

Non-invasive inhaled nitric oxide in the treatment of hypoxemic respiratory failure in term and preterm infants

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OBJECTIVES: Inhaled nitric oxide (iNO) is effective in conjunction with tracheal intubation (TI) and mechanical ventilation (MV) for treating arterial pulmonary hypertension and hypoxemic respiratory failure (HRF) in near-term and term newborns. Non-invasive respiratory support with nasal continuous positive airway pressure (CPAP) is increasingly used to avoid morbidity associated with TI and MV, yet the effectiveness of iNO delivery via nasal CPAP remains unknown. To evaluate the effectiveness of iNO delivered via the bubble nasal CPAP system in term and preterm newborns with HRF.

STUDY DESIGN: Electronic medical records from all infants admitted to the neonatal intensive care unit (NICU) during 2005 to 2014 ($n = 10,895$) were screened for treatment with iNO therapy for HRF. Detailed data on population characteristics and cardiorespiratory, iNO and respiratory support indices were abstracted for all infants, who were administered iNO non-invasively using bubble nasal CPAP. Change in relevant indices at baseline (before initiating non-invasive iNO) and at 3, 6, 12 and 24 h after non-invasive iNO therapy were analyzed using repeated measures analysis of variance.

RESULTS: Of 795 infants treated with iNO (7.3% of total NICU admissions) over a 10-year period, 107 infants (13.4% of iNO treated) with birth weight 2448 ± 1112 g and gestational age 35.3 ± 5.8 weeks received iNO non-invasively. 25 infants received iNO exclusively non-invasively, whereas in remaining 82 infants non-invasive route followed invasive delivery via TI and MV. Indications for using non-invasive iNO included idiopathic pulmonary hypertension (39%), congenital heart disease (37%), bronchopulmonary dysplasia (10%), meconium aspiration syndrome (9%) and congenital diaphragmatic hernia (5%). Over the 24 h following initiation of non-invasive iNO, fractional oxygen requirements decreased (0.38 to 0.32; $P < 0.0005$) and SpO_2 increased (90.7 to 91.6%; $P < 0.01$) with no significant changes in heart rate, respiratory rate, blood pressure, pH and $PaCO_2$. On average non-invasive iNO was initiated on day of life 9 with a maximal dose was 20 p.p.m. The average duration of iNO therapy and the duration over which it was weaned off were 134 and 51 h, respectively. Analysis of environmental gases during non-invasive iNO therapy revealed median ambient nitrogen dioxide and nitric oxide levels of 0.30 and 0.01 p.p.m., respectively.

CONCLUSIONS: Initiation of iNO in infants on bubble nasal CPAP or continuation of iNO in infants transitioning from MV to bubble nasal CPAP is associated with improved oxygenation during HRF in term and preterm infants. Non-invasive iNO may have a synergistic effect with airway recruitment strategies such as nasal CPAP.

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INTRODUCTION

Inhaled nitric oxide (iNO) has been proven to be safe and effective treatment for pulmonary hypertension and hypoxemic respiratory failure (HRF) in near-term and term newborns.[1–4] Accordingly, its use is currently approved in US only in near-term and term newborn infants in conjunction with ventilatory support and other appropriate agents.[5,6] In infants born prematurely, the effects of iNO on lung function are not well defined. Available evidence from randomized control trials does not support use of iNO in early-routine, early-rescue or later-rescue regimens to prevent bronchopulmonary dysplasia in premature newborns of < 34 weeks' gestation, who require mechanical ventilation (MV).[7] Currently, there is lack of approved therapies for HRF in preterm infants. However, recent studies suggest that less sick preterm infants could benefit from this therapy both in short- and long-term.[8,9] Moreover, non-invasive respiratory support with nasal continuous positive airway pressure (CPAP) is being increasingly used to avoid morbidity associated with tracheal intubation (TI) and MV,[10] yet the effectiveness of iNO delivery via nasal CPAP in these infants remains unknown. Lindwall *et al.*[11–13] have recently reported safe and effective delivery of iNO in preterm infants using the Infant Flow Nasal CPAP system. It appears that iNO may have synergistic effect with airway recruitment strategies such as CPAP in improving oxygenation during HRF. Experimental work in animals also suggests that the combination of iNO and CPAP may be beneficial.[14]

We have been using iNO with bubble nasal CPAP in term and preterm infants with HRF for over 10 years at Morgan Stanley Children's Hospital, Columbia University Medical Center and had access to the electronic medical record (EMR) with detailed daily clinical management flow sheet data on all infants treated with the combination of these two modalities during this time period. The overall aim of our study was to evaluate the effectiveness of iNO delivered via the bubble nasal CPAP system in term and preterm newborns with HRF over a 10 year period in a single center that practices uniform gentle respiratory care strategy with permissive hypercarbia. In addition, in view of concerns raised over possible insidious release of nitrogen oxides into the workplace environment during iNO-bubble nasal CPAP therapy exposure,[15,16] we evaluated the maximum ambient nitric

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oxide (NO) and nitrogen dioxide (NO_2) levels in the breathing zone environment of the caregiver.

