

Respiratory Function During Infancy in Survivors of the INNOVO Trial

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Summary. Rationale: Despite encouraging reports suggesting that inhaled nitric oxide (iNO) appear to improve outcome in hypoxemic term and near term infants by improving oxygenation and reducing need for ECMO, the long-term benefits of iNO remain unclear. This study aimed to compare lung function at approximately 1 year in infants who were and were not randomly allocated to iNO as part of their neonatal management for severe respiratory failure at birth. Furthermore, results were compared to lung function of healthy infants. Methods: Maximal expiratory flow at functional residual capacity (V'_{maxFRC}) was measured at approximately 1 year of age (corrected for any prematurity) in survivors of the INNOVO trial. Results were expressed as Z-scores, adjusted for sex and body size, based on data from healthy controls using identical techniques. Results: Technically satisfactory results were obtained in 30 infants (53% < 34 weeks gestation), 19 of whom were randomized to receive iNO V'_{maxFRC} . Z-score was significantly reduced in infants with prior respiratory failure, whether or not they had been allocated to iNO (mean (SD) Z-score: -2.0 (1.2) and -2.6 (1.1), respectively, 95% CI difference; iNO vs. no iNO: -0.3 ; 1.6, $P=0.2$). There was significant respiratory morbidity in both groups during the first year of life. Conclusions: These results suggest that airway function remains reduced at 1 year of age following severe respiratory failure at birth, whether or not iNO is administered. **Pediatr Pulmonol.** © 2009 Wiley-Liss, Inc.

Key words: infant; respiratory function tests; randomized controlled trial; inhaled nitric oxide; follow-up study.

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INTRODUCTION

Severe but potentially reversible respiratory problems are major causes of death and morbidity among newborn infants. An important aspect of the respiratory pathophysiology in both preterm and term babies is persistence of pulmonary vasoconstriction and high pulmonary vascular resistance, resulting from hypoxia and failure of normal lung expansion.

During recent years, inhaled nitric oxide (iNO) has been increasingly used as part of the management of babies with severe respiratory failure at birth.^{1–3} Exogenous NO improves matching of ventilation and perfusion by enhancing perfusion of well ventilated areas of the lungs. Although there has been concern about potential toxicity,⁴ some studies have reported anti-inflammatory properties and other protective effects on the lung.⁵ In animal models, iNO improves both gas exchange and lung structural development.^{6–8}

A recent Cochrane review concluded that iNO appears to improve outcome in hypoxemic term and near term infants by improving oxygenation and reducing need for ECMO, but without any accompanying reduction in mortality.⁹ Despite some encouraging reports,^{10–14} the benefits of iNO in sick preterm infants remain more controversial and appear to be dependent on disease severity, timing of treatment, and underlying pathophysiology.^{14–18} Indeed, the recent Cochrane review concluded that current evidence does not support the use of iNO in preterm infants with hypoxic respiratory failure and that further trials are necessary.¹⁹

Despite growing awareness of the potential long term effects of insults to the developing lung during both prenatal and early postnatal life,^{20–25} and evidence of ongoing respiratory morbidity among infants treated with iNO for severe respiratory failure at birth,^{26–28} most follow-up has concentrated on neurodevelopment.^{13,29} Of the two studies that have reported respiratory function at follow-up in this population, one found no differences in those requiring iNO for PPHN when compared with healthy controls,³⁰ whereas the other reported a significant reduction in airway function at approximately 1 year of age.³ Neither of these studies included a comparator group of infants with severe respiratory failure randomized not to receive iNO.

The UK INNOVO trial was designed to assess both the clinical and cost effectiveness of a policy of adding or not adding iNO to the ventilator gases of eligible preterm and term infants with severe respiratory failure.^{31,32} This manuscript focuses on the respiratory outcomes of the INNOVO trial to 1 year of age. We hypothesized that airway function would be reduced at 1 year of age in survivors of severe respiratory failure when compared with healthy term infants, and that airway function would be reduced in those who were not

allocated to receive iNO when compared with those who were.

