NONINVASIVE DELIVERY OF INHALED NITRIC OXIDE THERAPY FOR LATE PULMONARY HYPERTENSION IN NEWBORN INFANTS WITH CONGENITAL DIAPHRAGMATIC HERNIA

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Objective To determine the incidence of late pulmonary hypertension (late PH) in congenital diaphragmatic hernia (CDH) and whether prolonged treatment with noninvasive inhaled NO therapy delivered through a nasal cannula (NC) would sustain pulmonary vasodilation during a period of transition from mechanical ventilation to spontaneous breathing.

Study design We collected data on all patients with a diagnosis of CDH admitted to the Children's Hospital, Denver, from January 1996 through December 2001. Patients who had suprasystemic pulmonary hypertension when inhaled NO was discontinued before extubation were treated with inhaled NO delivered with the nasal cannula.

Results Newborn infants (n = 47) with CDH were treated during this time period. Short-term (<3 months) and long-term (>1 year) survival was 85% and 75%, respectively; 30 newborn infants were treated with inhaled NO (64%). Inhaled NO was successfully discontinued in 16 patients before extubation, and 10 (21%) were treated with inhaled NO through NC after extubation because of pulmonary hypertension and marked hypoxemia when trials off inhaled NO were performed. Nasopharyngeal NO concentrations were 5.4 ± 0.5 ppm and 2.4 ± 0.4 ppm with inhaled NO measured proximally in the delivery device at 10 and 5 ppm, respectively.

Conclusions Late PH occurs in a significant subset of newborn infants with CDH. Noninvasive inhaled NO treatment may reduce the duration of mechanical ventilation while safely treating late PH. *(J Pediatr 2003;142:397-401)*

Pulmonary hypertension (PH) contributes to hypoxemia in newborn infants with severe hypoxemic respiratory failure (HRF). New therapies, such as inhaled nitric oxide (inhaled NO), have reduced the need for extracorporeal membrane oxygenation support (ECMO) for many disorders associated with PH in the newborn period. However, congenital diaphragmatic hernia (CDH) remains a challenging clinical problem, with a high treatment failure rate and need for ECMO in the most severe cases. Despite the widespread availability of ECMO, newborn infants with CDH continue to have a relatively high mortality rate, and optimal strategies for the management of CDH remain controversial.[1]

CDH is a complex syndrome that causes severe HRF and is associated with a high mortality rate.[2] CDH is characterized by pulmonary hypoplasia and severe PH with structural and functional pulmonary vascular abnormalities. Although PH complicates the clinical course of newborn infants with CDH, the role of selective pulmonary vasodilation with inhaled NO therapy has not been clearly defined. Despite early reports describing the successful use of inhaled NO in some newborn infants with CDH,[3] a randomized trial of early inhaled NO use in CDH did not show improved survival or decreased ECMO utilization.[4] However, many patients with CDH also have clinically evident protracted or late PH that can lead to prolonged mechanical ventilation, a second course of ECMO, or death.[5-9]

CDH	Congenital diaphragmatic hernia
ECMO	Extracorporeal membrane oxygenation support
HFOV	High-frequency oscillatory ventilation
HRF	Hypoxemic respiratory failure
NC	Nasal cannula
OI	Oxygenation index
PH	Pulmonary hypertension
PVR	Pulmonary vascular resistance

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Late pulmonary hypertension (late PH) in newborn infants with CDH is clinically evident when pulmonary vascular resistance (PVR) becomes suprasystemic with right-to-left venoarterial admixture of blood across the foramen ovale and/or the ductus arteriosus causing hypoxemia. However, suprasystemic levels of PVR may be masked during treatment with ECMO or inhaled NO, and subsystemic levels of PVR can only be determined by direct pulmonary artery measurements or echocardiography. Moreover, some newborn infants with CDH may have persistent pulmonary vascular abnormalities despite marked improvements in respiratory function, necessitating inhaled NO therapy to reduce PVR even when mechanical ventilation is no longer required.

