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NEONATOLOGY

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Disease-related response to inhaled nitric oxide in newborns with severe hypoxaemic respiratory failure

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Abstract Inhaled nitric oxide (iNO) has been shown to improve oxygenation in severe persistent pulmonary hypertension of the newborn (PPHN). However, PPHN is often associated with various lung diseases. Thus, response to iNO may depend upon the aetiology of neonatal acute respiratory failure. A total of 150 (29 preterm and 121 term) newborns with PPHN were prospectively enrolled on the basis of oxygenation index (OI) higher than 30 and 40, respectively. NO dosage was stepwise increased (10–80 ppm) during conventional mechanical or high-frequency oscillatory ventilation while monitoring the oxygenation. Effective dosages ranged from 5 to 20 ppm in the responders, whereas iNO levels were unsuccessfully increased up to 80 ppm in the nonresponders. Within 30 min of iNO therapy, OI was significantly reduced in either preterm neonates (51 ± 21 vs 23 ± 17, $P < .0001$) or term infants with idiopathic or acute respiratory distress syndrome (45 ± 20 vs 20 ± 17, $P < .0001$), 'idiopathic' PPHN (39 ± 14 vs 14 ± 9, $P < .0001$), and sepsis (55 ± 25 vs 26 ± 20, $P < .0001$) provided there was no associated refractory shock. Improvement in oxygenation was less significant and sustained ($OI = 41 \pm 16$ vs 28 ± 18, $P < .001$) in term neonates with meconium aspiration syndrome and much less ($OI = 58 \pm 25$ vs 46 ± 32, $P < .01$) in those with congenital diaphragmatic hernia. Only 21 of the 129 term newborns (16%) required extracorporeal membrane oxygenation (57% survival). Survival was significantly associated with the magnitude in the reduction in OI at 30 min of iNO therapy, a gestational age ≥34 weeks, and associated diagnosis other than congenital diaphragmatic hernia. Conclusion, iNO improves the oxygenation in most newborns with severe hypoxaemic respiratory failure including preterm neonates. However, response to iNO is disease-specific. Furthermore, iNO when combined with adequate alveolar recruitment and limited barotrauma using exogenous surfactant and HFOV may obviate the need for extracorporeal membrane oxygenation in many term infants.

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Key words Newborn · Acute respiratory failure · Persistent pulmonary hypertension of the newborn · Inhaled nitric oxide

Abbreviations *BPD* bronchopulmonary dysplasia · *CDH* congenital diaphragmatic hernia · *CMV* conventional mechanical ventilation · *ECMO* extracorporeal membrane oxygenation · *HFOV* high frequency oscillatory ventilation · *iNO* inhaled nitric oxide · *MAS* meconium aspiration syndrome · *OI* oxygenation index · *PPHN* persistent pulmonary hypertension of the newborn · *PVR* pulmonary vascular resistance · *RDS* respiratory distress syndrome

Introduction

Inhaled nitric oxide (iNO) has been shown to improve oxygenation in near or full-term neonates with severe persistent pulmonary hypertension of the newborn (PPHN) [13, 27]. However, PPHN is frequently asociated with various lung conditions (e.g. surfactant deficiency, bacterial pneumonia, meconium aspiration pneumonitis, and lung hypoplasia) which may further aggravate hypoxaemia [6, 19], and even impede the specific pulmonary vasodilatory effect of iNO. It has been suggested that more prolonged iNO therapy may obviate the need for extracorporeal membrane oxygenation (ECMO) in many term infants, except those with associated septic shock [14]. iNO has been found to improve oxygenation in a premature infant with severe respiratory distress syndrome (RDS) who did not respond to exogenous surfactant and high frequency oscillatory ventilation (HFOV) [1], but there are limited data on the potential value of iNO in this population. Thus, the aim of this study was twofold: (1) to assess the effects of iNO on systemic oxygenation in a large group of preterm and term neonates with refractory hypoxaemia, and (2) to investigate whether response to iNO depends upon the aetiology of neonatal acute respiratory failure.