AIMS

The study aimed to compare lung function at 1 year, corrected for any prematurity, in infants recruited to the INNOVO trial, who were randomly allocated to having iNO or no iNO added to the ventilator gases during the neonatal period, and to assess the magnitude of any impairment in respiratory function at 1 year in both groups when compared with healthy infants.

MATERIALS AND METHODS

Subjects

Entry criteria for the main INNOVO trial have been described previously.^{31,32} In brief, infants from 15 neonatal units in the United Kingdom, Republic of Ireland, Finland, and Belgium were eligible for recruitment if they were <28 days old, with severe respiratory failure (mainly due to acute and chronic respiratory distress syndrome associated with preterm birth, persistent pulmonary hypertension of the newborn (PPHN) and congenital diaphragmatic hernia) requiring ventilatory support, and if the responsible clinician was uncertain about whether they might benefit from iNO.

Following recruitment, infants were stratified according to whether they were born less than or ≥ 34 weeks gestational age, and were then randomized to have or not have iNO added to the ventilator gases. The study was not blinded to clinical staff, but investigators undertaking respiratory follow up were masked to allocation until data collection and analyses were complete.

Attempts were made to follow up all survivors, who underwent a pediatric assessment at their local hospitals at 1 year of age, corrected for any prematurity. All infants recruited into the INNOVO trial were eligible for respiratory function tests, provided they lived within the British Isles and were deemed fit enough to travel to the test centers and be sedated for the tests.

Study Protocol

Respiratory function tests were undertaken at one of two specialized infant lung function laboratories (UCL Institute of Child Health (ICH), London, or Leicester Royal Infirmary, UK), which used similar equipment and methodology.^{25,33} Families who fulfilled the inclusion criteria were contacted by the INNOVO data co-ordinating center to ascertain willingness to participate. Appointments were deferred for at least 3 weeks following any respiratory tract illness. Medication including bronchodilators, sodium cromoglycate, and inhaled steroids were stopped for at least 8 hr prior to tests provided this did not compromise the infant's well being.

When attending for lung function tests, parents were asked to conceal to which limb of the trial their infants belonged. Details of respiratory symptoms and morbidity since discharge from the neonatal unit were collected from parents, and current medication recorded. Infants were sedated with oral chloral hydrate (50–100 mg/kg) and measurements of maximal expiratory flow at functional residual capacity ($V'_{\max\text{FRC}}$) were made using the rapid thoraco-abdominal compression (RTC) technique, according to international guidelines³⁴ and following a standardized protocol described previously.^{25,35} Measures of forced flows and volumes reflect an integrated output of lung and airway mechanics and as such cannot be used to locate airway obstruction at any particular airway generation or anatomic location. Nevertheless, because $V'_{\max\text{FRC}}$ is measured at low lung volumes, it is thought to reflect primarily airway caliber upstream (i.e., distal) to the airway segment subjected to flow limitation.³⁶ This makes it a useful measure of intrathoracic airway function in infants, in whom nasal resistance comprises a large proportion of total resistance. All measurements were performed during consecutive periods of behaviorally determined quiet sleep with the infant supine and breathing regularly. Both test centers maintained a standard approach to data collection and analysis, and the agreement for $V'_{\max\text{FRC}}$ between the two centers was within 10%.³³

The study was approved by the Ethics Committees of the participating centers, and informed written consent obtained from parents.

Sample Size and Data Analysis

The potential number of infants who could be recruited to this study was dependent on the number of survivors from the INNOVO trial, and on the proportion eligible for respiratory function tests at 1 year. With 16 infants per group, who were and were not allocated to iNO, there would be approximately 80% power at the 5% significance level to detect a difference in $V'_{\max\text{FRC}}$ of 1.0 Z-score between the groups.

Values of $V'_{\max\text{FRC}}$ were expressed as Z-scores, to adjust for sex and body size. The latter were derived from prediction equations from 459 healthy infants, including many studied at ICH using identical equipment and techniques.³⁷ Comparisons between groups were made using unpaired *t*-tests with 95% confidence intervals (CI) or ANOVA (SPSS for Windows, v.15, Chicago, IL).

