Childhood Pulmonary Function, Exercise Capacity, and Exhaled Nitric Oxide Levels: Outcomes following Neonatal Treatment with Inhaled Nitric Oxide to Prevent Bronchopulmonary Dysplasia

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Abstract

Objective The goal was to determine if inhaled nitric oxide (iNO) for 3 weeks during neonatal care of high-risk preterm infants was associated with improved pulmonary function and exercise capacity or altered exhaled nitric oxide (FeNO) levels in later childhood.

Study Design Thirty-four very preterm children previously enrolled in a randomized, neonatal trial of iNO to prevent chronic lung disease, were assessed in follow-up at 7 to 9 years of age, including pulmonary function testing (PFT), exercise testing, and measurement of FeNO.

Results There were no differences in PFTs or exercise capacity between iNO treated and controls. FeNO levels showed large interpatient variability but tended to be lower in the iNO treated.

Conclusion Findings indicate no overall differences in pulmonary function or exercise capacity for children who had neonatal iNO treatment compared with placebo.

Keywords
- bronchopulmonary dysplasia
- extreme prematurity
- inhaled nitric oxide
- pulmonary function
- exercise capacity
- exhaled nitric oxide (FeNO)

Bronchopulmonary dysplasia (BPD) is a common and serious disorder of preterm birth. The incidence of BPD varies inversely by gestational age (GA) and, depending on the definition, may exceed 50% in the lowest birth weight (BW) category (< 750 g).[1] BPD is associated with increased neonatal mortality and morbidity, prolonged neonatal hospitalization, and long-term medical and neurodevelopmental sequelae. Unfortunately, few interventions evaluated in the last 10 years have been associated with improvement in severity or incidence of BPD when studied in controlled multicenter, randomized clinical trials (RCTs).[2,3]

Inhaled nitric oxide (iNO) is an accepted treatment for respiratory failure associated with pulmonary hypertension in term infants; however, its use in preterm infants remains investigational.[4] Animal models have shown benefits of NO in reducing oxidative injury, enhancing lung development, alveolarization, and vascular remodeling.[5,6] However, only 2 of 7 RCTs of iNO have reported a reduction in the incidence of BPD, and a meta-analysis did not confirm its use for that purpose.[7] The Nitric Oxide Chronic Lung Disease (NO CLD) investigation by Ballard et al[8] was the largest study reporting a decrease in BPD with iNO. The approach to treatment in that investigation differed from other studies, in that iNO was used earlier and longer, beginning during the second week of life and continuing for 24 days in high-risk infants. The reported findings were decreased need for supplemental oxygen at 36 weeks' postmenstrual age, less pulmonary morbidity at 1 year corrected age by parent report,[9] and no difference in rates of neurodevelopmental disabilities at 2 years of age.[10]

BPD is associated with long-term pulmonary morbidity, including abnormal pulmonary function testing consistent with airway obstruction, reduced air flow measurements,

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and reduced gas transfer at school age.[11–13] Increased resonant frequency and decreased reactance assessed by forced oscillometry suggest impaired elastic properties and lung stiffness in children with BPD.[14] There are no data regarding the effects of neonatal iNO treatment on these longer term cardiopulmonary functional outcomes.

Children who survive BPD may frequently have wheezing with variable response to β (2)-agonists. Exhaled nitric oxide (FeNO) measurements are used to assess allergic inflammation in asthmatics, but there are limited studies of FeNO in former preterm infants with or without BPD. Mieskonen et al found no differences at school age in FeNO between preterm infants with or without chronic lung disease and nonatopic term controls.[15] Baraldi et al[16] showed school-age children with BPD had significantly lower FeNO levels compared with asthmatics with comparable airflow limitations, suggesting different mechanisms of airway obstruction. It is unknown if neonatal exposure to iNO could modify NO production or FeNO measures in childhood, although there have been observations suggesting iNO during acute treatment may suppress endogenous production.[17]

The goal of this study was to evaluate the cohort of children who had been enrolled at our institution in the NO CLD trial to compare pulmonary function and exercise capability at early school age between those treated with iNO versus those treated with placebo. A secondary objective was to determine if there were differences in FeNO levels between groups in childhood.

