Journal of Critical Care (2005) **20**, 288–295

ELSEVIER

Journal of Critical Care

Clinical Research—Pediatric

Hypoxic respiratory failure in term newborns: clinical indicators for inhaled nitric oxide and extracorporeal membrane oxygenation therapy☆

Harun Fakioglu MD, Balagangadhar R. Totapally MD, Dan Torbati PhD*, Andre Raszynski MD, Jeffrey B. Sussmane MD, Jack Wolfsdorf MD

Division of Critical Care Medicine, Miami Children's Hospital, Miami, FL 33155-3009, USA

Received 15 November 2004; revised 18 March 2005; accepted 10 May 2005

Keywords:
Extracorporeal membrane oxygenation;
Hypoxic respiratory failure;
Inhaled nitric oxide;
Persistent pulmonary hypertension of newborn;
Term newborns

Abstract

Purpose: The criteria for starting extracorporeal membrane oxygenation (ECMO) therapy in term newborn patients with hypoxemic respiratory failure consist of an oxygenation index (OI) of 25 or higher and alveolar-arterial oxygen (AaO_2) gradient of more than 600 at sea level. In such conditions, inhaled nitric oxide (iNO) may improve oxygenation and reduce the need for ECMO therapy. We studied early changes in OI and AaO_2 gradients in response to iNO treatment that may indicate a need to continue iNO treatment or the necessity to start an ECMO therapy.

Materials and Methods: In this prospective study, we used 34 outborn neonatal patients that were referred to our pediatric critical care unit in a children's hospital for ECMO therapy with diagnosis of hypoxemic respiratory failure. In all patients, iNO therapy, starting at 80 ppm, was instituted either during transport or on arrival to hospital. Response to iNO was assessed after 1 hour, at which time, iNO concentration was reduced to 40 ppm, provided there was more than 20% improvement in either or both oxygenation indices. Patients who did not respond positively to continuous iNO therapy and met ECMO criteria were given ECMO therapy.

Results: Inhaled nitric oxide therapy alone was successful in 10 (29%) of 34 patients. Eighteen patients (53%) required ECMO therapy within the first 10 hours of iNO treatment (early ECMO therapy), whereas 6 other neonates (18%) became eligible for ECMO therapy after prolonged (2-4 days) iNO treatment (late ECMO therapy). No mortality occurred with any treatment. Within 4 hours after iNO therapy, patients who required early ECMO therapy had significantly higher OI and AaO_2 gradients than patients who were treated with iNO therapy alone ($P < .01$, analysis of variance followed by Tukey-Kramer multiple comparison test). Six of 34 patients (18%), categorized as late ECMO therapy, on the average, had initially higher levels of OI and mean airway pressure than neonates in iNO treatment and early ECMO therapy.

☆ Supported by Alex Simberg Endowment for Critical Care Medicine.

* Corresponding author. Tel.: +1 305 663 8526; fax: +1 305 662 0530.
E-mail address: dan.torbati@mch.com (D. Torbati).

0883-9441/$ – see front matter
doi:10.1016/j.jcrc.2005.05.011

Conclusion: Persisting levels of OI of more than 20 or AaO_2 gradients of more than 600 after 4 hours of iNO therapy could be indicative of an immediate need for ECMO therapy.