Methods

Patient population

Sixteen French Neonatal/Paediatric Intensive Care Units participated in this study. Term newborns were eligible on the basis of two subsequent oxygenation indices (OI) $=$ MAP $\times$ FiO_2 $\times$ 100 $\div$ post-ductal PaO_2 consistently above 40 (ECMO criteria) [12]. In preterm newborns, OIs for inclusion were chosen above 30 and 35 in those <32 and <34 weeks of gestation, respectively. When available, shunting through the ductus arteriosus, pulmonary blood flow mean velocity, and tricuspid regurgitation were assessed using Doppler echocardiography. Infants with cardiac and multiple or karyotypic anomalies precluding full supportive care were excluded.

Diseases associated with PPHN were mostly based upon history and radiographic changes. Idiopathic RDS or acute RDS required diffuse lung infiltrates with or without a context of prematurity. 'Idiopathic' PPHN was characterized by minimal radiographic lung markings with severe hypoxaemia and no evidence of congenital heart disease. Neonatal sepsis was diagnosed on a history suggestive of maternal infection, clinical evidence of sepsis, leukopenia and/or thrombocytopenia, elevated CRP, and isolation of suspected pathogens in the amniotic fluid, gastric and/or tracheal aspirates, blood and/or urine cultures. Meconium aspiration syndrome (MAS) diagnosis was based upon a documented history of meconium staining of the amniotic fluid and an abnormal chest radiograph showing heterogeneous interstitial markings co-existent with hyperinflated areas. Finally, congenital diaphragmatic hernia (CDH) was recognized either prenatally by ultrasound or postnatally by chest X-ray showing a displaced heart and intrathoracic abdominal organs.

Medical therapy before NO treatment included optimized ventilation, haemodynamic support, and sedation. Guidelines for conventional mechanical ventilation (CMV) were both to obtain an aerated lung volume with more than 8–9 ribs on chest X-ray using sufficient levels of PEEP and to use the minimal levels of peak inspiratory pressure obtaining visible chest excursion. Guidelines for HFOV were to increase MAP by 2 to 3 cm H_2O increments until PaO_2 plateaued, and to increase pressure amplitude until chest oscillations were readily apparent. Cardiac function and systemic arterial pressure were supported by volume loading and titrated catecholamines. Prior to enrollment, all newborns with a history suggestive of RDS received exogenous surfactant (Exosurf, Burroughs Wellcome, NC, or Curosurf, Chiesi Farmaceutici, Italia).

This study was approved by the Institutional Review Board of Paris-VII University and informed consent was obtained from the parents.

Protocol

Certified NO (450 ppm in N_2, Air Liquide Santé, France) was delivered into the inspiratory limb of a time-cycled pressure-limited neonatal ventilator (Babylog 8000, Dräger, Germany, Sechrist 100IV-B, Riverside, CA) or a high-frequency oscillator (OHF-1, Dufour, France), with continuous flow set at $\geq$10 L/min in order to limit NO oxidation [2]. Inspiratory NO and NO_2 levels were continuously measured at the Y-piece level using electrochemical sensors (Polytron, Dräger-Industrie, France) [21].

Inhaled NO concentrations were increased by 15 min steps of 10 ppm, with upper limits of 80 ppm, and 1.0 ppm for NO_2. Infants who improved continued to receive iNO at the minimum levels found to be effective. Then, FiO_2 and ventilation were reduced in order to prevent further lung injury. NO levels were then lowered to 5 ppm for at least 24 h before discontinuation. When FiO_2 could be lowered to 0.4 or less, iNO therapy was terminated by slow weaning over several hours. Newborns who deteriorated were switched from CMV to HFOV while continuing to receive iNO at the same or incremental doses. If it failed (OI >40), ECMO was considered in term infants in the absence of a contra-indication.