RESULTS

Of the 168 babies (108 preterm) recruited into the INNOVO trial, 90 (54%) were discharged alive. Eighty-nine infants survived to 1 year: 60 of these subjects were potentially eligible for recruitment to the respiratory follow-up, of whom 33 attended for lung function

measurements (55%) (see Fig. 1 for details). Parental consent was obtained in 62% of eligible infants but four of who had to be excluded due to repeated respiratory infections. Technically acceptable results were obtained in 30 infants (50% born <34 weeks gestational age), 13 of whom were studied at the ICH and 17 at Leicester Royal Infirmary. As expected, primary diagnosis varied according to gestational age; 86% of those recruited <34 weeks having the acute or chronic respiratory distress syndrome, although respiratory failure in the majority of those >34 weeks was attributed to either secondary (60%) or primary (20%) PPHN. There were no significant differences in background characteristics, including primary diagnosis and duration of neonatal ventilatory support between infants who did or did not undergo respiratory function tests (data not shown). Approximately one-third of all survivors had wheezed at least once in the 3 months prior to the 1-year pediatric check up and had been prescribed medication other than antibiotics (generally bronchodilators or inhaled corticosteroids) for respiratory illnesses since discharge,³¹ this proportion being similar in those with and without lung function measurements. Although, as expected, those <34 weeks had significantly longer ventilatory support and supplementary oxygen than the more mature infants (average of 12 days vs. 6 days and 71 days vs. 12 days of oxygen, respectively), the prevalence of respiratory illness and need for medication during the first year of life was similar between these two gestation groups, and results have been combined when comparing effects of iNO on subsequent lung function.

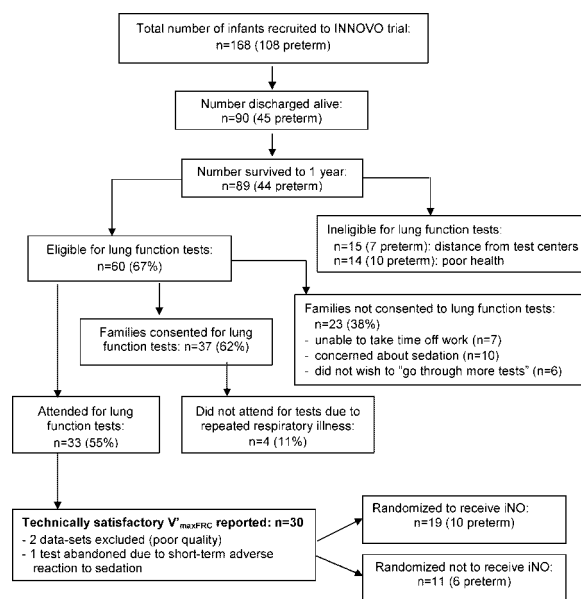


Fig. 1. Flow diagram illustrating eligible infants from the INNOVO trial who attended respiratory function follow-up at 1 year. The term “preterm” refers to infants born <34 weeks gestation. $V'_{\max\text{FRC}}$: Maximal expired flow at functional residual capacity.

TABLE 1—Infant Details During the Neonatal Period According to Randomization to Inhaled Nitric Oxide