1. Introduction

Severe hypoxemic respiratory failure due to persistent pulmonary hypertension of newborn (PPHN) is associated with high morbidity and mortality [1,2]. These patients are usually treated with oxygen, conventional and/or high-frequency mechanical ventilation, inotropic support, induction of alkalosis, and sedation. When these measures fail, extracorporeal membrane oxygenation (ECMO) has been shown to improve the outcome [3]. However, ECMO procedures are complex because they require systemic anticoagulation and major vessel cannulation. Studies on inhaled nitric oxide (iNO) therapy for PPHN have shown rapid improvement in oxygenation, reducing the need for ECMO therapy without affecting the mortality [4-11]. Finer and Barrington [11] showed that iNO treatment improves oxygenation in approximately 50% of term or near-term neonates with hypoxemic respiratory failure and reduces the combined end point of death or the need for ECMO therapy (relative risk, 0.73) as compared with control subjects. Recently, in a retrospective study, Truog et al [12] tried to identify the clinical factors for patients with sustained response to iNO therapy, as well as nonresponders, or those who transiently respond to iNO treatment. They found a significant association between the age of patient and the sustained response to iNO therapy. However, response to iNO therapy is varied, could be age-dependent [12], and may not be sustained in all patients [11-15].

In practice, patients with either an oxygenation index (OI) of 25 or higher, or an alveolar-arterial oxygen (AaO_2) gradient of greater than 600 at sea level despite optimal medical management are candidates for ECMO therapy. We tested the hypothesis that lack of an early response to iNO therapy in the presence of PPHN may indicate an immediate need for ECMO therapy.

2. Materials and methods

The protocol for this study was approved by the Institutional Review Board of Miami Children's Hospital. The investigational new drug exemption was obtained from the Federal Drug Administration. Patients were admitted to the pediatric intensive care unit at Miami Children's Hospital between June 1995 and January 1999. Patients who met the study criteria (OI of >20 and/or AaO_2 gradient of >500 for more than 4 hours) were enrolled for the study (n = 34) after obtaining informed consent from the parents. All patients that were referred to our pediatric intensive care unit to be evaluated for ECMO therapy had hypoxic respiratory failure, were mechanically ventilated, and were at a gestational age of more than 36 weeks. Patients with congenital diaphragmatic hernia or congenital heart disease were excluded.

Clinical diagnosis of PPHN was made with persistent postductal hypoxemia (PaO_2 of <60 mm Hg at a fraction of inspired oxygen of 1.0) despite optimal medical management and echocardiographic evidence of pulmonary hypertension. The latter consisted of right-to-left or bidirectional shunting at the ductus arteriosus or the foramen ovale, or evidence of elevated pulmonary artery pressure (estimated by Doppler assessment of tricuspid regurgitation or ventricular septal position). Inhaled nitric oxide therapy, starting at 80 ppm, was instituted either during transport or on arrival to hospital. This dose was reduced to 40 ppm after 1 hour if the patient showed a 20% or more improvement in oxygenation indices. Those who did not respond or deteriorated during iNO therapy and met the criteria were given ECMO therapy.

2.1. Supply and monitoring of nitric oxide

Nitric oxide was supplied by Scott Medical Products (Plumstead, Pa) in cylinders with concentrations of 800 or 2200 ppm in pure nitrogen and had less than 8 and 22 ppm of nitrous oxide, respectively. The nitric oxide cylinders were mounted on a cart with a flow meter, 2 blenders, and a chemiluminescence device to form a single portable unit. Nitrogen and nitric oxide gases were each fed separately into a Bird low flow blender referred to as the nitric blender (Bird Products Corporation, Palm Springs, Calif) at 50 psi. The nitric oxide gas was passed through the "oxygen" port and the nitrogen gas into the "air" port. The nitric oxide–nitrogen mixture passed through an air inlet of a second Bird blender where it was mixed with 100% oxygen. A sampling port at the airway allowed a volume of inspiratory gas mixture to be aspirated by a chemiluminescence analyzer for nitric oxide and nitrous oxide analysis. The Teflon sampling line contains a hydrophobic filter that prevents moisture from influencing the accuracy of the nitric oxide/nitrous oxide analyzer. The chemiluminescence analyzer (Echo Physics CLD 700AL-MED-MULTI Analytical Inc, Mountain View, Calif) or a Pulmonox II (Pulmonox Research and Development Co, Tofield, Alberta, Canada) was used to determine the concentration of these gasses.