Methaemoglobin levels were measured before iNO and 4 h later, then every 12 h thereafter. If it rose above 5%, NO therapy was discontinued.

Statistical analysis

Results are expressed as mean $\pm$ SD. Quantitative variables were investigated for difference before and at 30 min of iNO by a two-tailed paired *t*-test. Differences between the aetiological groups were assessed using a one-way analysis of variance with Bonferroni

Table 1 Characteristics of the newborns with severe respiratory failure

	Preterm (n = 29)		Term (n = 121)	
Gestational age (weeks)	30.3 ± 2*	(26–33)	38.2 ± .2	(34–42)
Body weight (g)	1,444 ± 623	(750–2,760)	3,101 ± 531	(1,800–4,660)
RDS/acuteRDS	18		18	
'Idiopathic' PPHN	2		12	
Sepsis	9		30	
MAS	–		21	
CDH	–		40	
OI before iNO	51 ± 21	(30–100)	50 ± 25	(40–138)
Age (h) on iNO	29 ± 32	(4–124)	26 ± 17	(1–72)
Time (h) on iNO	77 ± 54	(6–245)	59 ± 54	(1–216)
iNO dosage (ppm)	21 ± 14	(6–60)	28 ± 19	(7–80)

* mean ± SD (range)

correction for multiple comparisons. In the preterm infants, Mann-Whitney test and non parametric Kriskal-Wallis analysis of variance were used because of small samples. In the term infants, a multivariate logistic regression was performed to investigate the relative risk of various variables in predicting death. Results are expressed as odds ratio with 95% confidence interval. A P-value of 0.05 was considered significant.

Results

From April 1993 to December 1994, 150 (29 preterm and 121 term) consecutive newborns with refractory hypoxaemia were treated with iNO in the 16 centres (Table 1). NO therapy was initiated at 29 ± 32 h and 26 ± 17 h, and lasted for 77 ± 54 h and 59 ± 54 h in preterm and term infants, respectively. Maximal NO dosages were 21 ± 14 and 28 ± 19 ppm, respectively. None of the neonates who failed to respond to 20 ppm responded to higher doses. In no instance did methaemoglobin levels rise above 5%.

Preterm newborns (< 34 weeks)

Of the 29 preterm newborns, 18 (62%) developed severe RDS. Only two were given prenatal steroids. Despite early administration of exogenous surfactant and aggressive CMV (n = 15) or HFOV (n = 3), they remained hypoxaemic. Nine (31%) premature infants had in addition sepsis, and two (7%) were considered as having 'idiopathic' PPHN. In all but three with septic shock who rapidly expired, iNO reversed right-to-left shunting, and improved oxygenation lowering the OI from 51 ± 21 to 23 ± 17 (P < .0001) within 30 min. Response to iNO, however, was not necessarily indicative of good outcome, mainly because of the other complications of prematurity. Severe intracranial haemorrhage or leukomalacia occurred in three of nine (33%) infants < 30 weeks and 3 of 20 (15%) between 30 and 33 weeks. Likewise, bronchopulmonary dysplasia (BPD) was observed in three of three (100%) survivors of < 30 weeks and 5 of 13 (38%) survivors of 30–33 weeks. Two very premature (gestational age = 26 weeks) neonates could never be weaned off NO, required increasing levels of oxygen, and died from BPD.

Term newborns (≥34 weeks)

Primary diagnoses included 18 actue RDS, 12 'idiopathic' PPHN, 30 sepsis, 21 MAS, and 40 CDH. Response to iNO was disease-related (Fig. 1). Within 30 min of iNO therapy, OI significantly decreased in the 18 neonates with acute RDS (45 ± 20 vs 20 ± 17, P < .0001), the 12 with 'idiopathic' PPHN (39 ± 14 vs 14 ± 9, P < .0001), and the 30 with sepsis (55 ± 25 vs 26 ± 20, P < .0001) provided there was no associated refractory shock (n = 5). Improvement in oxygenation was less significant and sustained in the 21 neonates with MAS (OI = 41 ± 16 vs 28 ± 18, P < .001). Switch from CMV to HFOV, however, improved the oxygenation in five neonates with MAS, but was not helpful in two. In contrast, despite a significant reduction (58 ± 25 vs 46 ± 32, P < .01) on iNO, OI remained > 40 in 18 (45%) of the 40 infants with CDH.