We determined the frequency of late PH and the potential role of noninvasive delivery of inhaled NO. We hypothesized that treatment with inhaled NO through a nasal cannula (NC) would sustain pulmonary vasodilation during a period of transition from mechanical ventilation to spontaneous breathing.

METHODS

To evaluate the incidence of late PH in patients with CDH and the potential role of noninvasive inhaled NO treatment, we collected data on all patients with a diagnosis of CDH and HRF admitted to the Children's Hospital, Denver, from January 1996 through December 2001. All patients were outborn and required transport to the Children's Hospital for therapy. In general, our initial approach to the clinical treatment of newborn infants with severe CDH included the use of serial chest radiographs and echocardiograms upon admission to assess lung inflation, to document the severity of PH and the presence of extrapulmonary shunting, and to help with the assessment of cardiac performance. If the infant had signs of lung underinflation on chest radiography, high-frequency oscillatory ventilation (HFOV) was used to recruit lung volume. If extrapulmonary right-to-left shunting was identified by echocardiography, despite adequate lung inflation, inhaled NO therapy (20 ppm) was initiated as previously described.[10] Early inhaled NO therapy was not used without evidence of bidirectional or right-to-left shunting of blood across the ductus arteriosus and foramen ovale or if there was evidence of severe left ventricular dysfunction by echocardiography.[11] Until December 1999 (after FDA approval), NO therapy was used under an investigator-initiated Investigational New Drug exemption after informed consent was obtained. ECMO was used to treat patients with CDH who had persistent signs of hemodynamic instability despite aggressive ventilator and cardiotonic support.

In all patients, inhaled NO was reduced to 6 ppm within the first 24 hours of treatment. After 96 hours of treatment with inhaled NO, the dose was reduced to 2 to 5 ppm. Attempts to withdraw inhaled NO (2 to 5 ppm) were performed during echocardiography to determine changes in pulmonary artery pressure on discontinuation of inhaled NO. In patients who had hypoxemia requiring increase in Fio_2 >60% and/or marked elevation of PH to systemic or suprasystemic levels of pulmonary artery pressure (as assessed by using the peak velocity of the tricuspid regurgitant jet or direction of shunting), inhaled NO was immediately restarted. If, upon inhaled NO withdrawal, pulmonary artery pressure remained less than two thirds of systemic arterial blood pressure, then inhaled NO was not restarted.

Some patients with CDH had marked elevation of pulmonary artery pressure upon the discontinuation of inhaled NO, despite gas exchange criteria for extubation (Fio_2 <.40 and ventilator rate <15). For this subgroup, the protocol was modified to allow prolonged treatment with inhaled NO after extubation. Patients were extubated to hood oxygen (≤40%), and NO gas was blended with the inspired air/oxygen mixture to provide 5 ppm NO within the hood. Ambient levels of NO and NO_2 were monitored during inhaled NO delivery by using the hood system.

After 12 to 24 hours of treatment with inhaled NO by hood, the inhaled NO delivery system was changed to provide inhaled NO by nasal cannula, as previously described.[12] The nasal cannula system was configured to mix low-flow nitric oxide with a blended source of oxygen at a flow rate of 1 L/min to achieve inhaled NO concentrations of 5 to 10 ppm within the delivery system. Beginning in 1998, the configuration was modified to incorporate the iNOVent delivery device (Datex-Ohmeda, Madison, Wis). We incorporated the iNOVent delivery and sampling devices into the inspiratory side of the system, thus allowing for continuous monitoring of delivered NO concentrations, similar to the conventional mechanical ventilator configuration.

Delivered (ie, posterior-pharyngeal concentrations) and ambient concentrations of NO were monitored with the use of a chemiluminescence analyzer (Model 280 NOA, Sievers Instruments, Boulder, Colo). Actual inspired concentrations of NO (posterior pharyngeal concentrations) were measured in infants in a quiet state, with the use of a pacifier through which an 8-F suction catheter was inserted. This allowed nonnutritive sucking, assuring nasal breathing alone, while the catheter tip was advanced into the posterior pharynx for NO analysis.

