Intensive Care Med (1996) 22: 71–76

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Inhaled nitric oxide for avoidance of extracorporeal membrane oxygenation in the treatment of severe persistent pulmonary hypertension of the newborn

Received: 18 March 1994
Accepted: 23 March 1995

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Abstract Inhaled nitric oxide (NO) is thought to provide a noninvasive therapeutic alternative to extracorporeal membrane oxygenation (ECMO) in the treatment of persistent pulmonary hypertension of the newborn (PPHN).
Objective: Since January 1993, we have studied inhalation of NO in PPHN patients meeting the ECMO criteria of our institution. We focused on the questions of whether or not the need for ECMO could be obviated and whether differences could be found between NO responders and nonresponders.
Design: NO gas was delivered via conventional IPPV ventilation in incrementally increasing concentrations from 20 to 80 ppm.
Patients: NO therapy was attempted in ten ECMO candidates with clinical and echocardiographical evidence of PPHN (mean OI 51.9, SD 10.4).
Results: At various NO levels (30–60 ppm), five patients showed a significant increase in mean PaO_2 (range 32.9–85.9 mmHg). Improvement was transient in three patients (6–10 h) and prolonged in two others (54–80 h); in the latter cases, ECMO was avoided. Five patients did not respond at all to treatment. Responders and nonresponders differed in their mean respiratory tidal volume (8.9 vs 4.18 ml/kg, $P < 0.05$).
Conclusions: In our study, inhalation of NO obviated the necessity of ECMO therapy in only two out of ten PPHN patients. Thus, we would discourage any overoptimistic expectations about the effectiveness of NO therapy in PPHN until larger clinical trials have been performed.

Key words Nitric oxide · Persistent pulmonary hypertension · Extracorporeal membrane oxygenation

Introduction

Persistent pulmonary hypertension of the newborn (PPHN) is the most frequent cause of failure of conventional respirator therapy in neonates. PPHN occurs either as a primary idiopathic disease or as a secondary complication of various underlying conditions, such as sepsis, pneumonia, meconium aspiration, diaphragmatic hernia and hyaline membrane disease [1, 2]. A result of elevated pulmonary vascular resistance, PPHN causes persistence of – or relapse into – prenatal circulatory conditions and is associated with severe hypoxaemia and high mortality.

Presently, none of the various common approaches to overcoming PPHN is satisfactory: the success of

intravenously administered vasodilator drugs (tolazoline, prostacycline), is limited as they do not reduce pulmonary hypertension selectively. They can also reduce systemic arterial blood pressure to a critical level [3]. Alternative therapies, such as high-frequency oscillatory ventilation (HFOV), hyperventilation and blood alkalization may cause severe side effects, such as barotrauma of the lungs or reduced cerebral blood flow [2, 4].

Extracorporeal membrane oxygenation (ECMO) offers a chance of survival to PPHN patients who have failed to respond to the conventional approaches. Depending on the PPHN-associated condition, 75–95% of ECMO patients survive [5, 6]. However, this treatment is extremely invasive and is only available at a few centres.

Nitric oxide (NO), derived from the endothelium cells [7–10], has been identified as an endogenous relaxation factor of the vascular muscles. Therefore, several teams have tested inhalation of NO as therapy for PPHN patients [11–15]. In the majority of such patients (responders), PaO_2 increased markedly during NO inhalation; in some others (nonresponders) it did not improve. The studies imply that inhalation of NO can selectively reduce pulmonary hypertension without any impact on systemic arterial pressure. In conclusion, NO therapy may obviate the need for ECMO in some critically hypoxaemic PPHN patients [15].

We studied NO inhalation in ten hypoxaemic PPHN patients meeting our ECMO entry criteria and focused on the questions of whether it can replace ECMO and of whether any predictive parameter of successful NO response can be found.

Methods

Subjects

Beginning in January 1993, inhalation of NO was studied in PPHN patients admitted to our institution for optional ECMO therapy. Diagnosis of PPHN was confirmed by echocardiographic findings [16–18] showing right-to-left shunting of blood across the ductus arteriosus or the foramen ovale, tricuspid regurgitation, and diastolic interventricular septal flattening. Inclusion criteria for NO therapy were defined according to the ECMO criteria applied at our institution (briefly, at least 35 weeks of gestational age, severe hypoxaemia despite optimized respirator therapy and conventional supportive management, $PaO_2 < 40$ mmHg for > 2 h or $PaO_2 < 50$ mmHg for > 4 h, or oxygenation index (OI) > 40 for > 1 h). Oxygenation index OI = (mean airway pressure [cmH_2O] × fractional inspired oxygen × 100/arterial oxygen tension [mmHg]). Exclusion criteria were congenital heart disease, severe malformations, intracranial bleeding, family history of red blood cell disease and lack of informed parental consent. The study was approved by our regional ethics committee.