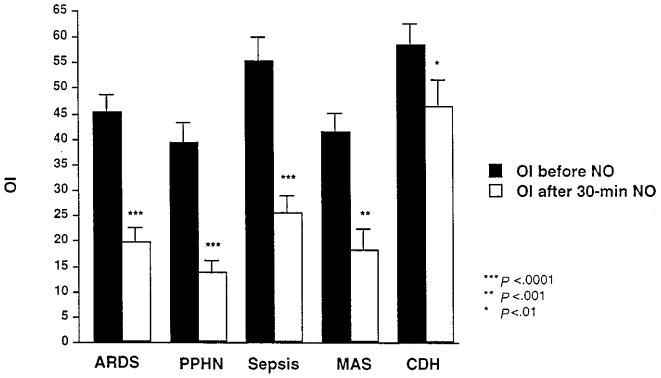

Fig. 1 Disease-related response to iNO in term newborns with severe hypoxaemic respiratory failure. OI (m ± SEM) was significantly reduced (paired t-test) at 30 min of iNO either in acute RDS (n = 18), 'idiopathic' PPHN (n = 12), sepsis (n = 30) (***P < .001), MAS (n = 21) (**P < .01), and CDH (n = 40) (*P < .05). However, OI remained > 40 in 19/40 infants with CDH

A sustained response to iNO appeared to be both disease-specific and quite indicative of survival (Fig. 2). Of the 18 newborns with acute RDS, 16 (89%) responded to iNO and survived. Two poor responders were denied ECMO, one because of neonatal haemochromatosis and the other because of ischaemic-anoxic encephalopathy, and both died. Of the 12 infants with 'idiopathic' PPHN, 11 (92%) likewise responded to iNO and survived; one died from the sequeleae of birth asphyxia. Of the 30 neonates with sepsis 25 (83%) responded to iNO and survived. Among the five non responders with severe septic shock, only one survived after ECMO. Of the 21 newborns with MAS, 15 (67%) responded to iNO, and 13 (62%) survived. ECMO was used in three non responders (two survivors), and denied in three others who suffered prolonged perinatal asphyxia and multiple organ dysfunction. In contrast, only 14 of 40 (35%) newborns with CDH survived. Significant improvement in the oxygenation on iNO occurred in 12 infants, but this was not sustained in six, four of whom were supported by ECMO. Two of them died from ECMO complications, and one other from sudden death after ECMO. A slight improvement in the oxygenation on iNO was observed in seven infants, but rapid relapse required ECMO. In three, weaning off ECMO was not possible, and they died. Finally, no response was observed in 21 infants. Five of them were offered ECMO, and three survived. Sixteen of them were denied ECMO: 5 because of associated multiple abnormalities, and 11 in whom prenatal and postnatal signs were suggestive of severe pulmonary hypoplasia which was confirmed in 6 at post-mortem. Thus, the overall survival in these term neonates was 60% after iNO, and 68% if one includes ECMO (53% survival). In contrast to the preterm newborns, only three of the survivors developed BPD.

Analysis of prognostic factors

Odds ratio for predicting death increased by 1.06 (0.95 CI 1.03–1.08, $P < .0001$) for each decrement in OI decrease observed at 30 min of iNO, by 5.6 (0.95 CI 1.92–16.3, $P < .0001$) for a gestational age < 34 weeks, and by 6.8 (0.95 CI 2.44–19.0, $P < .0001$) whenever the underlying disease was CDH.