Binomial data were analyzed by means of χ^2 or Fisher exact test when appropriate. Comparisons of normally distributed continuous data were analyzed by means of the Student *t* test. Comparisons of continuous data that were not normally distributed were analyzed by means of the Mann-Whitney *U* test. The level of statistical significance was set at $P < .05$. Data are presented as mean ± SD values or percentages.

RESULTS

Forty-seven newborn infants with CDH were treated during this 6-year study period. All infants were term or near-term (39 ± 2 weeks); 17 (36%) were female, 41 (87%) had a left-sided defect, 18 (38%) were diagnosed before delivery, and 18 (43% of patients who survived to operative repair) required a prosthetic patch for closure of the diaphragmatic defect.

Thirty (64%) of the patients were treated with endotracheal inhaled NO; however, 10 (21%) had severe PH at the time of elective extubation and required treatment with inhaled NO by nasal cannula. Eight of the 47 patients with

Table I. Outcome of subset of newborn infants with CDH treated with endotracheal iNO compared with subset not treated with iNO

	iNO-treated (n = 30)	Not treated with iNO (n = 17)
Admission OI	45 ± 44	4.5 ± 2.3
ECMO	8 (27%)	0
Short-term survival (<3 mos)	26 (87%)	15 (88%)
Long-term survival (>1 y)	21 (70%)	14 (82%)
Isolated CDH: long-term survival	25 (83%)	15 (88%)

Data are given as mean ± SD or n (%).

Table II. Ventilator settings and blood gas tensions in patients with CDH treated with endotracheal iNO (2 to 5 ppm) before extubation and treatment with nasal cannula iNO

Age (d)	26 ± 3
FiO_2	0.34 ± 0.02
Ventilator rate (bpm)	12 ± 2
Peak inspiratory pressure (cm/H_2O)	23 ± 1
PEEP (cm/H_2O)	4.9 ± 0.3
Mean airway pressure	7.1 ± 0.3
PH	7.38 ± 0.02
$PaCO_2$ (mm Hg)	43 ± 2
PaO_2 (mm Hg)	62 ± 5
Oxygenation index	4 ± 1

CDH (17%) were treated with ECMO. Nine patients died without ECMO therapy. Five were late deaths (after 3 months of age). Four patients who died within the first week of life were not treated with ECMO because of parental refusal (n = 2) or associated major malformations (transposition of the great vessels [n = 1] and hypoplastic left heart syndrome [n = 1]). Short-term survival (<3 months) was 85%. Five patients died (2 after discharge home) between 3 months and 1 year of age (late deaths), yielding long-term survival of 75%.

Table I shows the outcome of the subset of newborn infants (n = 30) who were treated with endotracheal inhaled NO at any time during the hospital course compared with the subset not treated with inhaled NO (n = 17). Inhaled NO was initiated (median, 2 days of age; range, 1-7 days of age) only if there was echocardiographic evidence of severe PH (estimated pulmonary artery pressure more than two thirds of systemic pressure) with adequate left ventricular performance. Inhaled NO was successfully discontinued in 16 patients before extubation after a median duration of 13.5 days (range, 2-65 days), and 10 (21%) were treated with inhaled NO through a NC

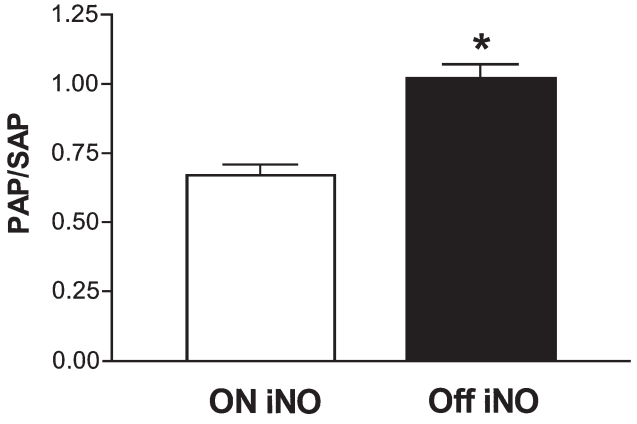

Figure. Ratio of systolic pulmonary arterial pressure (measured by echocardiography)/systolic systemic arterial pressure before extubation. Pulmonary artery pressure was approximately two thirds of systemic artery pressure while on low-dose iNO. During brief trial off iNO, pulmonary artery pressure increased to systemic levels (n = 9, $*P < .05$).