Of 14 consecutive patients meeting the entry criteria, ten were enrolled in the study. One patient with congenital heart disease and one patient whose parents did not consent to the study had to be excluded. Two patients were transferred in a desperate clinical condition ($PaO_2 < 20$ mmHg combined with cardicirculatory instability) requiring immediate ECMO treatment. Clinical data and PPHN-associated diseases of the enrolled infants are shown in Table 1.

The age of the neonates at onset of NO therapy ranged from 2 to 72 h, with a median of 23 h. In one case, that of a patient with diaphragmatic hernia who developed PPHN 7 days after surgical correction as a result of septic pneumonia, therapy was initiated 13 days after birth. Prior to NO therapy, all patients had a history of severe hypoxaemia, characterized by arterial oxygen-saturation lower than 80% or PaO_2 lower than 35 mmHg. This hypoxic interval ranged from 2 to 18 h, with a median of 8 h.

Prior to referral to our hospital, three infants had been treated with tolazoline, and two others with prostacycline. Five of the patients had received a surfactant (Survanta or Alveofact) and three had been treated with high-frequency oscillatory ventilation. Following previous application of vasodilating drugs, a minimum waiting period of 6 h was observed before NO inhalation was started. In our institution, all patients received morphine for pain relief, and vecuronium was used to induce muscular paralysis. All patients received catecholamines (either norepinephrine or dobutamine combined with dopamine) to maintain sufficient arterial pressure. Acidosis was corrected by infusions of sodium bicarbonate.

Method of NO delivery

NO gas was stocked in cylinders containing concentrations of approximately 800 ppm NO diluted in nitrogen (Messer-Griessheim, Duisburg, Germany). It was certified for $< 1\%$ (< 8 ppm) contamination with higher oxides of nitrogen. Using a flowmeter (Rotameter, Rota Yokogawa, Wehr, Germany) to adjust the desired flow rate, this source gas was delivered into the inspiratory limb of the ventilator circuit through a Y-shaped connector. This connector was placed approximately 30 cm from the endotracheal tube in order to obtain a homogeneous mixture of NO with the breathing gas delivered by the ventilator.

The resulting NO and NO_2 concentrations were continuously measured in the expiratory limb using electrochemical cells (PAC II NO/NO_2, Dräger AG, Lübeck, Germany). As a safety measure, these electrochemical cells respond to changes in the NO/NO_2 concentration within less than 20 s, thus precluding accidental overdosing of NO.

In all patients, a Babylog 8000 neonatal respirator (Dräger, Lübeck, Germany) was used in the mode of time-cycled, pressure-limited IPPV ventilation with a constant flow of gas during both in- and expiration. The Babylog 8000 provides constant monitoring of airway pressure and respiratory tidal volume.

Protocol of NO application

NO dosage was gradually increased from 20 to 80 ppm (in 10-ppm increments at 15-min intervals) in order to determine the individual optimum effective level. Treatment was considered successful if PaO_2 levels rose by more than 10 mmHg (responders). During the trials, all other respirator settings and crucial parameters like systemic arterial blood pressure or medical treatment of the patients were kept constant for at least 2 h.

If the treatment did not succeed (nonresponders), the trial was discontinued after 2 h and the patients received ECMO therapy. Among the responders, we reduced the NO concentration in decrements of 5 ppm every 15 min at 6-h intervals to determine the

Table 1 Patient characteristics/clinical data prior to NO treatment (*BPM* mean arterial blood pressure, *MAP* meanairway pressure, *CDH* congenital diaphragmatic hernia, *MAS meconium aspiration syndrome*, *ECMO* extracorporeal membrane oxygenation)