| | Randomized to receive iNO (n = 19) | Randomized to receive no iNO (n = 11) | Mean difference (95% CI) iNO–No iNO | P-value |
|--|---------------------------------------|--|---|---------|
| Boys, n (%) | 10 (53%) | 5 (45%) | 7% (–13%; 27%) | 0.7 |
| Gestation, weeks | 33.0 (6.0) | 33.4 (6.8) | –0.4 (–5.5; 4.8) | 0.7 |
| Birth weight, g | 2,188 (1,338) | 1,908 (1,227) | 280 (–716; 1,276) | 0.7 |
| Birth weight Z-score [¶] | –0.04 (0.9) | –1.0 (1.4) | 1.0 (–0.03; 1.9) | 0.04 |
| Maternal smoking during pregnancy, n (%) | 3 (16%) | 1 (9%) | 7% (–17%; 30%) | 0.6 |
| Primary diagnosis, n (%) | | | | |
| Respiratory distress syndrome | 8 (42%) | 4 (36%) | 6% (–28%; 36%) | 0.8 |
| Chronic lung disease | 1 (5%) | 1 (9%) | –4% (–33%; 17%) | 0.7 |
| Primary PPHN | 2 (11%) | 0 | 11% (–16%; 31%) | 0.1 |
| Secondary PPHN | 5 (26%) | 3 (27%) | –1% (–34%; 28%) | 1.0 |
| Other diagnoses | 3 (16%) | 3 (27%) | –11% (–43%; 16%) | 0.5 |
| Oxygen index at entry [#] | 34 (19–48) | 25 (19–42) | 6.3 (–8.2; 20.9) | 0.4 |
| Days on supplemental oxygen [#] | 21 (7–65) ¹ | 21 (9–85) ² | –8.1 (–45.9; 29.6) | 0.6 |
| Days in hospital [#] | 41 (17–84) | 42 (21–106) | –9.0 (–45.3; 27.3) | 0.6 |
| Assisted ventilation, days [#] | 7 (3–14) | 8 (4–12) | –3.5 (–14.4; 7.5) | 0.5 |

Unless expressed as n (%), data are shown as mean (SD) or [#] median (IQR). [¶] Birth weight Z-score calculated according to Freeman et al.⁴⁵

PPHN, persistent pulmonary hypertension of the newborn.

¹n = 16.

²n = 10.

Details of infants in whom respiratory function was measured are summarized in Table 1. Data have been analyzed by intention to treat. Two infants were crossed over; one was allocated to iNO therapy but did not receive it, although another who was randomized to ‘no iNO’ received it. With the exception of birth weight Z-score, which was higher in infants allocated to iNO, background characteristics of the two groups were similar.

At time of lung function test, the two groups were well matched for age and body size (Table 2). Once corrected for body size and sex, there was no difference in ($V'_{\max\text{FRC}}$) between infants who had or had not been allocated to iNO (–2.0 and –2.6 Z-scores respectively, 95% CI of difference: –0.3; 1.6; Table 2 and Fig. 2), though values were significantly lower than predicted when compared to reference values obtained from healthy infants, in whom

expected values fall between ± 2 Z-scores with an average of zero.³⁷ Although values were slightly lower among those <34 weeks when compared to more mature infants (–2.3 vs. –2.1 Z-scores, respectively), these differences were not significant (95% CI of difference: <34 weeks vs. >34 weeks: –1.1; 0.7 Z-scores, $P = 0.6$).

There was a high prevalence of respiratory illness and hospital admissions during the first year of life among those who attended for respiratory follow-up; with 63% of those <34 weeks and 73% more mature infants having had at least one hospital admission for respiratory illness. There was no difference in the prevalence of respiratory morbidity between those who had and had not been allocated to iNO; approximately 60% in each group having had a wheezing illness at some time since discharge with approximately 20% being on respiratory

TABLE 2—Infant Details and Lung Function at Time of Test According to Randomization to Inhaled Nitric Oxide

| | Randomized to receive iNO (n = 19) | Randomized to receive no iNO (n = 11) | Mean difference (95% CI) iNO–No iNO | P-value |
|--|---------------------------------------|--|---|---------|
| Test age, months (corrected for any prematurity) | 14.4 (1.8) | 14.1 (3.6) | 0.2 (–2.3; 2.8) | 0.8 |
| Test weight, kg | 9.8 (2.0) | 9.1 (1.4) | 0.7 (–0.5; 2.0) | 0.3 |
| Test weight Z-score [¶] | –0.7 (1.8) | –1.1 (1.6) | 0.5 (–0.9; 1.7) | 0.5 |
| Test length, cm | 78.6 (5.2) | 75.4 (4.7) | 3.2 (–0.7; 7.0) | 0.1 |
| Test length Z-score [¶] | 0.4 (1.5) | –0.5 (1.3) | 0.9 (–0.1; 2.0) | 0.1 |
| $V'_{\max\text{FRC}}$ Z-score | –2.0 (1.2) | –2.6 (1.1) | 0.6 (–0.3; 1.6) | 0.2 |
| Hospital respiratory admissions since discharge, n (%) | 12 (63%) | 9 (82%) | –19% (–50%; 13%) | 0.3 |
| Wheezing since discharge, n (%) | 11 (58%) | 7 (64%) | –6% (–42%; 30%) | 0.8 |
| Respiratory medication since discharge, n (%) | 9 (47%) | 7 (64%) | –17% (–52%; 20%) | 0.4 |
| Respiratory medication at time of test, n (%) | 4 (21%) | 2 (18%) | 3% (–26%; 32%) | 0.9 |
| Maternal smoking at time of test, n (%) | 5 (26%) | 3 (27%) | –1% (–34%; 32%) | 1.0 |