Methods

Study Population

Eligible children were those previously enrolled at Children's Mercy Hospital (CMH) in the NO CLD study: BW $\leq$ 1,250 g, $\leq$ 32-week GA, and born between 2000 and 2005 ($N = 58$). The Institutional Review Board of the University of Missouri–Kansas City School of Medicine approved the study. Families were contacted by letter, and then contacted by phone to request consent for follow-up visit. At study visit, informed written consent and assent were obtained from one parent and each child, respectively. Descriptive information and neonatal data were available from the NO CLD study database for group comparisons.

Data Collection

The study was conducted at the CMH pulmonology clinic and the exercise physiology laboratory. Participants were initially weighed and height measured. Parents accompanying the child were interviewed regarding medical history, including asthma occurrence and treatment, other pulmonary conditions, exercise tolerance, and review of environmental tobacco smoke exposure. FeNO was measured using NIOX MINO® with slow exhalation. After initial exhalation, the child was instructed to inhale deeply through a disposable filter then exhale slowly. Measurement was recorded in parts per billion (ppb). FeNO levels were reported as mean during 3-second FeNO plateau.[18] Impulse oscillometry (iOS) was assessed through modification of forced oscillatory technique,[19] which primarily measures respiratory system resistance (Rrs) and reactance (Xrs) at different frequencies. Measurements were completed during normal tidal breathing through a mouth piece with a minimum of three reproducible efforts performed for each subject. Efforts were averaged and compared with published values, presented as percent of predicted.[20]

Spirometry was performed, including forced vital capacity (FVC), forced expiration volume at 1 second (FEV_1), FEV_1/FVC, mid expiratory $flows_{(25–75\%)}$, and peak flow rates, determined as percentage of predicted levels for gender/age. Children with $FEV_1 < 80\%$ were restudied after inhaled bronchodilator (albuterol 90 mcg/puff, 4 puffs). Children with reactive bronchospasm were referred for treatment. All other children proceeded to exercise testing.

Children were exercised to volitional fatigue using a maximal ramped treadmill running protocol. Breath-by-breath oxygen consumption was measured using an open-circuit technique with a ParvoMedics TrueOne Metabolic Cart. Subjects were fitted with a two-way nonrebreathing valve attached to an appropriately sized oronasal mask. Oxygen consumption (VO_2), minute ventilation (V_E), tidal volume (V_t), respiratory exchange ratio (RER), oxygen pulse, and ventilatory anaerobic threshold (VAT) were measured. Blood pressure, oxygen saturation, and 12-lead electrocardiogram (ECG) were obtained at rest. Blood pressure and oxygen saturation were obtained periodically during exercise and in recovery. The ECG was continuously monitored throughout the exercise test and for 10 minutes following exercise test termination. Maximal exercise was defined as obtaining near-maximal heart rates, a plateau in oxygen consumption, reaching an RER of $\geq$ 1.1, or request to terminate testing due to volitional fatigue.

Statistical Analysis

Investigators performing follow-up studies were not aware of neonatal iNO exposure status of the children. Following completion of testing, blinding was removed and children were assigned to the appropriate groups for analysis. Pulmonary function, FeNO measurements, VO_2, and exercise testing parameters were compared between children treated with iNO and those with placebo in the neonatal period. Secondary analysis was performed to evaluate the independent effects of time of entry in the neonatal study (7–14 and 15–21 days of life), ethnicity, and sex.

Power analysis was performed using FEV_1 as the primary outcome variable, based on data from a previous study of extreme preterm pulmonary outcomes.[11] With a sample size of 12 in each group, we would have 80% power to detect a difference in FEV_1 between group means of 72 and 89, assuming a common standard deviation of 14 and using a two-group *t*-test with two-sided significance level of 0.05.