METHODS

Patient population

The goals of our study were achieved by retrospective review of the EMR of preterm and term infants admitted to the neonatal intensive care unit (NICU) in whom iNO was administered non-invasively using bubble nasal CPAP for HRF between 2005 and 2014. The study was approved by the Institutional Review Board of Columbia University Medical Center. EMRs on 10,895 infants (total NICU admissions) admitted during 10-year study period were screened for treatment with iNO therapy. During this period 795 (7.3% of total NICU admission) infants received iNO therapy for HRF. Of these 795 infants, 107 (13.4% of iNO treated) infants received iNO non-invasively. 25 infants, designated as group I, received iNO exclusively via bubble nasal CPAP and 82 infants, designated as group II, received iNO with bubble nasal CPAP after transitioning from iNO therapy with TI and MV to bubble nasal CPAP. All eligible infants were included in the study and there were no exclusions.

Non-invasive iNO delivery and monitoring

Non-invasive iNO was delivered using the INOMAX delivery system (Ikaria-Mallinckrodt Pharmaceuticals Inc., Hampton, NJ, USA), via a constant-flow, variable pressure bubble nasal CPAP device with Hudson (Hudson RCI-Teleflex, Morrisville, NC, USA) bi-nasal prongs (Figure 1). iNO therapy gas was delivered into the inspiratory limb of the respiratory circuit in a way that provided a constant concentration of iNO, as set by the user, throughout the inspired breath. To ensure correct flow measurements the iNO injector module was inserted on the dry side of the respiratory circuit before the humidifier. Based on the CPAP flow rate, the INOMAX cylinder concentration, and set INOMAX dose, the proportional valve delivers 800 p.p.m. INOMAX into the respiratory circuit via the injector module where it mixes with the breathing circuit gas flow to achieve the set dose. This allowed for delivery of a constant dose of iNO regardless of the CPAP flow pattern or infant's breathing rate. The sample gas was withdrawn from a sample tee placed >24 inches from the injector module on the inspiratory side of the breathing circuit to ensure proper gas mixing as per the manufacturer recommendations. The sample gas passed through a water trap, a zero valve, a sample pump before reaching a sample flow sensor, which measures concentrations of NO, NO_2 and O_2. As described in the Operators Manual, the same sample line was also used to assess environmental air sample from the breathing zone of the bedside caregiver in proximity to the infant every 12 h during treatment with iNO after disconnecting it from the main circuit.

Respiratory care and iNO weaning strategy

The respiratory care and iNO weaning strategy was uniform and consistent during the entire study period. Essentially, infants receiving iNO for HRF were very closely monitored clinically for pulmonary hypertension using continuous pre- and post-ductal oxygen saturations, frequent blood gases, intermittent echocardiography and chest roentgenography. If pulmonary vascular disease was persistent with near resolution of lung parenchymal disease MV was weaned off, infant was extubated to nasal CPAP and iNO was continued non-invasively as described above. In contrast, if pulmonary hypertension resolved but residual lung parenchymal disease persisted, iNO was weaned off and MV ventilation continued until parenchymal disease improved.

Data collection

For all eligible infants, data pertaining to the study population characteristics (birth weight, gestational age, inborn vs out-born status, and underlying etiology for HRF), cardiorespiratory and acid-base balance indices (changes in heart rate, respiratory rate, blood pressure, pH, $PaCO_2$, PaO_2, SpO_2 and base excess/deficit), iNO and respiratory support indices (iNO dose, duration of iNO therapy, duration of iNO weaning and FiO_2, duration of oxygen therapy), overall neonatal mortality, duration of hospitalization and maximum ambient oxygen, NO and NO_2 levels were extracted from the patients demographics, daily progress notes, daily clinical assessment flow sheets (vital signs and respiratory care), blood gas and discharge summary sections of the EMR. Data were collected keeping in mind that iNO therapy may have been used non-invasively with bubble nasal CPAP under any of the following scenarios,

Group I iNO + bubble nasal CPAP alone.
Group II iNO + bubble nasal CPAP after iNO + TI and MV.