2.2. Nitric oxide administration

Patients were given iNO either on arrival or during transport to our hospital. Arterial blood gas measurements served as the baseline value in assessing the response to iNO. If the OI or AaO_2 gradient did not show at least 20% improvement after 1 hour of iNO therapy, the patients were

labeled as possible candidates for ECMO therapy. These patients were given ECMO therapy if the OI or AaO_2 continued to increase (OI of >25 or AaO_2 of >600). One hour after iNO therapy, the nitric oxide dose was reduced to 40 ppm and maintained at this dose for at least 12 hours. The nitric oxide dose was then reduced to 20, 10, and 5 ppm at 15-minute intervals. The patients received the lowest dose of iNO providing an arterial PO_2 of more than 60 mm Hg or oxygen saturation of more than 90%. The patients were weaned from iNO therapy at 5 ppm if the inspired oxygen concentration was 60% or less. Weaning from iNO therapy was accomplished using iNO with 1 ppm decrements over several hours. If the patients failed to maintain acceptable oxygenation, the iNO therapy was resumed.

In all patients, echocardiography was performed and methemoglobin levels were determined at baseline after 1 hour and every 12 hours thereafter. Methemoglobin was determined more frequently if its level exceeded 5% and was treated primarily by a 50% reduction in iNO. If patients did not tolerate reduction in nitric oxide, they were treated with vitamin C (2 mg/kg per dose administered every 6 hours). Blood samples were taken to estimate methemoglobin reductase levels and to exclude glucose 6-phosphate dehydrogenase deficiency. Nitrous oxide and nitric oxide concentrations were monitored every hour, and iNO concentrations were adjusted to maintain nitrous oxide levels at less than 2 ppm. Mean arterial blood pressure (MABP), mean airway pressure (MAP), and gas exchange variables (PaO_2, $PaCO_2$, and pH) were obtained as a part of routine monitoring.

2.3. Statistical evaluation

All values were expressed as mean ± SD. Patients were categorized in 3 groups according to their response to iNO therapy. These included (1) patients who positively responded to iNO therapy and did not require ECMO therapy before being discharged from the hospital, (2) patients with poor or negative response to iNO within 10 hours after initiating the therapy, and (3) patients who initially responded positively to iNO therapy but required ECMO treatment after 48 to 96 hours of continuous iNO therapy. These ECMO therapy groups were referred to as "early ECMO" and "late ECMO" groups. Data collected from these 3 categories were compared using 1-way analysis of variance (ANOVA) followed by the parametric Tukey-Kramer multiple comparisons test. The same data were also evaluated by nonparametric Kruskal-Wallis test, if SD in different categories were not comparable (skewed data). Changes within the same treatment category (ie, either iNO or ECMO therapy) were evaluated by ANOVA followed with Dunnett multiple comparisons test. Fisher exact test was used to calculate the relative risk using OI of more than 20 and AaO_2 of more than 600 after 4 hours of iNO therapy as risk factors.

3. Results

All patients had echocardiographic evidence of pulmonary hypertension and/or extracardiac shunt and, at the time of enrollment into the study, met our hospital criteria for ECMO therapy. Of the 34 patients, 10 (29%) were managed successfully with iNO therapy alone, whereas 24 patients (71%) required either an early or late ECMO therapy (Table 1). These patients are referred to as early ECMO therapy group and late ECMO therapy group, respectively. No mortality occurred in either group. Gestational age and weight of infants who required early or late ECMO and those who were treated only with iNO were not significantly different. On the average, however, patients in early and late ECMO therapy groups were 1 day

Table 1 Demographic variables, duration of iNO therapy, and maximum concentrations of nitrous oxide and methemoglobin in newborn patients with pulmonary hypertension subjected to iNO therapy or iNO therapy followed by either an early or late ECMO therapy