Data are shown as mean (SD) or n (%). [¶] Weight and length Z-scores calculated according to Freeman et al.⁴⁵

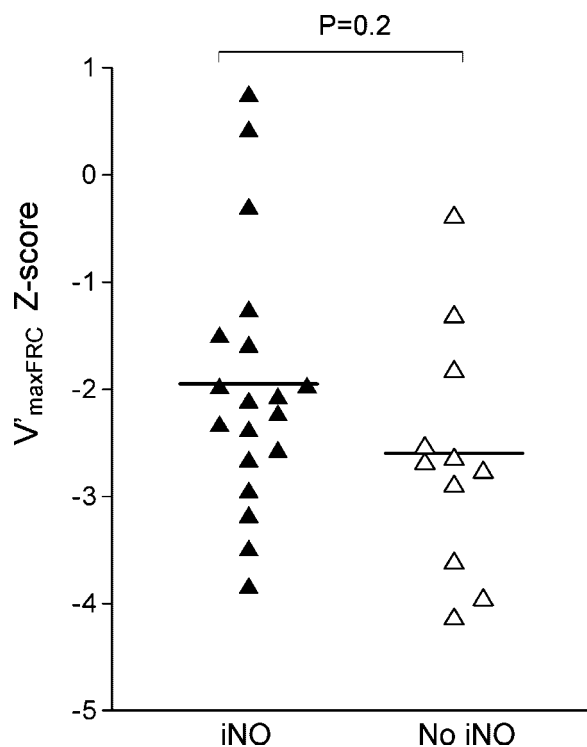


Fig. 2. Comparison of maximal expired flow at FRC in infants who were and were not allocated to inhaled nitric oxide during the neonatal period. Data show individual values of $V'_{\max FRC}$ expressed as Z-scores.³⁷ The horizontal lines indicate the mean $V'_{\max FRC}$ Z-score (-2.0 and -2.6 Z-score, respectively) for each group according to whether or not infants were randomized to receive inhaled nitric oxide.

medication (primarily bronchodilator or corticosteroids) at time of test (Table 2). There were no adverse reactions to withholding respiratory medication for ≥ 8 hr prior to the lung function measurements.

DISCUSSION

Results from this study highlight the considerable respiratory morbidity that may occur, even in relatively mature (i.e., ≥ 34 weeks gestation) infants, following severe respiratory failure at birth and the accompanying reductions in airway function that persist to at least 1 year of age. Given the relatively small sample size, which was constrained both by numbers who could be recruited to the INNOVO trial^{31,32} and by those excluded from respiratory tests due to continuing poor health, comparison of results between those who were and were not allocated to iNO requires caution. Nevertheless, there is clear evidence of a significant reduction in respiratory function at 1 year of age, irrespective of treatment group.

Strengths and Limitations of Study

In addition to being one of the few studies to assess respiratory function after treatment with iNO in the