Data analysis

Data on all infants was collated and summarized to obtain study population characteristics, incidence of overall mortality, iNO and respiratory support indices and the duration of hospitalization. Changes in gas exchange, acid–base balance and cardiorespiratory indices were

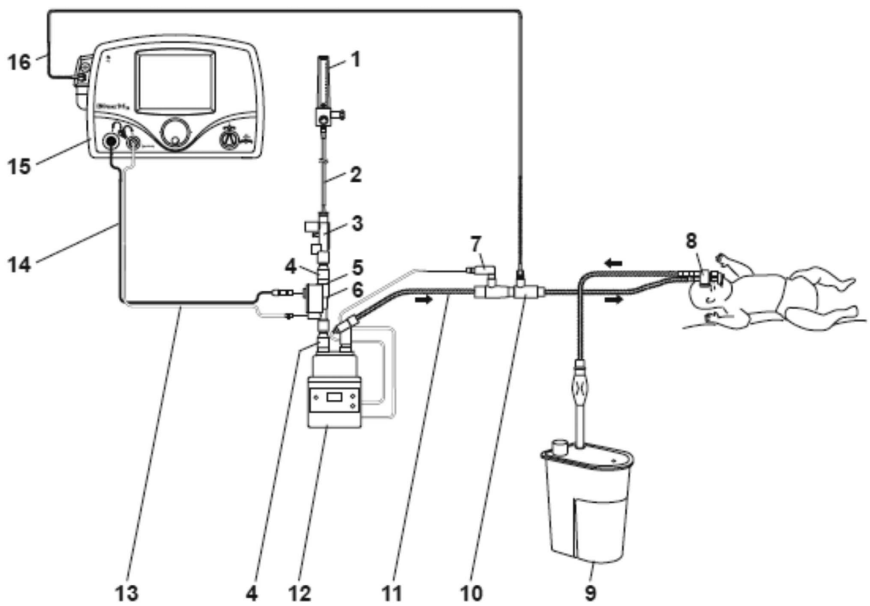

Figure 1. Non-invasive inhaled nitric oxide (iNO) delivery using the INOMAX delivery system connected to nasal prong infant interface and Fischer and Paykel bubble continuous positive airway pressure (CPAP) system (1 = oxygen source, 2 = oxygen tubing, 3 = bubble CPAP pressure manifold, 4 = 22F × 15M adapter, 5 = 22M/15F × 22M/15F adapter, 6 = injection module, 7 = temperature probe, 8 = nasal prong infant interface, 9 = bubble CPAP generator, 10 = F/P inline infant nebulizer kit (RT010) adapter, 11 = breathing circuit, 12 = humidifier, 13 = NO/N_2 injector tube, 14 = injector module electrical cable, 15 = INOMax DS_{IR} and 16 = patient gas line with Nafion).

made at baseline (before initiating non-invasive iNO) and at 3 h, at 6, 12 and 24 h of non-invasive iNO therapy was analyzed using repeated measures analysis of variance.

RESULTS

Patient demographics

A total of 107 infants were treated with non-invasive iNO during the 10-year period. The mean birth weight was 2448 ± 1112 g (range 375 to 4075 g) and mean gestational age was 35.3 ± 5.8 weeks (range 23 to 41 weeks). 39 (36.4%) of these infants were preterm, 51 (47.4%) were males, 59 (55.1%) were out-born, 95 (88.8%) survived, 56 (52.3%) discharged home and 39 (36.5%) transferred back to other institutions). Infants treated exclusively with non-invasive iNO (group I) had relatively lower birth weight, gestational age, male predominance, incidence of extramural birth and survival as compared with those in whom non-invasive iNO was continued following transitioning from MV to bubble nasal CPAP (group II; Table 1).

Indications for non-invasive iNO therapy

Distribution of patients by underlying diagnosis for non-invasive iNO therapy is shown in Figure 2. Overall the most common underlying etiologies for HRF were idiopathic pulmonary hypertension and congenital heart disease during the postoperative period followed by bronchopulmonary dysplasia, meconium aspiration syndrome, congenital diaphragmatic hernia and congenital heart disease during the preoperative period. In group I, idiopathic pulmonary hypertension was the predominant cause (76%) for non-invasive iNO therapy. Although in group II, congenital heart disease postoperative period (43%) and idiopathic pulmonary hypertension (27%) accounted for most of the patients.

Non-invasive iNO and gas exchange/acid–base balance indices

Over the 24h following initiation of non-invasive iNO therapy the fractional oxygen requirement decreased (0.38 to 0.32; $P < 0.0005$) in face of improving oxygen saturation (90.7% to 91.6%; $P < 0.01$; Figure 3). Infants in both groups demonstrated decline in need for supplemental oxygen over the 24 h period with group I infants dropping from 0.45 to 0.38 ($P < 0.05$) and group II from 0.36 to 0.29 ($P < 0.0002$; Figure 3). There were no significant differences in pH, pCO_2 and base excess/deficit during this period as shown in Figure 4.