Variables	Treatment			Statistical tests
	iNO without ECMO	iNO + early ECMO	iNO + late ECMO	
No. of patients	10	18	6	
Gestation age (w)	39.5 ± 1.0	39.1 ± 1.6	39.8 ± 2.2	T-K
Body weight (kg)	3.5 ± 0.4	3.3 ± 0.4	3.0 ± 0.5	T-K
Age (d)	2.5 ± 1.8	1.4 ± 0.6	1.1 ± 0.4	T-K and K-W
Duration of iNO therapy (h)	70.2 ± 42.6[a] ($P < .001$)	4.1 ± 4.2	68.3 ± 23.2[b] ($P < .001$)	T-K and K-W
Maximum blood nitrous oxide (ppm)	2.0 ± 1.2	4.4 ± 4.2	4.3 ± 2.8	T-K and K-W
Maximum blood MetHb (%)	2.6 ± 1.8[a] ($P < .05$)	0.9 ± 1.2 (95% CI, 0.1%-1.6%)	4.7 ± 3.3[b] ($P < .01$) (95% CI, 1.2%-8.2%)	T-K and K-W

Values are presented as mean ± SD unless otherwise indicated. No significant differences were found between iNO therapy and late ECMO therapy. T-K indicates parametric Tukey-Kramer multiple comparisons test; K-W, nonparametric Kruskal-Wallis multiple comparisons test; MetHb, methemoglobin; CI, confidence interval.

[a] Statistically significant; comparing iNO vs early ECMO therapy.

[b] Statistically significant; comparing early ECMO vs late ECMO therapy.

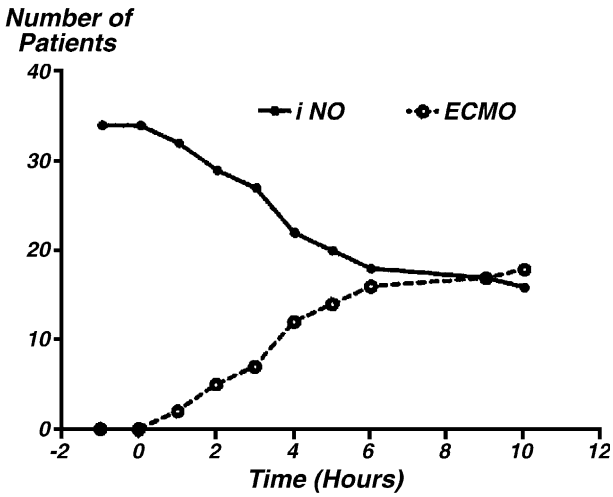

Fig. 1 Distribution pattern of number of neonatal patients subjected to iNO treatment with or without ECMO therapy. Approximately 50% of patients required ECMO therapy within 10 hours after initiating an iNO treatment.

younger than those in the iNO therapy group (Table 1). Younger patients (1-2 days old), as compared with older neonates (3-7 days old), needed ECMO therapy (Fisher exact test, $P < .02$). More than 50% of patients were given ECMO therapy within 10 hours after starting iNO therapy (Fig. 1). Of 34 patients, only 6 (18%) required ECMO therapy after a long period of iNO therapy (Table 1).

Neonates with sustained iNO therapy demonstrated significantly lower OI in the first 4 hours of the treatment compared with early ECMO group (Table 2). Similarly, the AaO_2 gradient in the iNO therapy group, unlike in the early ECMO therapy patients, was significantly reduced at 4 hours of iNO treatment. The late ECMO therapy group had initially higher OI than the iNO or early ECMO therapy groups. Although iNO therapy in this group was initially effective (Table 2), ultimately they required ECMO therapy. The PaO_2, $PaCO_2$, pH, MAP, and MABP within the first 4 hours of iNO treatment were not significantly different in iNO- and ECMO-treated neonates (Table 2). However, the MAP baselines, as well as MAP values at 1 and 4 hours of iNO treatment, were significantly higher in the late ECMO therapy group than in iNO and early ECMO therapy groups ($P < .05$, ANOVA followed by Tukey-Kramer multiple comparisons test). Patients who continued on iNO therapy, without requiring ECMO therapy, showed an average of 48% decrease in OI and 23% decrease in AaO_2 at 4 hours of treatment (Fig. 2). At the same time, patients who required ECMO therapy showed only an average of 17% decrease in OI and less than 3% decrease in AaO_2 gradient (Fig. 2). Persistently high levels of OI (>20) or AaO_2 (>600) after 4 hours of iNO therapy indicated an urgent need to initiate ECMO therapy (relative risks of 7 and 4.5, respectively, using n = 10 in iNO group and n = 9 in early ECMO group; Fisher exact test, $P < .015$).