neonatal period, and the only one to our knowledge that has been based on a randomized controlled trial, an additional strength of this study is that investigators were blinded to treatment allocation. With the exception of the need to exclude the sickest babies, such that the reported reduction in airway function may be an underestimation of that within the entire group, there did not appear to be any bias in those who did and did not attend for respiratory follow-up, or between the allocation groups. The greatest weakness is the relatively small sample size, which was dictated by circumstances beyond our control, including relatively low recruitment into the main trial.^{31,32} Ideally, we would like to have recruited at least 32 infants, with equal numbers in each arm of the trial in order to have adequate power to detect a difference of 1 Z-score between groups. In reality, we obtained successful measurements in 30 infants, split as 19 randomized to iNO and 11 to no iNO (i.e., a ratio of 1.7:1.0). After taking the unequal subgroup sample sizes into account, the study population was equivalent to studying a total sample of 26 subjects with 13 per group.³⁸ This would provide 80% power at the 5% significance level to detect a slightly larger difference in $V'_{\max FRC}$ of 1.1 Z-scores between the subgroups. Given that $V'_{\max FRC}$ was substantially reduced in both groups, the difference of 0.6 Z-score that was actually observed between those who did and did not receive iNO (Table 2), is unlikely to be of any clinical significance. Retrospective power calculations showed that a total sample size of 88 (44 infants per group) would have been required to achieve 80% power to detect a difference of 0.6 Z-score.

Comparison With Literature

Lung Function Following Neonatal Respiratory Failure

There have been relatively few respiratory follow-ups of infants treated with iNO at birth. Dobyns et al.³⁰ measured lung volume and passive respiratory mechanics, 4–12 months after discharge from the neonatal unit, in infants treated for severe PPHN with ($n = 15$) or without ($n = 7$) iNO, and in 18 healthy infants. No differences in lung function were found either between the treatment groups or in comparison to controls. The authors concluded that iNO therapy for the treatment of severe PPHN did not alter lung function during early infancy, but airway function was not assessed.

The reduction in $V'_{\max FRC}$ observed in the current study is of similar magnitude to that observed at 1 year of age in infants treated with iNO by Hoskote et al.,³ in survivors of the ECMO trial²⁵ and in a study of over 100 infants receiving ECMO outside the context of a trial,³⁹ suggesting that even in the absence of respiratory symptoms and irrespective of mode of treatment, ongoing subclinical changes in airway function occur following neonatal lung disease. Diminished lung function

during infancy has been shown to persist to school age,⁴⁰ suggesting that such insults may have a prolonged impact on respiratory health. Despite the recognized risk factors associated with preterm birth,^{21,41} the reduction of $V'_{\max\text{FRC}}$ was similar in the preterm and more mature survivors of the INNOVO trial. This may reflect a selection bias in that many of the most severely affected preterm infants in the INNOVO trial died and, of those who survived, only the fittest could attend for lung function tests, exclusions due to poor health being more frequent than in those born <34 weeks gestation (Fig. 1).

Respiratory Morbidity

The prevalence of wheezing during the first year of life in survivors of the INNOVO trial was considerably higher than that in healthy infants, which is commonly reported to be approximately 30%.^{42,43} In keeping with previous reports,²⁷ a large proportion of these infants also required re-hospitalization for respiratory problems. These findings are, however, in contrast to our recent findings in a group of term infants treated with iNO for PPHN in whom, despite similar reductions in $V'_{\max\text{FRC}}$ at 1 year, respiratory morbidity was low.³ This may partially reflect differences in criteria for recruitment in the two studies, including the fact that children whom the clinician felt would clearly benefit from iNO (i.e., term infants with a primary diagnosis of PPHN) were rarely recruited to INNOVO.

Follow-up of the INNOVO trial to 4 years of age found no difference in the longer-term outcome between babies who were and were not treated with iNO,⁴⁴ although the authors pointed out that babies treated in the INNOVO trial might have been too sick by time of recruitment and initiation of iNO therapy, thereby limiting the potential for benefits.

CONCLUSIONS

Although the small sample size in this study warrants caution when interpreting results, significant respiratory morbidity and reduced airway function were observed at 1 year of age in both preterm and more mature survivors of the INNOVO trial, irrespective of whether or not iNO had been added to the ventilator gases during treatment for severe neonatal lung disease. Diminished respiratory function during early life is known to track through childhood and those with lower respiratory function tend to retain this position thereafter. Continuing efforts are required to minimize lung injury during the neonatal period in order to maximize lung health in later life, and to monitor the degree of respiratory morbidity and potential loss of lung function in survivors of neonatal lung disease with continuing growth.

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