Table 1. Study population demographics (means)

	Group I (n = *25*)	*Group II* (n = *82*)	*All* (n = *107*)
Birth weight (g)	2277 (480–4075)	2501 (375–4040)	2448 (375–4075)
Gestational age (weeks)	33.7 (23–40)	35.7 (23–41)	35.2 (23–41)
Gestational age < 37 weeks (%)	44.0	34.1	36.4
Males (%)	48.0	59.7	47.7
Out-born (%)	52.0	56.1	55.1
Outcome (%)			
Discharged home	40.0	56.2	52.3
Transferred	44.0	34.1	36.5
Died	16.0	9.7	11.2

Non-invasive iNO and cardiorespiratory indices

Over the 24 h following initiation of non-invasive iNO there were no significant changes in heart rate, respiratory rate or blood pressure (systolic, diastolic and mean; Figure 5).

iNO & respiratory support characteristics

The median age for initiation of iNO was 9 days (range 1 to 217 days) and the maximal median dose of iNO used was 20 p.p.m. (range 5 to 20 p.p.m.). The median duration of iNO therapy was 134 h (range 7 tp 3773 h) and iNO was weaned off over a median of 51 h (range 1 to 3497 h). These infants received bubble nasal CPAP for a median 54 h (range 1 to 3773 h) and supplemental oxygen ($FiO_2 > 0.21$) for a median of 128 h (range 18 to 3729 h; Table 2).

Environmental gases during non-invasive iNO therapy

Maximal NO and NO_2 levels obtained from the environmental air sample in the breathing zone of the care-taker near the infant were 0.6 p.p.m. (median 0.01 p.p.m.) and 0.8 p.p.m. (median 0.30 p.p.m.) respectively, suggesting that non-invasive iNO therapy contributed only minor amounts of nitrogen oxides to the NICU environmental gases (Table 3).

DISCUSSION

Our study demonstrates that consistent delivery of iNO with negligible contamination of the immediate environment is feasible and that initiation of iNO to infants on bubble nasal CPAP or continuation of iNO in infants transitioning from TI and MV to bubble nasal CPAP is associated with improved oxygenation in the face of decreasing need for supplemental oxygen during HRF in term and preterm infants. Non-invasive delivery of iNO resulted in no alteration in respiratory drive as assessed by repeated measurements of respiratory rate and carbon dioxide tension. The acid–base balance was well maintained and no significant cardiovascular (heart rate and blood pressure) alterations were noted. In 25 (23.3%) of the study infants iNO was successfully delivered exclusively through bubble nasal, thus avoiding the need for TI and MV in the treatment of HRF. In the other 82 infants (group II), iNO treatment was effectively continued following extubation and transitioning from MV to non-invasive bubble nasal CPAP. One of the limitations of our study is that there were no controls, therefore the possibility that improved oxygenation and decreased need for supplemental oxygen in group II infants may have occurred over time with resolution of underlying pathology even without iNO.

Infants were treated for HRF with non-invasive iNO for varying underlying etiologies that included meconium aspiration syndrome, congenital heart disease, congenital diaphragmatic hernia,

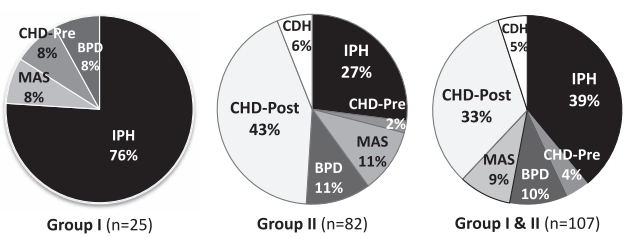

Figure 2. Underlying etiologies for HRF during non-invasive iNO therapy in groups I, II and combined (groups I and II). BPD, bronchopulmonary dysplasia; CDH, congenital diaphragmatic hernia; CHD-Pre, congenital heart disease-preoperatively; CHD-Post, congenital heart disease-postoperatively, HRF, hypoxemic respiratory failure; iNO, inhaled nitric oxide; IPH, idiopathic pulmonary hypertension; MAS, meconium aspiration syndrome).

