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Clinical Response to Inhaled Nitric Oxide in Persistent Pulmonary Hypertension of the Newborn

We observed clinical response to inhaled nitric oxide (iNO) in 12 neonates with persistent pulmonary hypertension of the newborn (PPHN). Clinical response was defined as a decrease in oxygenation index (OI) by 40%. Ten of 12 neonates had response to iNO showing decrease OI from 46.1±7.6 to 14.4±6.8 at 1 hour after inhalation. Sustained improvement of OI was achieved in 8 neonates and two neonates were relapsed. In the group of neonates who had OI above 40 (n=7), 6 of them showed the decrease of OI from 66.1±4.8 to 18.3± 8.0 at 1 hour. In two groups, one had OI of 40 or greater, and the other OI of 40 or less, there were no differences in pattern of response and early death rate. The response rates according to underlying diseases were as follows; idiopathic PPHN 100%, respiratory distress syndrome 100%, and diaphragmatic hernia 66.7%. Relapse was observed in one neonate with sepsis caused by pneumonia and in one infant with meconium aspiration syndrome. Two infants showed no response to iNO (one diaphragmatic hernia and one suspected pulmonary hypoplasia). We conclude that iNO therapy could improve oxygenation in high percentage of newborn infants with severe PPHN of various underlying conditions except pulmonary hypoplasia.

Key Words : *Persistent pulmonary hypertension of the newborn; Respiratory therapy; Nitric oxide*

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INTRODUCTION

Persistent pulmonary hypertension of the newborn (PPHN) is a clinical syndrome, which has unknown causes in most cases. It has developed pulmonary hypertension, resulting R-L shunt through patent ductus arteriosus or patent foramen ovale. These R-L shunt related to increased pulmonary vascular resistance cause critical hypoxemia. On the other hand, various pulmonary disorders, such as meconium aspiration syndrome, pneumonia, pulmonary hypoplasia, and respiratory distress syndrome form intrapulmonary R-L shunt and cause severe hypoxic respiratory failure (1-3). Current therapies (4) with good oxygenation, alkalization, and vasodilation for PPHN are aimed at lowering pulmonary vascular resistance. For the cases of no response to these managements, extracorporeal membrane oxygenation (ECMO) should be considered. Vasodilator drug therapies have been limited by the lack of the pharmacologic agents with selective and sustained pulmonary vasodilating effects without adverse systemic hemodynamic actions (4). Moreover they are not effective for severe parenchymal lung disease and systemic hemodynamic collapse. Also ECMO which is a very expensive and invasive procedure has many limitations (5). The results of all these therapies are not favorable. It has been reported that the incidence of residual lung disease and neurologic sequelae was high in infants survived from PPHN (6, 7).

Recent studies have suggested that endogenous vasodilator NO might be a key factor responsible for the decline of pulmonary vascular resistance at birth and that decreased production of endogenous NO caused by endothelial dysfunction may play a critical role in the evolution of PPHN (8-10). Therefore, exogenous NO in the form of iNO gas has been regarded as an attractive new selective pulmonary vasodilator in the management of PPHN. After early reports of effective NO therapy in PPHN (11, 12), many clinical trials have been following.

We previously demonstrated that iNO could selectively lower the pulmonary artery pressure in the newborn piglet with induced hypoxic pulmonary hypertension (13). And as the first clinical report in Korea, we successfully treated 2 cases with PPHN after surgical repair of congenital diaphragmatic hernia by using iNO

(14). The objectives of this study were to observe the acute effect and safety of iNO and to evaluate the pattern of response in severe PPHN of various causes.

MATERIALS AND METHODS

Study population

Between October 1995 and April 1997, 12 newborn infants with severe PPHN were enrolled in this study. PPHN was defined by the echocardiographic evidence of pulmonary hypertension based on the presence of right-to-left shunt at ductus arteriosus or foramen ovale, or the estimated right ventricular systolic pressure greater than 75% of the systemic systolic blood pressure, or by the clinical evidence of difference in oxygen saturation more than 10% between pre- and postductal circulation.

As initial treatment of PPHN, we started with conventional mechanical pressure-limited ventilator (Infant Star, Infrasonics Inc. USA), inotropic agents (dopamine and dobutamine) and sedating drugs (fentanyl, midazolam) with occasional paralysis with pancuronium. In the case of treatment failure with these managements, we changed the ventilator to high frequency oscillatory ventilator (HFOV, SensorMedics 3100A, Metran Humming V). iNO therapy was introduced to the twelve neonates with PPHN who failed to improve oxygenation with full conservative management.