Discussion

This study further extends the findings of preliminary reports of improved oxygenation in newborns with severe hypoxaemia and/or PPHN with iNO [1, 13, 14, 27]. This is one of the first investigations to demonstrate response to iNO in a large group of preterm newborns with RDS refractory to exogenous surfactant. Our data also indicates that response to iNO is disease-specific, as shown by others [5, 8, 14]. Furthermore, our data suggest that iNO, in combination with other therapeutic strategies including exogenous surfactant and HFOV, may obviate the need for ECMO in many term neonates with severe hypoxaemic respiratory failure not associated with pulmonary hypoplasia [9].

In preterm newborns, hypoxaemia often results from ventilation-perfusion mismatching with low lung volumes due to surfactant deficiency and/or structural immaturity. Current therapeutic approaches to RDS include the administration of exogenous surfactant [10], and ventilator strategies aiming at recruiting the lung volume, i.e. optimized PEEP levels with CMV [33], and 'high-volume' strategy with HFOV [3]. Hypoxaemia may also result from associated PPHN. Walther et al. [34] compared aortopulmonary gradients and left pulmonary artery flow velocities as measured by colour flow-directed Doppler echocardiography in infants with mild, severe or fatal RDS . Neonates with severe or fatal RDS had significant right-to-left shunting, nearly sys-

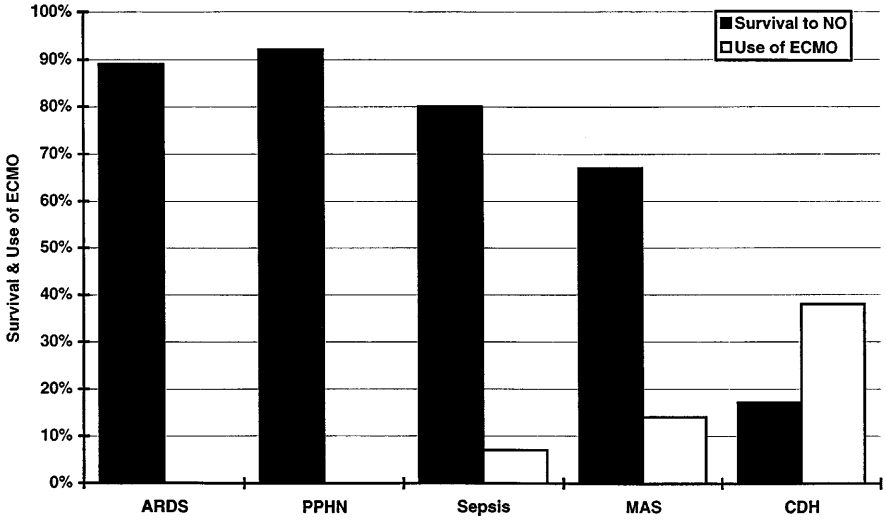

Fig. 2 Survival (%) in term neonates who responded to iNO, and use of ECMO (%) in those who did not. Abbreviations as in Fig. 1. Survival to ECMO was 50%, 67%, and 53% in sepsis, MAS, and CDH, respectively

temic or suprasystemic levels of pulmonary hypertension, and reduced pulmonary blood flow. Multiple factors can contribute to high pulmonary vascular resistance (PVR) including hypoxia, acidosis, low lung volumes or conversely lung overinflation. The immature pulmonary circulation is responsive to iNO [15], which may represent a more selective approach to improve oxygenation in the preterm newborn [1, 31]. iNO may have additional benefits in reducing pulmonary oedema and lung neutrophil accumulation in severe experimental hyaline membrane disease [16]. However, potential NO toxicity may be questioned [20], since two of our very premature infants could never be weaned off iNO and died from BPD.