Table III. Patient characteristics and outcome of patients treated with nasal cannula iNO compared with control group of patients with CDH who survived to operative repair

	Control (n = 32)	NC iNO (n = 10)	*P* value
Admission OI	19 ± 20	48 ± 22	< .01
Prosthetic patch	11 (34%)	7 (70%)	NS
Surfactant	9 (28%)	1 (10%)	NS
HFOV	16 (50%)	10 (100%)	< .01
Endotracheal iNO	17 (53%)	10 (100%)	< .01
ECMO	5 (16%)	2 (20%)	NS
Short-term survival (<3 mo)	30 (94%)	10 (100%)	NS
Long-term survival (>1 y)	26 (81%)	9 (90%)	NS
Isolated CDH long-term survival	27 (84%)	9 (100%)	NS

Data are given as mean ± SD or n (%).

after extubation because of PH and marked hypoxemia when trials off inhaled NO were performed.

The Figure shows that the mean baseline pulmonary artery pressure (measured by echocardiography) was approximately two thirds of systemic artery pressure despite treatment with endotracheal inhaled NO. Moreover, a brief "trial-off" inhaled NO caused acute increases in pulmonary artery pressure to near-systemic levels.

As shown in Table II, the severity of underlying PH was disproportionate to the respiratory status of these infants at the time of elective extubation (26 ± 3 days). The mean FiO_2 was 0.34 ± 0.02 and the mean (oxygen index) OI was 4 ± 1. Despite a very low OI, late PH occurred in 10 of 30 patients who required treatment with inhaled NO (33%).

Table III shows a comparison of patient characteristics and outcomes between patients treated with NC-inhaled NO and a control group of patients with CDH who survived to operative repair. Patients who required inhaled NO after extubation were more likely to have more severe early disease (as measured by admission OI, the use of HFOV, and the use of endotracheally inhaled NO).

The median duration of NC-inhaled NO treatment was 17 days (range, 5 to 60 days). NC-inhaled NO was discontinued when echocardiographic evidence of subsystemic pulmonary artery pressure was demonstrated after weekly trials off inhaled NO. Nasopharyngeal NO concentrations were 5.4 ± 0.5 ppm and 2.4 ± 0.4 ppm with inhaled NO measured proximally in the delivery device at 10 and 5 ppm, respectively. Bedside ambient concentrations of NO and NO_2 were routinely monitored and did not change from baseline values during treatment with NO by hood or nasal cannula.

DISCUSSION

Blending low doses of NO gas with oxygen in the inspiratory limb of mechanical ventilators is an effective method for reducing pulmonary vascular resistance and decreasing extrapulmonary right-to-left shunting at the ductus arteriosus and foramen ovale in many patients with PH. However, in some patients with CDH, sustained elevations of PVR may persist despite improvement in the parenchymal lung disease such that mechanical ventilation is not needed for maintaining adequate gas exchange. We found that some patients with CDH had protracted PH despite marked improvement in respiratory support requirements. In this setting, selective pulmonary vasodilation with inhaled NO without mechanical ventilation may provide sustained improvement in oxygenation (by lowering pulmonary vascular resistance and decreasing extrapulmonary right-to-left shunting) without the potential adverse affects of tidal volume ventilation in the hypoplastic lung. In this series, 10 of 47 (21%) newborn infants with CDH had protracted PH; inhaled NO therapy as administered by NC successfully treated PH in each of these patients after discontinuing mechanical ventilation.