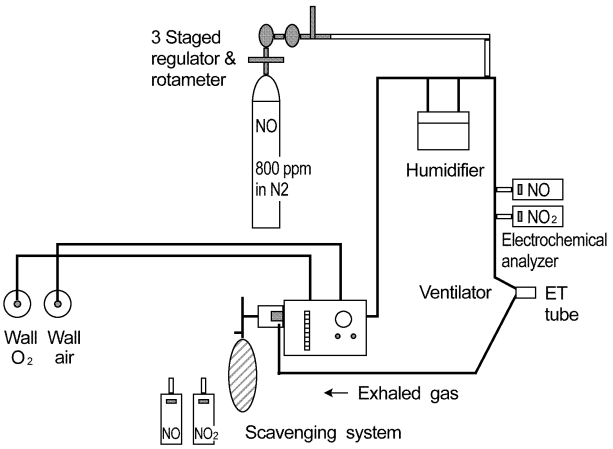

Fig. 1. Diagram of NO delivery system with mechanical ventilator: NO in nitrogen gas was injected into the inspiratory line above humidifier of ventilator with a regulated pressure after passing 3 staged regulator. The concentrations of NO and NO_2 in the inspiratory limb of the circuit of ventilator just before entry to the E-tube were monitored by using electrochemical analyzer. The concentrations of NO and NO_2 around the air of expiratory line of ventilator were also measured.

Administration and monitoring of iNO

The NO gas was obtained as a gas in balance nitrogen in a concentration of approximately 800 ppm (Korea Industrial Gases). This source is certified to be under 2% error of the analyzed component (NO) and to contain less than 5 ppm nitrogen dioxide. For NO gas delivery, we used Massmixer (Metran, Japan) delivery system and three staged stainless steel diffusion-free regulators specially invented at the Department of Medical Engineering of Samsung Medical Center (Fig. 1, source; J Kor Pediatr Soc 1997;40:1397). NO source gas was connected at a regulated pressure by means of teflon tubing to the input port of the flowmeter and was then injected at the desired flow rate into the inspiratory line of ventilator circuit by using a specially designed adapter fitted within 25 cm from the endotracheal tube, thus mixing the NO gas with the fixed flow rate of circuit gas. We gradually increased the dose of NO until the clinical response occurred, starting from 6 ppm to maximum 80 ppm, and then kept the lowest effective dose of iNO. The gas mixture sampled from the site between the entry to the inspiratory circuit and the infant's endotracheal tube was analysed for nitric oxide and nitrogen dioxide with electrochemical analysers (Pulmonox, Draeger, USA). We kept the level of nitrogen dioxide less than 5 ppm. During iNO therapy, monitoring of arterial blood methemoglobin concentration was done every 24 hours with a co-oximeter model IL-482 (Instrumentation Laboratory Co. Italy).

Outcome measures

PaO_2 and associated FiO_2, ventilator settings, and oxygenation index (OI; percent inspired oxygen × mean airway pressure/descending aortic oxygen tension) were recorded at baseline, 0.5, 1, 2, 6, 12, 24, 48, 72 hr after iNO administration.

Reduction of OI of 40% or more after iNO was defined as clinical response. The pattern of response was categorized as rapid, intermediate, and delay according to the time of clinical response, within 1 hour, within 6 hours and after 6 hours, respectively. Those cases who had shown initial clinical response and then deteriorated were classified as "relapses".

RESULTS

Characteristics of patients

Twelve newborn infants with a broad spectrum of diagnosis within the clinical entity of PPHN were given

Table 1. Demographic data on the 12 neonates with PPHN studied

Patient	BW (g)	GA (week)	Diagnosis	Baseline OI	OI at initial response	NO (ppm) at initial response	Duration of iNO (hour)	Outcome
Rapid responders (n=7)								
1.	3,800	41^{+1}	CDH	81	17.9	67	384	dead$^{\dagger 1}$
2.	3,370	39	CDH	68	11.8	12	84	survived
3*.	2,900	39	Pn	13.2	3.3	36	29	dead$^{\dagger 2}$
4.	4,190	40	idiopathic	20.8	5.3	12	72	AMA$^{\dagger 3}$
5.	2,540	36^{+5}	idiopathic	62	11.7	50	5	dead†
6.	3,360	39^{+3}	RDS	68	8.4	6	120	survived
7.	3,070	36^{+5}	idiopathic	44.7	8.7	9	30	survived
Intermediate responders (n=2)								
8.	1,769	31^{+2}	RDS	36.8	17.6	24	30	survived
9.	824	26^{+2}	RDS	51.4	29.7	36	240	AMA$^{\dagger 3}$
Delayed responder (n=1)								
10*.	3,660	40	MAS	15.4	6.9	15	316	survived
Nonresponders (n=2)								
11.	3,355	41	CDH	24.3	-	-	72	dead†
12.	3,350	40^{+4}	lung hypoplasia	39.8	-	-	24	dead†

Abbreviations: CDH, congenital diaphragmatic hernia; Pn, pneumonia; RDS, respiratory distress syndrome; MAS, meconium aspiration syndrome; idiopathic, idiopathic PPHN.
*: relapse, †: early death due to PPHN itself, †: late death after recovery from PPHN (the causes of deaths; 1. Respiratory-Syncytial virus pneumonia 2. post-operative sepsis 3. discharge against medical advice).

a trial of iNO between October 1995 and April 1997. Their mean gestational age and birth weight were 37.5 $\pm$1.3 weeks (range; 26.2-41.1 weeks) and 3016$\pm$268 kg (range; 824-4190 kg). Four neonates were premature babies. The underlying diseases of PPHN were as follows; idiopathic PPHN (n=3), respiratory distress syndrome (n=3), congenital diaphragmatic hernia (n=3), meconium aspiration syndrome (n=1), sepsis with pneumonia (n=1), and suspected pulmonary hypoplasia (n=1) (Table 1). The mean baseline OI was 44.1$\pm$7.9 (range; 13.2-81) and seven neonates had baseline OI greater than 40 (Table 2).