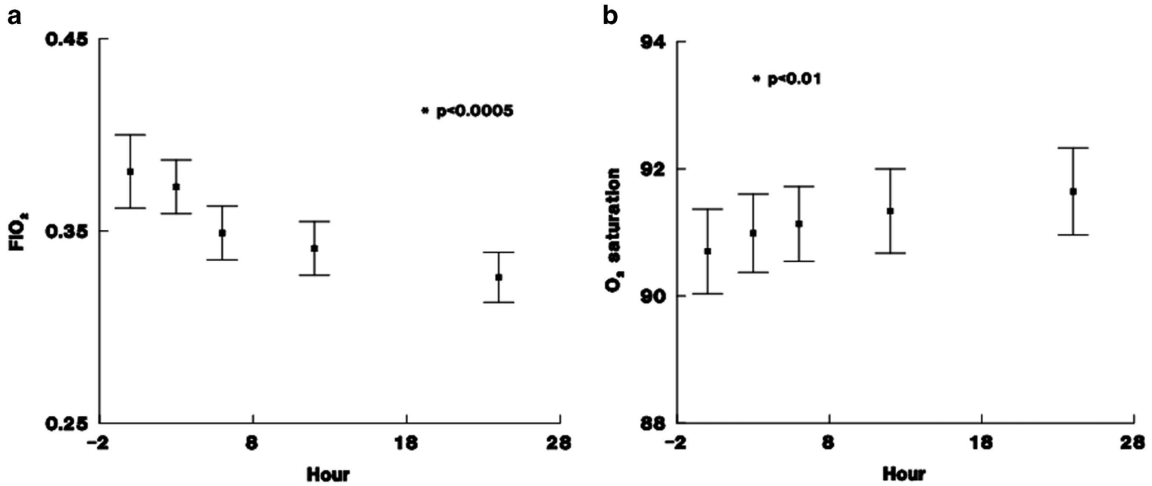

Figure 3. Changes in oxygen requirement (FiO_2) (**a**) and O_2 saturation (**b**) over 24 h following initiation of non-invasive iNO therapy for HRF in groups I and II ($n = 107$) (means/ standard errors). HRF, hypoxemic respiratory failure.

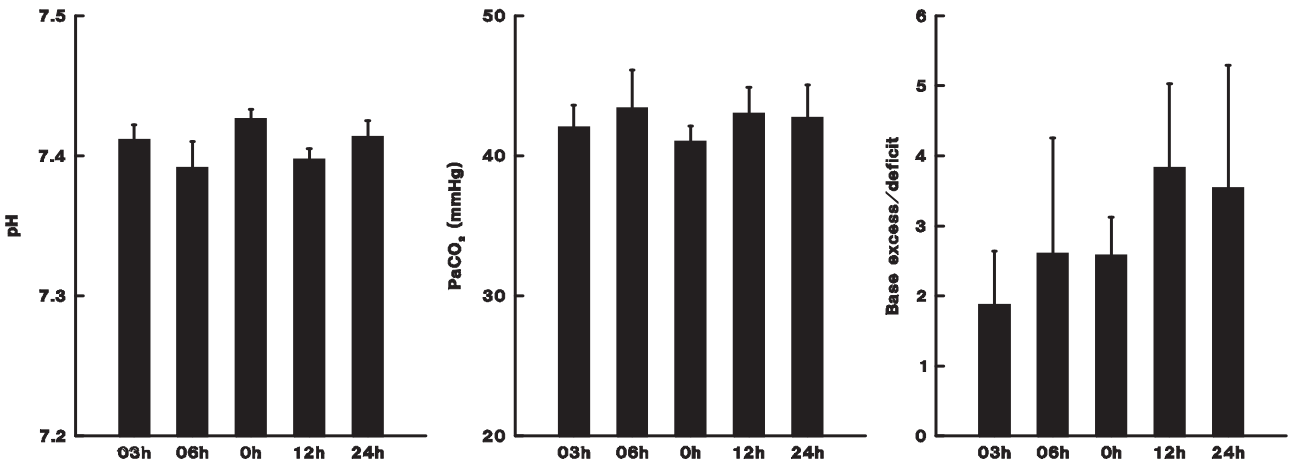

Figure 4. Acid–base balance changes over 24 h following initiation of non-invasive iNO therapy for HRF in groups I and II ($n = 107$; means/ standard errors). HRF, hypoxemic respiratory failure; iNO, inhaled nitric oxide.