3.1. Causes of PPHN and mode of ventilation

In our iNO-treated patients, 5 of 10 neonates had meconium aspiration syndrome and the rest had PPHN. In the ECMO groups, 17 of 24 patients had meconium aspiration syndrome, 4 patients had PPHN, whereas 3 other

Table 2 Changes in respiratory and hemodynamic variables in neonatal patients referred for ECMO therapy in response to iNO. Neonates were given ECMO if OI and/or AaO_2 were greater than 25 and 600 units, respectively

Variables	iNO (n = 10)			iNO + early ECMO (n = 18)			iNO + late ECMO (n = 6)		
	0 h	1 h	4 h	0 h	1 h	4 h	0 h	1 h	4 h
OI	31.4 ± 7.7	19.0 ± 11.9*	16.2 ± 11.6**	42.7 ± 21.8	33.1 ± 18.2	35.4 ± 21.0	63.0 ± 27.0	20.6 ± 13.9**	17.0 ± 11.2**
AaO_2 gradient (mm Hg)	625 ± 23	557 ± 99	481 ± 111**	626 ± 28	608 ± 38	610 ± 43	645 ± 16	495 ± 160	458 ± 159
PaO_2 (mm Hg)	51.2 ± 16.7	125 ± 102	129 ± 55	52.7 ± 16.2	64.4 ± 43.8	72.0 ± 49.2	38.8 ± 13.8	164 ± 120	192 ± 137
$PaCO_2$ (mm Hg)	26.0 ± 9.6	32.2 ± 9.6	32.9 ± 10.3	31.3 ± 4.8	40.8 ± 14.8	32.2 ± 8.8	30.5 ± 4.6	29.5 ± 7.3	36.3 ± 14.8
pH	7.52 ± 0.10	7.52 ± 0.12	7.48 ± 0.12	7.41 ± 0.06	7.37 ± 0.12	7.45 ± 0.09	7.44 ± 0.12	7.49 ± 0.08	7.45 ± 0.12
MAP (cm H_2O)	14.8 ± 3.0	18.0 ± 4.3	19.6 ± 7.3	17.4 ± 3.0	18.7 ± 3.5	18.3 ± 3.9	23.7 ± 5.5	23.0 ± 5.7	22.8 ± 6.0
MABP (mm Hg)	56.1 ± 15.0	56.3 ± 8.4	54.1 ± 10.9	47.7 ± 9.1	53.0 ± 9.4	55.1 ± 9.0	47.5 ± 5.4	49.0 ± 5.7	51.4 ± 5.6

Values are presented as mean ± SD.

* $P < .05$ and

** $P < .01$: 1-way ANOVA followed by Dunnett multiple comparisons test, comparing baselines with 1 and 4 hours of iNO treatment within the same category.