Data analysis was conducted using Statistical Package for the Social Sciences (release 23, Chicago, IL). Depending on the normality of the data, group differences in continuous variables were assessed with two-sample *t*-tests and one-way analysis of variance or Mann–Whitney *U* and Kruskal–Wallis tests. Group differences in categorical variables were

analyzed using chi-square or Fisher's exact tests. All analyses used a two-sided significance level of 0.05.

Results

This study included 34 of 54 surviving children who were enrolled in the neonatal NO CLD trial (►**Fig. 1**). There were no significant demographic differences, including sex, race, BW, or GA, or differences in prevalence of neonatal complications between participants and those not included in this study (data not shown). ►**Table 1** displays demographic and clinical variables for those enrolled in the follow-up study, comparing groups by neonatal iNO and placebo exposure. There were no group differences in demographics or age at treatment. However, the iNO group tended to have less days on mechanical ventilation, less days of supplemental oxygen exposure, and were less likely to be diagnosed with BPD. On average, children were evaluated at 9.5 ± 1.5 years of age. Some testing was not able to be completed because of insufficient cooperation or physical limitations. All 34 children completed the iOS pulmonary testing, 32 completed the spirometry, 29 performed maximal exercise testing, and 27 had FeNO measurements.

Pulmonary function results from spirometry are displayed in ►**Table 2**. There were no significant group differences in any measures. Overall, 41% (13/32) had a low FEV_1 (< 80% predicted), 47% of placebo and 35% of iNO treated. iOS findings were also not different between groups (►**Table 3**).

Six children in the iNO group and 7 children in the placebo group received inhaled albuterol because of FEV_1 < 80%.

Table 1 Study sample demographics and neonatal clinical descriptors

	NO $N = 18$	Placebo $N = 16$	*p*-Value
Male gender	8 (44%)	11 (69%)	0.15
Race			0.07
White	9 (50%)	4 (25%)	
Black	9 (50%)	7 (44%)	
Other	0	5 (31%)	
Age at evaluation (y)	9.1 ± 1.5	9.9 ± 1.4	0.13
Weight (kg)	37.9 ± 14.4	36.1 ± 11.8	0.70
Height (cm)	137.5 ± 11.9	139.1 ± 10.8	0.69
BW (g)	766 ± 179	731 ± 145	0.54
GA (wk)	25.6 ± 1.5	25.3 ± 1.5	0.56
Maternal age	26.9 ± 7.2	28.3 ± 7.0	0.63
CS delivery	7 (39%)	9 (56%)	0.31
Days on ventilator	30 ± 16	42 ± 21	0.07
Days on supplement O_2	77 ± 25	90 ± 38	0.17
BPD (O_2 at 36 wk GA)	8 (44%)	12 (75%)	0.07
Discharged on O_2	8 (44%)	10 (63%)	0.29

Abbreviations: BPD, bronchopulmonary dysplasia; BW, birth weight; CS, caesarean section; GA, gestational age; NO, nitric oxide.