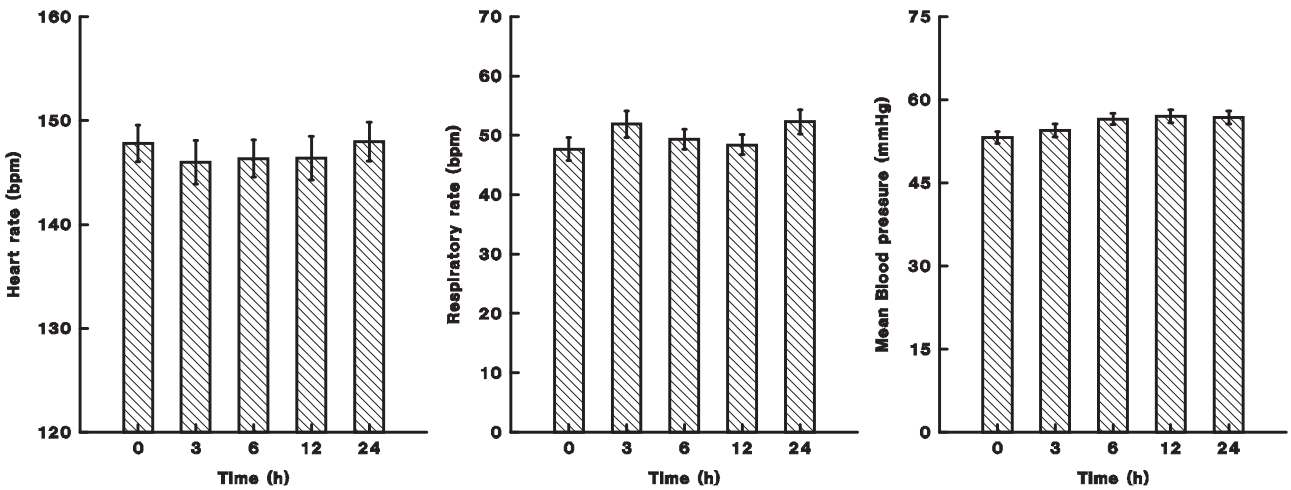

Figure 5. Cardiorespiratory changes over 24 h following initiation of non-invasive iNO therapy for HRF in groups I and II ($n = 107$; means/ standard errors). HRF, hypoxemic respiratory failure; iNO, inhaled nitric oxide.

Table 2. iNO and respiratory support characteristics during non-invasive iNO therapy for HRF

	Median (range)
Age at initiation of iNO (day of life)	9 (1–217)
Maximum dose of iNO used (p.p.m.)	20 (5–20)
Duration of iNO therapy (h)	134 (7–3773)
Duration of iNO weaning (h)	51 (1–3497)
Duration of bubble nasal CPAP (h)	54 (1–3773)
Duration of supplemental O_2 (h)	128 (18–3729)

Abbreviations: CPAP, continuous positive airway pressure; HRF, hypoxemic respiratory failure; iNO, inhaled nitric oxide.

Table 3. Environmental gases in the breathing zone of the care-taker during non-invasive iNO therapy

	Maximum (median)
Ambient oxygen level	0.21 (0.21)
Ambient NO_2 level	0.8 (0.30)
Ambient NO level	0.6 (0.01)

Abbreviations: NO, nitric oxide; NO_2, nitrogen dioxide.

bronchopulmonary dysplasia and idiopathic pulmonary hypertension. The hypoxemia in these conditions was secondary to elevated pulmonary vascular resistance and right-to-left shunting of blood across foramen ovale and/or patent ductus arteriosus. Acute indications for non-invasive iNO treatment included meconium aspiration syndrome, congenital heart disease preoperatively and idiopathic pulmonary hypertension while iNO was used for prolonged periods in chronic conditions such as bronchopulmonary dysplasia and during recovery phase of HRF as infants transitioned from MV to bubble nasal CPAP while on invasive iNO (congenital heart disease postoperatively and congenital diaphragmatic hernia). Accordingly, the day of life non-invasive iNO was initiated varied from 1 to 217 depending on the underlying etiology for HRF. In most of the infants a maximal dose of 20 p.p.m. was used while for a few with chronic indication for use (bronchopulmonary dysplasia) the maximum dose use was as low as 5 p.p.m. During the treatment of HRF, infants required supplemental oxygen and iNO for an average of 5 to 6 days of which ~40% of time was spend during weaning. iNO was invariably weaned off before discontinuation of bubble nasal CPAP. We performed environmental air sampling from the breathing zone of the caregiving with ongoing iNO to evaluate for occupational exposure during iNO-bubble nasal CPAP treatment. The median NO values in the breathing zone were lower compared with those reported by others during iNO and MV.[17]