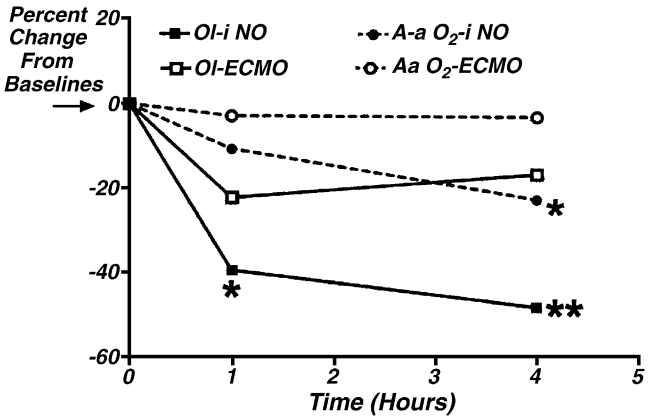

Fig. 2 Percentage of change in OI and AaO_2 gradient at 1 and 4 hours after initiating iNO therapy for patients with continuous iNO therapy, early ECMO therapy, and late ECMO therapy groups. Lack of a positive response to iNO therapy (within 1-4 hours), as reflected on a consistently high OI, may signal the need for an early ECMO therapy. Conversely, a continuously positive response (within 4-hour period) to iNO therapy may be an indicator for continuation of iNO therapy.

patients had sepsis. Mode of ventilation in the first hour of treatment, when all patients were on iNO therapy, included 15 patients with conventional mechanical ventilation and 19 patients on high-frequency oscillatory ventilation. In the iNO therapy group, 5 patients were supported with conventional mechanical ventilation and 5 others with high-frequency oscillatory ventilation. Ten patients in the combined early and late ECMO groups were on conventional mechanical ventilation, whereas 14 others were on high-frequency oscillatory ventilation.

4. Discussion

The morbidity and mortality associated with PPHN are related to the severity and duration of systemic hypoxemia. The current treatment of PPHN includes ECMO, which is an invasive procedure. Alternatively, iNO selectively dilates the pulmonary vasculature and has been shown to be effective and safe in improving oxygenation and decreasing the need for ECMO in neonates with hypoxemic respiratory failure [4-10]. In a retrospective study, Truog et al [12] evaluated the records of ECMO-eligible infants who were consecutively treated with iNO. They showed that all patients who were treated with iNO for longer than 48 hours (59%, 52/88 infants) survived without requiring ECMO therapy. However, not all infants with hypoxemic respiratory failure respond to iNO therapy [12-15]. In the Truog et al study [12], for instance, 41% of patients (36/88 infants) eventually had to be given ECMO after being treated for few hours (up to 48 hours) with iNO. The question is if an early response to iNO therapy could signal the need for either ECMO therapy or continuation of the iNO treatment. Our data demonstrate that the magnitude of the response to iNO therapy within the first 4 hours can identify at least 50% of the patients who need an early ECMO therapy. Statistically, patients with OI of more than 20 or AaO_2 gradient of more than 600 mm Hg at 4 hours of iNO therapy have a relative risk of requiring ECMO therapy of 7 and 4.5, respectively. Therefore, this observation may be particularly helpful as a guide for health-care facilities without ECMO services, indicating the need for a rapid transport of such patients to an ECMO center.

Our data are consistent with previous observations demonstrating that iNO can rapidly increase oxygenation in the presence of severe PPHN and systemic hypoxemia without causing systemic hypotension or other adverse effects [4-12]. In a retrospective study involving 30 infants and children (age, 1 month–13 years) with severe hypoxemic respiratory failure, Goldman et al [14] demonstrated that early exposure to iNO appears to be associated with improved outcome and may serve as a bedside marker of disease stage. In our study, 29% of patients responded to iNO therapy with lasting improvement in oxygenation, thereby eliminating the need for ECMO therapy. Of 34 patients, 18 (53%) did not adequately respond to iNO therapy and deteriorated within 1 to 10 hours and had to be given ECMO therapy (Fig. 1). A smaller group of 6 patients (18%) responded to iNO therapy for up to 2 to 4 days before an abrupt deterioration in oxygenation, which required ECMO therapy. The reason(s) why oxygenation in this subgroup of patients deteriorated after a long period of iNO therapy, despite a positive response to iNO during the first 4 hours of therapy, cannot be determined. Interestingly, however, the 6 patients in the late ECMO therapy group, on the average, had significantly higher MAP both on arrival and within 4 hours after iNO treatment (Table 2). Moreover, the initial OI (baseline) in the late ECMO therapy group was significantly higher than in the iNO therapy patients ($P < .05$, comparing 63.0 ± 27 with 31.4 ± 7.7, respectively; ANOVA followed by Tukey-Kramer multiple comparison test).