The first report of the use of inhaled NO in newborn infants with CDH suggested that early, acute improvement in oxygenation was possible when adequate lung inflation was first achieved.[3] However, the largest randomized, controlled trial of early inhaled NO treatment in patients with CDH found no difference in the combined end point of death/ECMO utilization between NO-treated and control infants.[4] Indeed, in this trial, ECMO utilization was higher in the inhaled-NO–treated group. However, the use of inhaled NO to treat PH after ECMO treatment of CDH is a promising adjuvant therapy.[13] Moreover, the observation that sustained pulmonary vasodilation can be achieved with the use of NC delivery of inhaled NO, as demonstrated in this report, suggests the potential for noninvasive chronic treatment of the most severely affected newborn infants with CDH and PH.

Pulmonary recovery in patients with CDH is typically measured by improvement in oxygenation, based on arterial blood gas measurements. Although sustained PH is a common problem in patients with CDH, systemic hypoxemia only occurs when pulmonary vascular resistance becomes suprasystemic, leading to extrapulmonary right-to-left shunting. Elevation of PVR alone (without extrapulmonary right-to-left shunting) does not cause severe hypoxemia in this setting. Indeed, in our patients who had near-systemic levels of PH despite inhaled NO therapy, inspired oxygen requirements were routinely below an Fio_2 of 0.35.

Recent studies suggest that endogenous vasodilator substances may modulate not only pulmonary vascular tone but also pulmonary vascular medial proliferation. Considering the important role of vascular remodeling in CDH,[14] therapies that may favorably affect the structural basis of PH could have potential advantages beyond pulmonary vasodilation alone.

We conclude that late or protracted PH occurs in a significant subset of newborn infants with CDH. Inhaled NO can be effectively delivered by a NC to newborn infants with CDH who have protracted PH, potentially reducing the duration of mechanical ventilation, while safely treating PH. A dose of 10 ppm measured within the delivery device is sufficient to maintain nasopharyngeal concentrations within a range of 1 to 5 ppm.

REFERENCES

1. Clark RH, Hardin WD, Hirschl RB, Jaksie T, Lally KP, Langham M, et al. Current surgical management of congenital diaphragmatic hernia: a report from the Congenital Diaphragmatic Hernia Study Group. J Pediatr Surg 1998;33:1004-9.

2. Greenholz SK. Congenital diaphragmatic hernia: an overview. Semin Pediatr Surg 1996;5:216-23.

3. Kinsella JP, Neish SR, Ivy DD, Abman SH. Clinical responses to prolonged treatment of persistent pulmonary hypertension of the newborn with low doses of nitric oxide. J Pediatr 1993;123:103-8.

4. Neonatal Inhaled Nitric Oxide Study Group. Inhaled nitric oxide and hypoxic respiratory failure in infants with congenital diaphragmatic respiratory failure. Pediatrics 1997;99:838-45.

5. Thiebeault DW, Haney B. Lung volume, pulmonary vasculature, and factors affecting survival in congenital diaphragmatic hernia. Pediatrics 1998;101:289-95.

6. de la Cruz TV, Stewart DL, Robinson TW, Bond SJ. The use of a second course of extracorporeal membrane oxygenation in neonatal patients. ASAIO J 1996;42:230-2.

7. Lally KP, Breaux CW. A second course of extracorporeal membrane oxygenation in the neonate: is there a benefit? Surgery 1995;117:175-8.

8. Iocono JA, Cilley RE, Mauger DT, Krummel TM, Dillon PW. Postnatal pulmonary hypertension after repair of congenital diaphragmatic hernia: predicting risk and outcome. J Pediatr Surg 1999;34:349-53.

9. Schwartz IP, Bernbaum JC, Rychik J, Grunstein M, D'Agostino J, Polin RA. Pulmonary hypertension in children following extracorporeal membrane oxygenation therapy and repair of congenital diaphragmatic hernia. J Perinatol 1999;19:220-6.

10. Kinsella JP, Truog WE, Walsh WF, Goldberg RN, Bancalari E, Mayock DE, et al. Randomized multicenter trial of inhaled nitric oxide and high frequency oscillatory ventilation in severe persistent pulmonary hypertension. J Pediatr 1997;131:55-62.