Patient number (initials)[a]	1 (A.N.)	2 (S.M.)	3 (S.M.-J.)	4 (G.M.)	5 (H.M.)	6 (B.A.)	7 (B.J)	8 (P.B)	9 (T.R.)	10 (L.M.)
GA (wk)	41	39	42	40	40	39	42	39	40	41
Birth weight (g)	3300	2660	3680	3110	3250	3600	3150	3220	4500	3200
Diagnosis	Pneumonia	MAS	CDH	MAS	CDH, pneumonia	CDH	MAS	CDH	Pneumonia	CDH
MAP (cmH_2O)	18.0	14.9	15.2	16.0	13.0	15.0	15.1	14.0	14.0	13.0
Tidal volume (ml/kg)	8.2	12.7	6.0	9.7	7.7	2.3	6.2	4.4	3.1	4.9
PaO_2 (mmHg)	41.4	35.5	29.8	28.3	29.3	28.5	28.0	23.5	18.6	31.7
$PaCO_2$ (mmHg)	40.9	29.7	39.0	36.3	55.8	36.5	23.6	42.2	63.5	27.9
pH	7.38	7.50	7.47	7.38	7.40	7.41	7.50	7.40	7.42	7.47
OI	43.5	42.0	51.0	56.5	44.3	52.6	53.9	59.6	75.2	40.6
BPM (mmHg)	54	61	63	46	60	61	55	51	55	45
Age at start of NO (h)	24	72	28	10	312	22	5	6	18	2
Duration of hypoxaemia (h)[b]	2	5	2	10	12	10	6	6	18	2
Surfacant treatment	No	Yes	No	No	Yes	Yes	No	No	Yes	No
Required further treatment	No	No	ECMO	ECMO	ECMO	ECMO	ECMO	ECMO	ECMO	ECMO
Survived	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes

[a] Patient 1–5 responded to NO; patients 6–10 were nonresponders

[b] Hypoxaemia was defined as O_2 saturation $< 80\%$ or $PaO_2 < 35$ mmHg

minimum effective level for sustaining optimal oxygenation for each patients. NO withdrawal was attempted at 12-h intervals by turning off the NO gas for at least 10 min. This mode of application was chosen to prevent overdosing as well as unnecessarily prolonged treatment.

Patient monitoring

Oxygen saturation (SpO_2) and systemic arterial blood pressure were monitored continuously and arterial blood gas tensions were controlled at 15-min intervals. Methaemoglobin levels were measured initially, at 2 h and (if the NO treatment was continued) subsequently at 12-hour intervals. Whenever methaemoglobin levels exceeded 1.5%, the time interval between checks was shortened to 6 h. Echocardiography and echoencephalography were repeated at 6–12-h intervals.

Statistical analysis

According to their initial response to the NO inhalation, patients were divided into two groups: NO responders and NO nonresponders. Both groups were compared with respect to differences in gestational age, birth weight, mean airway pressure, maximum achievable respiratory tidal volume (at peak inspiratory pressures of 39–43 cmH_2O), PaO_2, $PaCO_2$, pH, arterial blood pressure, duration of hypoxaemia, and oxygenation index. Statistical analysis was done by using unpaired *t*-test for heterogeneous variances (Welch approximation). The level of statistical significance was set at $P < 0.05$.

Results

Eight out of ten patients included in this study eventually required ECMO, because their oxygenation either did not increase at all or increased only transiently during NO inhalation (five nonresponders and three transient responders, Table 1, patients 3–10). In two further responders, NO effected a continuously improved oxygenation, thus obviating the need for ECMO (Table 1, patients 1 and 2).

Individual differences were apparent in the initially effective NO concentrations among the five responders. No patient responded within 15 min to the starting concentration of 20 ppm. Concentrations were increased stepwise until individual thresholds of efficacy were reached, as indicated by sudden improvements in SpO_2 and PaO_2. The effective levels ranged from 30 to 60 ppm, with a mean of 46 ppm. Once the threshold was crossed, further increases in NO concentration did not improve PaO_2 further in any of the patients.

After 1 h of treatment with the initially effective NO concentration, the mean PaO_2 of the responders had increased significantly ($P < 0.01$), from 32.9 (SD 5.6) mmHg to 85.9 (SD 16.5) mmHg and the mean OI had decreased from 47.5 (SD 6.1) to 18.2 (SD 2.9).