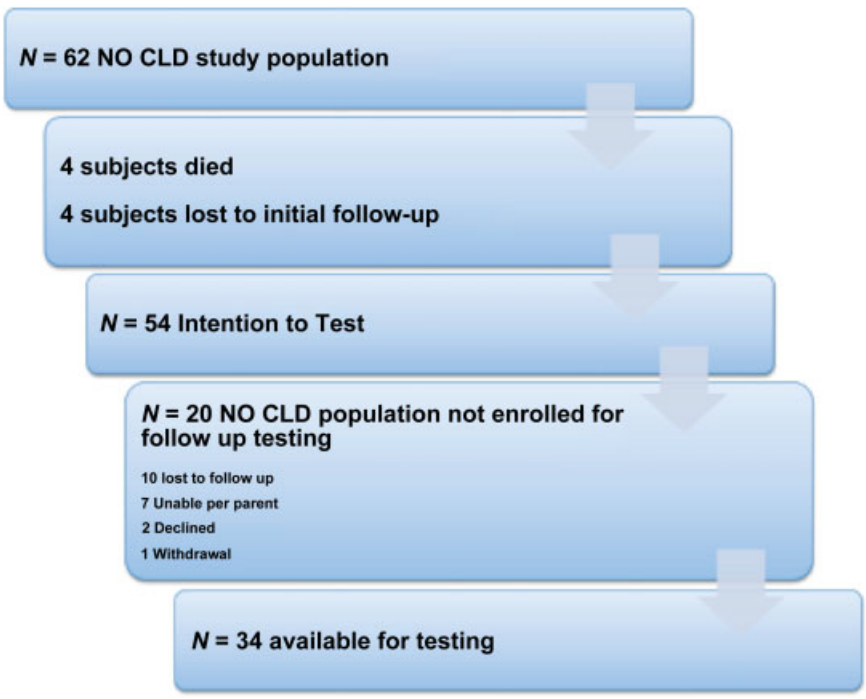

Fig. 1 Patient population.

Table 2 Spirometry results for iNO and placebo groups[a]

	NO $N = 17$	Placebo $N = 15$	*p*-Value
FVC	86 ± 15	92 ± 17	0.31
FEV_1	82 ± 14	83 ± 17	0.88
FEV_1/FVC	98 ± 14	95 ± 7	0.40
PEFR	82 ± 19	77 ± 21	0.69
$FEF_{25-75\%}$	69 ± 18	65 ± 20	0.52
Low FEV_1 (< 80%)	6 (35)	7 (47)	0.51

Abbreviations: $FEF_{25-75\%}$,forced midexpiratory flow rate; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; iNO, inhaled nitric oxide; NO, nitric oxide; PEFR, peak expiratory flow rate; SD, standard deviation.
[a]Values are expressed as mean ± SD and are percent predicted, adjusted for height, age, and sex.

None of the iNO-treated children responded and 2 of the placebo group had an increase in FEV_1 to > 80% (90 and 97%). By history, 6 children in each group had previous treatment for asthma. There was no statistical difference in environmental tobacco smoke exposure. Ten of 18 (56%) in the iNO group and 4/16 (25%) in the placebo group lived in a home with a smoker, $p = 0.092$.

Exercise testing data are shown in ►**Table 4**. There were no differences in peak exercise measures, VO_2, VAT, oxygen pulse, V_E, or exercise times between groups. There was no difference in resting heart rate, but the maximal heart rate was higher in the iNO group.

FeNO levels showed large interpatient variability with a trend toward lower levels for children with neonatal iNO treatment. The mean FeNO level for the iNO treated was 19.5 ± 10.3 (range: 10–49) ppb and 31.8 ± 18.6 (range: 10–69) ppb for those in the placebo group ($p = 0.056$). One of 15 (7%) children in the iNO treatment group and 5/12 (42%) in the placebo group had an elevated FeNO level at clinical threshold of > 35 ppb, $p = 0.06$.

Table 3 Impulse oscillometry results for iNO and placebo-treated groups[a]

	NO $N = 18$	Placebo $N = 16$	*p*-Value
Rrs at 5 Hz[a]	112 ± 32	104 ± 32	0.47
Z score R_{rs5}	0.013 ± 0.95	−0.10 ± 1.39	0.80
Rrs at 10 Hz[a]	95 ± 20	91 ± 20	0.59
Z score R_{rs10}	−0.53 ± 0.78	−0.51 ± 1.04	0.95
Rrs at 20 Hz[a]	86 ± 20	83 ± 23	0.67
Z score R_{rs20}	−0.91 ± 0.72	−0.69 ± 1.1	0.53
Xrs at 5 Hz[a]	104 ± 54	79 ± 68	0.25
Z score X_{rs5}	0.99 ± 1.56	0.76 ± 1.50	0.69
AX resonant frequency ($cm/H_2O/L$)	31.9 ± 21.0	22.4 ± 9.0	0.11

Abbreviations: AX, area of reactance; iNO, inhaled nitric oxide; NO, nitric oxide; Rrs, respiratory system resistance; SD, standard deviation; Xrs, respiratory system reactance.
[a]Values are expressed as mean ± SD and are percent predicted, adjusted for height, age, and sex.