In the early ECMO therapy patients, the differences in OI and AaO_2 gradients between them and those with sustained response to iNO treatment were remarkable (Fig. 2). The early ECMO therapy group of patients did not significantly reduce their OI and/or AaO_2 gradients in response to iNO therapy, whereas both oxygenation indices were significantly reduced within a 4-hour period in patients who did not require ECMO therapy. The initial OI of patients with iNO therapy was about 26% less than those who required early ECMO therapy ($P > .05$) and was 50% less than those with the late ECMO requirement ($P < .05$). These observations may imply that, perhaps, patients with initially lower OI could be a better candidate for a continuous iNO therapy, whereas patients with very high OI may eventually need ECMO therapy, despite an initial positive response to iNO therapy (Table 2).

In our study, 29% of patients who were referred for ECMO were successfully treated with iNO alone. This is in

close agreement with the prospective study by Biban et al [7] in which 8 (40%) of 20 patients, who met the criteria for ECMO, were treated with iNO alone. However, our success rate of 29% for iNO therapy differs from a much higher rate of 59% reported by Truog et al [12], demonstrating that most of the infants who were primarily eligible for ECMO therapy had no need for it after having variable periods of iNO therapy. A possible explanation for a higher rate of success of iNO therapy in Truog et al study [12], as compared with our data, could be related to the different types of studies, which were retrospective and prospective, respectively. Extracorporeal membrane oxygenation centers may treat a mixed group of both outborn and inborn patients. Although our patients were all outborn neonates, our results are consistent with a meta-analysis study reporting that the need for ECMO could be reduced by iNO therapy (relative risk, 0.73; 95% confidence interval, 0.6-0.9) in a mixed group of neonates with PPHN [16].

Consistent with our observation, Truog et al [12] also found that younger neonates with hypoxic respiratory failure may not respond as positively to iNO therapy as well as the older neonates. Moreover, responses to iNO in our study were similar to observations reported by Goldman et al [13], except that we did not have patients who were dependent on iNO therapy for a long-term period. This may be due to the absence of any patients with pulmonary hypoplasia or dysplasia in our patients.

4.1. Study limitations

A relatively small number of patients in our study may limit its power. Statistically, using proportions of patients with iNO therapy and those who qualified for ECMO therapy (both early and late), we found a relatively low power of 46% (n = 11 and n= 23, respectively; 2-tail χ^2 test with type I error of 5%). Furthermore, our study took place at a time when the initial doses of iNO therapy was different from current practice, as reflected on a relatively high dose of 80 ppm that was initially used in our patients. Recent studies indicate that an initial dose of 20 ppm appears to be optimum [6,17]. In fact, a neonatal iNO study group [6] has demonstrated that only 3 of 53 infants who did not respond initially to 20 ppm responded to a higher iNO dose, up to 80 ppm. Initial doses of iNO, lower than 20 ppm, may diminish the clinical response and have adverse clinical sequelae [18]. In a randomized double-blind study, Davidson et al [19] found no differences in response among groups that were treated with 5, 20, or 80 ppm of iNO. In the same study [19], however, 80 ppm iNO resulted in a higher methemoglobin and nitrous oxide level.

In conclusion, our data confirm previous reports indicating that neonatal iNO treatment during hypoxemic respiratory failure can reduce the need for ECMO therapy. However, lack of an early response to iNO treatment (within a few hours) in patients who are referred for ECMO therapy and younger age at the time of presentation may indicate the need for ECMO therapy at least in 50% of patients with hypoxic respiratory failure.