Table 2 Summarized statistics: NO responders vs nonresponders

		Responders [$n = 5$; mean (SD)]	Nonresponders [$n = 5$; mean (SD)]	Significance
	GA (weeks)	40.4 (1.14)	40.2 (1.30)	n.s.
	birth weight (g)	3200 (368)	3534 (569)	n.s.
Initial values	MAP (cmH_2O)	15.4 (1.81)	14.2 (0.86)	n.s.
	Tidal volume (ml/kg)	8.9 (2.5)	4.18 (1.53)	$P = 0.0121$
	PaO_2 (mmHg)	32.9 (5.6)	26.1 (5.1)	n.s.
	$PaCO_2$ (mmHg)	40.3 (9.6)	38.7 (15.6)	n.s.
	pH	7.426 (0.055)	7.44 (0.04)	n.s.
	BPM (mmHg)	56.8 (6.9)	53.4 (5.9)	n.s.
	Time of hypoxaemia (h)	6.2 (4.60)	8.4 (6.1)	n.s.
	OI	47.5 (6.1)	56.4 (12.5)	n.s.
After 1 h of NO at "best-effect" level	MAP (cmH_2O)	15.3 (1.88)	14.2 (0.83)	n.s.
	Tidal volume (ml/kg)	8.6 (2.3)	4.6 (2.1)	$P = 0.023$
	PaO_2 (mmHg)	85.9 (16.5)	27.4 (4.6)	$P < 0.01$
	$PaCO_2$ (mmHg)	31.2 (7.4)	40.7 (12.3)	n.s.
	pH	7.440 (0.042)	7.411 (0.061)	n.s.
	BPM (mmHg)	58.2 (5.6)	55.0 (3.7)	n.s.
	OI	18.2 (2.9)	53.2 (9.5)	$P < 0.01$

Within the same amount of time, $PaCO_2$ had decreased from 40.3 (SD 9.6) mmHg to 31.2 (SD 7.4) mmHg (not significant, $P = 0.19$). Mean airway pressure, respiratory tidal volume, mean arterial blood pressure and pH did not change (Table 2).

In the infants with only transient improvement, PaO_2 gradually decreased and ECMO was started as soon as their OI had worsened again to 40 or more (after 4–6 h; Fig. 1). Decreasing efficacy in these three cases could not be compensated for by increasing NO levels to 80 ppm.

In the two cases with lasting success, the total times of treatment were 80 h and 54 h. Administration of NO was discontinued every 6–12 h to reevaluate the need for further treatment. At concentrations above 10 ppm, each withdrawal was followed by a sharp decrease in arterial oxygenation within 3–15 min. This deterioration could always be quickly reversed by restarting NO inhalation. Finally, both patients could be weaned from NO by using slowly decreasing concentrations of as low as 1–3 ppm for 12–24 h.

Corresponding to their clinical improvement, both patients with lasting success were found on repeated echocardiographical examinations to have decreasing extrapulmonary right-to-left shunting of blood.

In five patients, NO therapy did not have any noticeable effect and was terminated after a maximum of 80 ppm NO had been applied for 30 min. PaO_2 and OI remained at baseline values during the trial. Finally, shutting off the supply of NO after 2 h was not followed by any change in PaO_2.

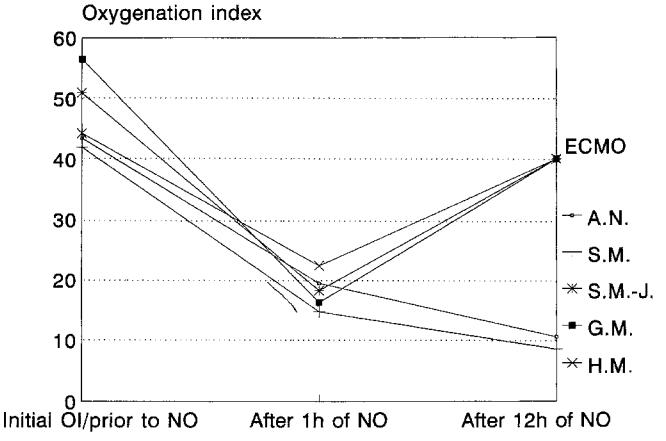

Fig. 1 Course of oxygenation index (OI) during NO inhalation in five responders $OI = (MAP \times FiO_2 \times 100)/PaO_2$. Relapsing to hypoxaemia after 4–6 h, three patients eventually required ECMO (transient responders)

Responders and nonresponders did not differ significantly in terms of gestational age, birth weight, duration of severe hypoxaemia prior to the NO trial, or initial values of MAP, PaO_2 $PaCO_2$, pH, OI, and BPM. The maximum respiratory tidal volume of the nonresponders was significantly lower than that of the responders (mean 4.18 vs 8.9 ml/kg, $P = 0.0121$).