11. Kinsella JP, Abman SH. Clinical approach to inhaled nitric oxide therapy in the newborn. J Pediatr 2000;136:717-26.

12. Ivy DD, Wiggins JW, Badesch D, Kinsella JP, Kelminson L, Abman SH. Nitric oxide and prostacyclin treatment of an infant with primary pulmonary hypertension. Am J Cardiol 1994;74:414-6.

13. Dillon PW, Cilley RE, Hudome SM, Ozkan EN, Krummel TM. Nitric oxide reversal of recurrent pulmonary hypertension and respiratory failure in an infant with CDH after successful ECMO therapy. J Pediatr Surg 1995;30:743-4.

14. Geggel RL, Murphy JD, Langleben D, Crone RK, Vacanti JP, Reid LM. Congenital diaphragmatic hernia: arterial structural changes and persistent pulmonary hypertension after surgical repair. J Pediatr 1985;107: 457-64.

50 Years Ago in *The Journal of Pediatrics*

FUNCTIONAL DISORDERS OF THE LARYNX IN EARLY INFANCY

Schwartz AB. J Pediatr 1953;42:457-61

A half century ago in *The Journal of Pediatrics*, Dr Schwartz presented vignettes from his practice that suggested four types of functional disorders of the infant larynx.

The first functional disorder described is prolonged deglutition apnea. The normal sequence of feeding involves suck, swallow, and breathe. A short "apnea" allows milk to flow past the larynx without aspiration. We have learned since then that the larynx has airway protective responses—the laryngeal chemoreflex.[1] In the premature infant, in whom prolonged deglutition apnea is most often seen, this reflex may be overzealous.[2] An experienced nurse feeding premature infants treats this apnea almost intuitively by removing the bottle from the baby's mouth and providing gentle stimulation.

Schwartz's second descriptive term, congenital laryngeal stridor, is now used infrequently. Laryngomalacia, the common term for congenital laryngeal stridor, results in an infolding of the supraglottic laryngeal structures over the glottis, causing partial obstruction of the airway during inspiration. This infolding may be caused by redundant arytenoid mucosa, short aryepiglottic folds or abnormal tone of the intrinsic muscles of the larynx.[3] In the child that feeds well, laryngomalacia is a benign disorder that fades within the first year of life.[3]

Schwartz's third vignette, the problem he calls stridor with dysphagia, is likely an infant with laryngomalacia that has difficulty coordinating breathing and swallowing in the face of a partially obstructed airway. In some children, this can lead to serious feeding difficulties and failure to thrive.[3] In 2003, modified feeding practices and, in some instances, surgery are needed for this unusual child.

Schwartz's fourth type is the child with noisy breathing whose inspiration has a moist quality. He called this exudative stridor. Often the child is indifferent to these symptoms, but the parents are frustrated that the child does not just swallow the secretions. Schwartz proposed that "humid stertor" may be caused by an "allergic anlage" with mucus hypersecretion. Twenty-first century clinicians must consider whether the child's indifference is appropriate or if wheezing or aspiration is occurring.

Schwartz's paper is a jewel for those interested in infant sucking, swallowing, and breathing. He realized that these automatic processes occasionally go awry but the resultant problems are not categorized in ways useful for clinicians. A search of MEDLINE from 1966 to the present shows few references to the colorful terms Schwartz used, and studies of the common and complex problems he described have been infrequent under other monikers. Then, as now, our patients would benefit if we knew more about the development of the coordination of sucking, swallowing, and breathing.

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REFERENCES

1. Downing SE, Lee JC. Laryngeal chemosensitivity: a possible mechanism for sudden infant death. Pediatrics 1975;55:640.

2. Pickens DL, Schefft G, Thach BT. Prolonged apnea associated with upper airway protective reflexes in apnea of prematurity. Am Rev Respir Dis 1988;137:113-8.

3. Belmont JR, Grundfast K. Congenital laryngeal stridor (laryngomalacia): etiologic factors and associated disorders. Ann Otol Rhinol Laryngol 1984;93:430-7.