Table 4 Exercise data for iNO and placebo-treated groups

	NO $N = 17$	Placebo $N = 12$	*p*-Value
Maximal VO_2 (mL/kg/min)	29.4 ± 6.4	32.2 ± 7.0	0.28
VAT (mL/kg/min) ($\%VO_2$ max)	18.89 ± 6.38 (65.6)	21.03 ± 6.95 (67.6)	0.418
RER at maximal exercise (VCO_2/VO_2)	1.15 ± 0.12	1.14 ± 0.08	0.93
Peak exercise V_E (L/min)	38.8 ± 15.0	40.9 ± 17.7	0.74
Peak exercise V_t/kg (mL/kg)	22.2 ± 4.6	22.2 ± 4.7	0.76
Oxygen pulse (mL/beat)	6.0 ± 1.8	7.1 ± 3.0	0.21
Total exercise time (min)	6.5 ± 1.1	7.1 ± 1.1	0.14
Resting HR (bpm)	79 ± 14	75 ± 13	0.51
Maximal HR (bpm)	188 ± 14	176 ± 15	0.049
Resting BP-systolic (mm Hg)	99 ± 7	102 ± 8	0.27
Resting BP-diastolic (mm Hg)	53 ± 3.8	54 ± 2.5	0.74
Maximal BP-systolic (mm Hg)	136 ± 11	132 ± 11	0.70
Maximal BP-diastolic	54 ± 2	54 ± 4	0.88
Oxygen saturation at maximal exercise (%)	97.4 ± 0.86	97.3 ± 1.1	0.14

Abbreviations: BP, blood pressure; bpm, beats per minute; HR, heart rate; RER, respiratory exchange ratio; V_E, minute ventilation; VAT, ventilatory anaerobic threshold; VCO_2; volume of carbon dioxide; VO_2, oxygen consumption; V_t, tidal volume.

There were no statistically significant sex or race effects on primary outcome measures. Children in the early study entry group (7–14 days) who had received iNO treatment had borderline higher mean FEV_1/FVC percentage, 104 ± 9.3 versus 90.8 ± 10.5, $p = 0.046$ (95% confidence interval [CI], 0.303, 32.35). There was also a trend for higher $FEF_{25-75\%}$ percentage for the early entry iNO children, 77.5 ± 20.9 versus 56.2 ± 33.1, $p = 0.052$ (95% CI, −0.235, 56.68).

Discussion

This single-center study provided follow-up evaluation for children who had been enrolled in the neonatal NO CLD investigation to assess if better pulmonary outcomes for iNO-treated children persisted to school age. Consistent with the findings from that multi-institutional study which showed less BPD for those in the treatment group, the iNO treated in our study cohort tended to have shorter duration of neonatal ventilation and less BPD. However, at school age evaluation, this study did not find significant differences in pulmonary function or exercise testing for the children who had received neonatal iNO treatment compared with placebo.

In post hoc analysis of the NO CLD study, there had been statistically significant interactions between age at study entry and ethnicity on treatment effect.[8,21] In that study, the benefit of survival without chronic lung disease was seen in the group treated at 7 to 14 days. Therefore, we performed secondary subgroup analyses to assess the effects of those variables on cardiopulmonary outcomes at school age. In our sample, there were no apparent racial differences. Within the cohort of children who had received early neonatal treatment (7–14 days), two pulmonary function results (FEV_1/FVC and $FEF_{25-75\%}$) tended to be higher in the iNO treated compared with placebo. These are marginal findings in a small number of study subjects and may reflect chance variation. Much larger studies would be needed to confirm a possible impact of early iNO treatment on long-term pulmonary outcomes.