The maximum Met-Hb values of the nonresponders did not differ from their baseline values (< 0.5%). Four responders showed maximum Met-Hb values of < 0.5–1.8%. In one of the lasting responders, a maximum value of 4.1% Met-Hb was detected after 24 h of

treatment at NO levels of 30–40 ppm. The following day, after NO was reduced to 10 ppm, Met-Hb decreased to 1.5% without specific therapy.

NO_2 concentrations in the breathing gas mixture did not exceed 1–2% of the NO concentrations applied. When we used 80 ppm of NO at $FiO_2 = 0.9$, we measured NO_2 concentrations ranging from 1.3 to 1.5 ppm.

None of the neonates showed an increased tendency to bleed, nor did any case of intracerebral haemorrhage occur. Repeated laboratory tests of coagulation parameters, including activated clotting time, revealed no influence of NO application. Systemic arterial blood pressure remained unchanged in all patients during NO inhalation.

Discussion

This study indicates that application of inhaled NO could not replace ECMO in the majority of hypoxaemic PPHN patients meeting our ECMO criteria (OI > 40). Eight out of ten such patients ultimately required ECMO in spite of NO inhalation, because this attempt to increase their oxygenation either failed completely (five nonresponders) or elicited only a brief transient response (three transient responders). Only two out of ten patients responded to NO with continuously increased oxygenation making ECMO unnecessary.

This result is in accordance with findings recently reported by Finer et al. [15]. In that study, inhalation of NO was attempted for the treatment of seven PPHN patients with OIs > 40, among whom five eventually required ECMO.

Our study further indicates that maximum achievable respiratory tidal volume can be a predictive parameter of successful NO response. The lasting and transient responders had maximum respiratory tidal volumes of 6 ml/kg or more (mean 8.9, SD 2.5), as against less than 5 ml/kg (mean 4.2, SD 1.5) in four out of five nonresponders. This result confirms the recently published finding that reponse to NO therapy in PPHN patients depends on adequate lung volume [19]. Furthermore, it is in accordance with the physiological models that characterize NO as a short-acting local vasodilator [8]. It seems likely that inhaled NO molecules only reach pulmonary vessels in the immediate neighbourhood of ventilated alveoli and that they cannot spread to distant vessels in non-ventilated areas of the lung. Thus, poor alveolar ventilation reduces the chances of inhaled NO decreasing overall pulmonary vascular resistance.

Three out of five responders showed a slowly progressing relapse within 4–6 h after initial improvement of their oxygenation. We do not know whether these relapses were due to the individual courses of the patients' diseases or to declining efficacy of inhaled NO. Kinsella et al. [13] reported one patient with only transient improvement who deteriorated progressively in the course of continued treatment, in association with progressively worsening left ventricular performance.

At present, the optimum dosage of NO is unknown. By increasing NO concentrations stepwise from 20 to 80 ppm, we achieved a significant initial improvement in PaO_2 at levels ranging from 30 to 60 ppm (mean 46 ppm) in five responders. The five nonresponders did not benefit from any of the concentrations administered. Roberts et al. [11], who used a similar study design with six infants, reported significant improvement in all patients at a level of 80 ppm NO within 30 min, whereas little improvement in postductal oxygen tension was shown at less than 80 ppm NO. Kinsella et al. [12, 13], on the other hand, did not follow a protocol of increasing concentrations. They achieved an immediate and significant rise in oxygenation in all patients treated at levels of 10–20 ppm NO. Finer et al. [15] administered NO in concentrations ranging from 5 to 80 ppm in random order to 23 neonatal ECMO candidates with and without PPHN. Thirteen infants showed a significant response, and the improvement in PaO_2 was independent of the NO dosage. From the data reported, we cannot determine any pathophysiological cause for the differences in the effective NO concentrations. According to previous observations [13, 15], the therapeutic effect was maintained in both lasting responders by gradually decreasing NO concentrations.

In conclusion, inhalation of NO could not replace ECMO in the majority of PPHN patients included in this study. It remains to be investigated whether earlier intervention with inhaled NO and/or NO combined with an exogenous surfactant and perhaps with HFOV for improvement of the alveolar ventilation might prove useful strategies for PPHN treatment.

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