References

[1] Weigel TJ, Hageman JR. National survey of diagnosis and management of persistent pulmonary hypertension of the newborn. J Perinatol 1990;10:369-75.

[2] Dworetz AR, Moya FR, Sabo B, et al. I. Survival of infants with persistent pulmonary hypertension without extracorporeal membrane oxygenation. Pediatrics 1989;84:1-6.

[3] UK Collaborative ECMO Trail Group. UK collaborative randomized trial of neonatal extracorporeal membrane oxygenation. Lancet 1996;348:75-82.

[4] Roberts Jr JD, Fineman JR, Morin III FC, et al. Inhaled nitric oxide and persistent pulmonary hypertension of the newborn. The Inhaled Nitric Oxide Study Group. N Engl J Med 1997;336:605-10.

[5] Hoffman GM, Ross GA, Day SE, et al. Inhaled nitric oxide reduces the utilization of extracorporeal membrane oxygenation in persistent pulmonary hypertension of the newborn. Crit Care Med 1997; 25:352-9.

[6] The Neonatal Inhaled Nitric Oxide Study Group. Inhaled nitric oxide in full-term and nearly full-term infants with hypoxic respiratory failure. N Engl J Med 1997;336:597-604.

[7] Biban P, Trevisanuto D, Pettenazzo A, et al. Inhaled nitric oxide in hypoxaemic newborns who are candidates for extracorporeal life support. Eur Respir J 1998;11:371-6.

[8] Lonnqvist PA. Efficacy and economy of inhaled nitric oxide in neonates accepted for extra-corporeal membrane oxygenation. Acta Physiol Scand 1999;167:175-9.

[9] Christou H, Van Marter LJ, Wessel DL, et al. Inhaled nitric oxide reduces the need for extracorporeal membrane oxygenation in infants with persistent pulmonary hypertension of the newborn. Crit Care Med 2000;28:3722-7.

[10] Clark RH, Kusser TJ, Walker MW, et al. Low-dose nitric oxide therapy for persistent pulmonary hypertension of the newborn. Clinical Inhaled Nitric Oxide Research Group. N Engl J Med 2000; 342:469-74.

[11] Finer NN, Barrington KJ. Nitric oxide therapy for the newborn infant. Semin Perinatol 2000;24:59-65.

[12] Truog WE, Castor CA, Shellield MJ. Neonatal nitric oxide use: predictors of response and financial implications. J Perinatol 2003; 23:128-213.

[13] Goldman AP, Tasker RC, Haworth SG, et al. Four patterns of response to inhaled nitric oxide for persistent pulmonary hypertension of the newborn. Pediatrics 1996;98:706-13.

[14] Goldman AP, Tasker RC, Hosiasson S, et al. Early response to inhaled nitric oxide and its relationship to outcome in children with severe hypoxemic respiratory failure. Chest 1997;12:752-8.

[15] Day RW, Lynch JM, White KS, et al. Acute response to inhaled nitric oxide in newborns with respiratory failure and pulmonary hypertension. Pediatrics 1996;98:698-705.

[16] Oliveira CA, Troster EJ, Pereira CR. Inhaled nitric oxide in the management of persistent pulmonary hypertension of the newborn: a meta-analysis. Rev Hosp Clin Fac Med Sao Paulo 2000;55:145-54.

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

[18] Cornfield DN, Maynard RC, deRegnier RA, et al. Randomized, controlled trial of low-dose inhaled nitric oxide in the treatment of term and near-term infants with respiratory failure and pulmonary hypertension. Pediatrics 1999;104:1089-94.

[19] Davidson D, Barefield ES, Kattwinkel J, et al. Inhaled nitric oxide for the early treatment of persistent pulmonary hypertension of the term newborn: a randomized, double-masked, placebo-controlled, dose-response, multicenter study. The I-NO/PPHN Study Group. Pediatrics 1998;101:325-34.