Overall, the spirometry measurement for subjects in this study tended to be lower than other reports of pulmonary outcomes in preterm infants. Forty-one percent of the FEV_1 measurements were less than 80% of predicted values. Mean $FEV_{25-75\%}$ was only 67% of predicted. We previously had evaluated pulmonary outcomes in preterm infants of lower BW ($<$ 801 g) at 9 to 15 years of age. In that study, mean FEV_1 was 85% and mean $FEF_{25-75\%}$ was 84% overall, and for those with BPD, the means were 72 and 67%, respectively.[11] Recent data from Doyle et al may provide a more appropriate comparison.[22] In that study, former $<$ 28-week GA preterm children born in 2005 and evaluated at 8 years of age had a mean FEV_1 of 85.4% of predicted value and $FEF_{25-75\%}$ of 72.3%. These findings are still somewhat higher than those of this follow-up cohort, but the infants enrolled in the NO CLD study were uniquely at high risk, since to be enrolled in the study, mechanical ventilation was required at or beyond 7 days of neonatal hospitalization. Our findings are in line with other studies of childhood outcomes of BPD which show expiratory flows continue to be low compared with expected values for age and sex. There is concern that persistence of these findings may portend development of chronic obstructive lung disease with pulmonary limitations in adulthood.[23] Although our exercise data showed no difference between groups, overall the maximum VO_2 and VAT measurements were also lower than would be expected for healthy individuals born at term gestation. Reduced exercise capacity has been reported for children who had BPD and others born extremely preterm.[11,24] Limited cardiopulmonary function for children with BPD also has implications for adult quality of life.[25] Continued investigation of treatments to ameliorate or prevent BPD and ongoing childhood pulmonary morbidity remains critically important.

The mean FeNO measurements in children in this study were higher than those reported by Baraldi et al for former preterm children with (7. 7 $\pm$ 1.1) or without BPD (9.9 $\pm$ 1.1 ppb).[16] Elevated levels have been associated with wheezing in young infants,[26] but they are generally reported to be low in BPD infants, even in those that wheeze.[15] There was a wide range of FeNO levels in our study children and the possible group difference could have resulted from the unexpectedly high levels of FeNO in some children in the placebo group. FeNO has been used as a quantitative measure of airway inflammation in asthmatics. Levels greater than 35 ppb indicate eosinophilic airway inflammation and levels less than 20 ppb suggest children are unlikely to be corticosteroid responsive.[27] Over 40% of the placebo group had FeNO levels exceeding 35 ppb. We did not explore detailed family history of atopy. None of the children had recent history of asthma and none was wheezing at the time of evaluation, although 6 children in each group did have history of prior medical treatment for asthma. As part of our study protocol, children with FEV_1 $<$ 80% were provided with inhaled albuterol and restudied. Two children in the placebo group responded with improved FEV_1, suggesting reactive airway constriction in at least two children. It is possible that in our study sample, there may have been a disproportionate number in the placebo group with underlying pulmonary disorders and/or atopy.

Our findings are limited by the small sample size. We only included children enrolled in this RCT at one institution and were only able to test 63% of surviving patients from that sample. There were no apparent demographic differences between those included and those not included in the study. However, it is possible that those who were not tested had greater medical or developmental complications than study subjects, since we did not evaluate children whose parents indicated they would not likely be able to perform the testing.

In summary, we found no evidence of improved pulmonary or exercise outcomes in childhood following prolonged neonatal iNO treatment. The possible trend toward lower FeNO levels for those who had received neonatal iNO suggests need for further study with a larger sample for confirmation and clinical correlations.

Conflict of Interest
None.

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