Most of near term or full-term neonates with RDS/acute RDS and/or 'idiopathic' PPHN exhibited marked improvement in oxygenation within 30 min of iNO therapy. In addition to lowering PVR, iNO may further improve oxygenation by dilating pulmonary arteries associated with the best ventilated lung units, thereby enhancing ventilation/perfusion matching [29]. Septic infants responded less consistently to iNO. Neonatal sepsis may associate infectious alveolitis mimicking RDS/acuteRDS, pulmonary hypertension indistinct from 'idiopathic' PPHN, and septic shock with various organ dysfunctions. The two former mechanisms may benefit from iNO, while the latter may not and highlights the role of cardiac dysfunction in severe PPHN and septic shock [12]. Improvement in oxygenation in response to iNO was often less impressive or short-lasting in newborns with MAS. The pathophysiology of MAS includes bronchial obstruction, surfactant inhibition by meconium [22], atelectasis, 'check-valve' type obstruction, pulmonary overinflation and air leaks, resulting in markedly heterogenous ventilation/perfusion mismatching that may impede NO delivery, and lastly PPHN [26]. The ventilator strategy employed in association with iNO may, therefore, play a critical role [17]. Potential benefits of HFOV over CMV in reducing barotrauma and preventing ECMO in infants with severe hypoxaemia ($OI > 40$) have been suggested [4]. Thus, iNO may be more successful with early pulmonary management including exogenous surfactant and HFOV.

In contrast, neonates with CDH inconsistently responded to iNO. In our series, most of the infants responded transiently or not at all. Many of them had markers rather indicative of poor survival, including prenatal diagnosis of herniated viscera before 25 weeks, underdevelopment of the left ventricle [30], and best postductal PaO_2 lower than 100 torr [25]. iNO has been shown to be effective in CDH only after ECMO [11]. This has been attributed to delayed maturation of the endogenous surfactant system, and exogenous surfactant therapy has been found helpful in the high-risk neonate with CDH [7]. Increased PVR may result from 'reactive' vasoconstriction, but in the most severe cases from small cross-sectional area of pulmonary vessels and a 'fixed' component to PPHN. While the former may respond to iNO, the latter does not [24]. Furthermore, as left ventricular mass is diminished in the non-surviving CDH [30], decreased left ventricular output and refractory pulmonary hypertension may also contribute to the lack of response to iNO.

We conclude that iNO improves systemic oxygenation in most newborns including preterm neonates with severely hypoxaemic respiratory failure. However, response to iNO was found to be disease-specific. Successful management of severe neonatal respiratory failure demands meticulous attention to the nature of the underlying pulmonary pathology. If parenchymal lung disease prevails, as in RDS, exogenous surfactant and early institution of HFOV should first recruit the atelectatic lung and sustain lung volume while minimizing baro/volutrauma. When this fails, low doses of iNO may selectivey vasodilate the pulmonary vessels, thereby improving oxygenation by better matching perfusion to ventilation. If pulmonary vasoconstriction dominates, as in 'idiopathic' PPHN, early iNO therapy should selectively vasodilate the pulmonary circulation, reverse right-to-left shunting and improve oxygenation, hence preventing the vicious cycle: hyperventilation, barotrauma, and PPHN exacerbation by capillary stretch failure. In contrast, poor survival in neonates with CDH appears to depend upon the various degrees of pulmonary hypoplasia, and maybe left ventricular underdevelopment.

Only multicentre randomized trials will definitely prove the value of iNO to reverse PPHN, improve oxygenation, and obviate the use of ECMO in severe neonatal respiratory failure [23, 28, 35]. In France, the number of newborns treated with ECMO has dramatically fallen since the introduction of iNO. However, these clinical trials should carefully take into account the various underlying pulmonary diseases associated with PPHN as well as the different ventilatory strategies [17, 32]. Therefore, our ongoing randomized clinical trial is currently stratifying preterm and term newborns into three groups according to the associated diseases (RDS/acuteRDS, 'idiopathic' PPHN, MAS), and the ventilatory strategy (CMV or HFOV), at an earlier stage of the disease ($OI = 15–40$) in order to assess whether the early introduction of iNO would significantly prevent the evolution towards refractory hypoxaemia.

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