Non-invasive methods of delivering iNO have been previously described anecdotally. Ivy *et al.*[18] were the first to demonstrate that iNO can be delivered effectively by continuous flow nasal cannulae in a 7-week-old infant with primary pulmonary hypertension in which iNO successfully aided the transition to chronic prostacyclin infusion. The use of iNO via a nasopharyngeal tube helped to maintain clinical improvement for a week in a 145-day-old infant with a severely hypoplastic lung and end-stage pulmonary hypertension.[19] Pulsed delivery of NO via nasal prongs to adult patients with primary pulmonary hypertension in home setting using an ambulatory delivery device has also been described.[20] iNO therapy via nasal CPAP was effectively used in a group of very low birth weight infants during the weaning phase for prevention of bronchopulmonary dysplasia.[8] Non-invasive iNO delivered through a nasal cannula may also reduce the duration of respiratory support during treatment of late pulmonary hypertension in newborn infants with congenital diaphragmatic hernia.[21] In a randomized, double-blind, cross-over pilot trial, Lindwall *et al.*,[12] demonstrated that addition of 10 p.p.m. iNO to nasal CPAP treatment in preterm infants (median gestational age 32 week) suffering from respiratory distress syndrome resulted in improvement in oxygenation, with no effects on respiratory drive or systemic circulatory parameters. In addition, INOMAX delivery systems have been validated and are approved by the Food And Drug Administration (FDA) for use with nasal cannulas and non-invasive delivery systems using various configurations described by the manufacturer.

Non-invasive iNO may have a synergistic effect with airway recruitment strategies such as nasal CPAP. In a canine oleic acid lung injury model application of CPAP augments iNO induced pulmonary gas exchange.[14] Application of CPAP during acute lung injury recruits additional lung units for gas exchange[22,23] and thereby may dilate additional blood vessels previously not exposed to the NO present in the gas phase. This contrasts with observations made during administration of intravenous vasodilators that have been reported to relieve regional hypoxic pulmonary vasoconstriction, increase pulmonary blood flow to shunt units and reduce arterial blood oxygenation.[24] Thus, the potential mechanism for improved gas exchange with the combination of iNO and nasal CPAP may be due to marked decrease in intrapulmonary shunt resulting from improved ventilation of the shunt units and redistribution of blood flow to previously non-perfused areas.

As more preterm infants are now being successfully managed without TI and MV,[25] the use non-invasive iNO therapy via nasal CPAP may play a role in reducing the neonatal morbidity by influencing morphological alterations in the vascular smooth muscle[26,27] and reducing white cell trapping in lung tissue during inflammation.[28,29] Our data have the potential utility in planning future randomized control studies to evaluate whether non-invasive iNO can be used to reduce the risk of chronic lung disease, pulmonary hypertension, and death in preterm infants that do not require MV.

APPENDIX

Case report

This is an example of successful use of non-invasive iNO therapy in a female infant weighing 1315 g who was born at 31 weeks' gestation following a monochorionic-diamniotic twin pregnancy. Early ultrasound findings during pregnancy were suggestive of aneuploidy with cystic hygroma for this twin and trisomy 21 was suspected. Fetal echocardiogram was positive for possible atrioventricular canal defect. Infant was delivered by cesarean section for non-reassuring fetal heart rate tracing. No active resuscitation was required following birth and Apgar scores were 8 and 8 at 1 and 5 min, respectively. Infant was admitted to the NICU in view of prematurity and respiratory distress syndrome and placed on bubble nasal CPAP with supplemental oxygen. However, due to persistently low oxygen saturations in 80's despite 100% supplemental oxygen infant was intubated and placed on MV. Over the next 24 h her blood gases improved, MV was weaned and she was extubated to bubble nasal CPAP without any supplemental oxygen. At 36 h her oxygen saturation dropped to low 80s and she required supplemental oxygen to maintain oxygen saturation in low 90s. By 41 h of life her oxygen requirement increased to 100% to maintain acceptable oxygen saturation and her echocardiogram revealed a small mid-muscular ventricular septal defect, mildly dilated right atrium with patent foramen ovale, mild-moderate tricuspid regurgitation, moderately dilated right ventricular chamber, right ventricular hypertension, mild right ventricular hypertrophy and moderate to large patent ductus arteriosus. Non-invasive iNO was initiated at 20 p.p.m.

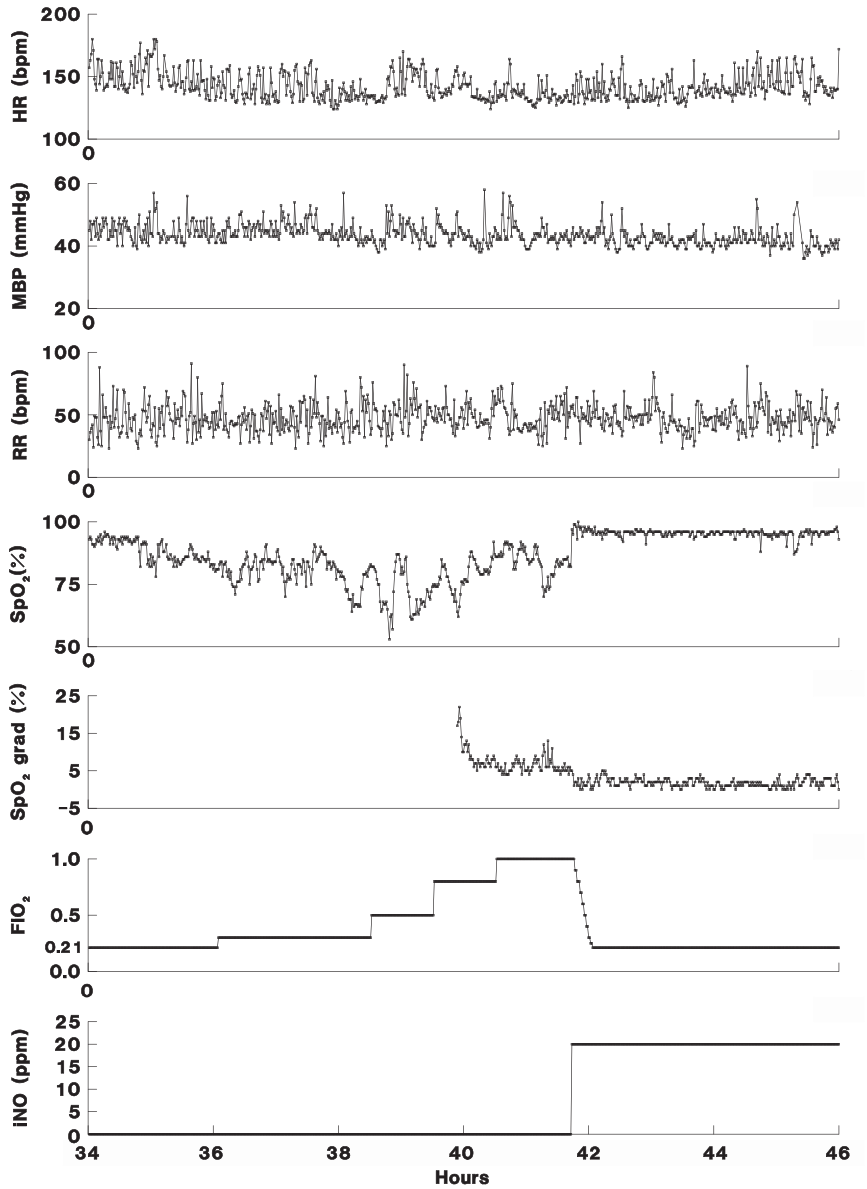

Figure 6. Cardiorespiratory changes during non-invasive iNO therapy for persistent pulmonary hypertension in a preterm infant. Note increasing O_2 requirement from hours 36 to 41, initiation of non-invasive iNO at 20 p.p.m. around 41.8 h, and subsequent marked improvement in SpO_2, decrease in pre- and post-ductal SpO_2 gradient, rapid weaning of supplemental oxygen and no changes in HR, RR and MBP. HR, heart rate; iNO, inhaled nitric oxide; MBP, mean blood pressure; RR, respiratory rate; SpO_2, oxygen saturation.

through bubble nasal CPAP. As shown in Figure 6, within 20 min of initiation of non-invasive iNO oxygen saturation improved markedly, pre- and post-ductal oxygen saturation gradient decreased and the supplemental oxygen was weaned off while the infant was maintained on bubble nasal CPAP. Infant remained on bubble nasal CPAP without any supplemental oxygen and subsequently iNO was weaned off over the next 4 days.

Repeat echocardiogram before discontinuation of non-invasive iNO did not reveal any tricuspid regurgitation and the infant was subsequently discharged home. The most likely underlying etiology of pulmonary hypertension in this infant with Down's syndrome was exposure to increased pulmonary blood flow due to left-to-right intracardiac shunting resulting in increased shear stress on pulmonary endothelium and impaired intrinsic NO production. Her labile hypoxemia was suggestive of pulmonary hypertension and the echocardiogram supported the diagnosis. With adequate respiratory drive, and no evidence of parenchymal lung disease on chest radiograph it was felt that she did not warrant TI and MV, and iNO could be delivered non-invasively via bubble nasal CPAP. This case illustrates that in newborn infants presenting with HRF with no evidence of parenchymal lung disease, non-invasive iNO therapy may reduce exposure to high levels of inspired oxygen and avoid TI and MV.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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