Table 2. Pattern of response according to baseline OI

	OI > 40 (n=7)	OI < 40 (n=5)	p value
Baseline OI (mean$\pm$SE)	66.1$\pm$4.8	22.1$\pm$4.2	
Response (n)	6	4	NS
rapid	5	2	NS
intermediate	1	1	NS
delayed	-	1	
Relapse after response	-	2	
No respose (n)	1	1	NS
Early death*(n)	2	1	NS

*: death due to PPHN itself.
NS: no significant difference between two groups p>0.05 by Fischer's exact test.

Initial response to iNO

Ten (83.3%) out of 12 neonates had shown successful initial response to iNO therapy. Seven neonates showed rapid response, two intermediate, one delayed response. The mean OI was decreased from 52.2$\pm$11.5 to 14.4$\pm$6.8, from 44.1$\pm$7.3 to 22.9$\pm$6.8, and from 15.4 to 6.9 in rapid, intermediate, and delayed response group, respectively. Percent reduction in OI of rapid and intermediate response groups were shown in Fig. 2. One with rapid response and one with delayed response were relapsed, therefore sustained response rate was 80% (8 out of 10 initial responders).

Response according to baseline OI

Seven neonates had baseline OI greater than 40. Six out of those seven (6/7, 86%) had immediate decrease in OI from 66.1$\pm$4.8 to 18.3$\pm$8.0 at 1 hr and all of them had sustained improvement in oxygenation. The other 5 neonates had OI of less than 40, and their mean OI was 22.1$\pm$4.2. They showed various responses; rapid, intermediate, delayed response, relapse, or nonresponse. But between the two groups (initial OI greater than 40 or less than 40), there were no significant differences in response patterns and early death rate related to PPHN (Table 2).

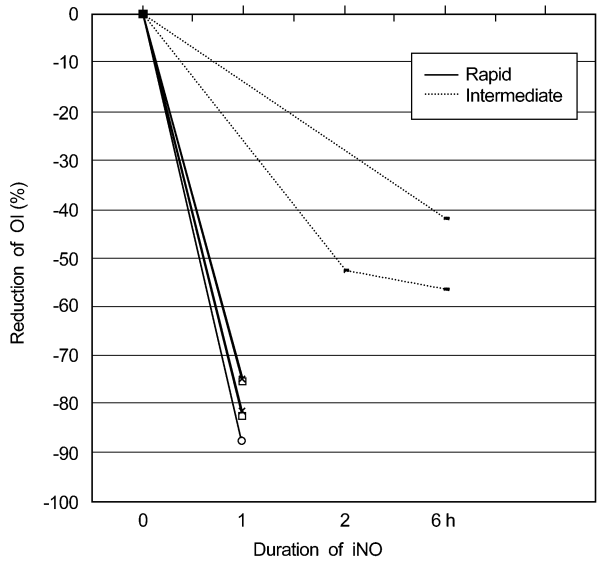

Fig. 2. Reduction of OI in rapid and intermediate responsers.

Response according to underlying diseases

Among our 12 neonates, there were three idiopathic PPHN patients. All of them showed immediate and sustained improvements in oxygenation. There were 3 respiratory distress syndrome patients; one was rapid responder and two were intermediate responders. There was one neonate who had sepsis with pneumonia and one neonate with meconium aspiration syndrome. But these two showed only initial response and relapsed. There were 3 neonates with congenital diaphragmatic hernia. Two of them showed rapid and sustained response and one of them did not respond. The last one with suspected pulmonary hypoplasia did not show improvement in systemic oxygenation.

Clinical outcome

Inhalation therapy of NO was started at 30.5±12.2 hr after birth in average. The mean duration of inhalation was 4.6±1.4 days; 5.1±1.6 day in responders and 2.0 ±1.0 days in non-responders. The longest therapy lasted for 16 days in one newborn infant with congenital diaphragmatic hernia. Mortality rate of PPHN in acute phase was 25% (three out of 12 died). Three neonates, i.e., two pulmonary hypoplasia and one idiopathic PPHN with complicated pneumothorax died due to PPHN before the recovery from PPHN. The acute stage mortality rate was 28.6% (2/7) in newborn infants with baseline OI greater than 40. Four neonates died after recovery from PPHN. The causes of this late mortality were Respiratory-Syncytial virus pneumonia, post-operative sepsis and discharge against medical advice (Table 1). During iNO therapy, there were no significant adverse effects on systemic circulation or hemoglobin metabolism. No one in this study had a systemic hypotension or methemoglobin level of more than 3%. The mean methemoglobin concentration was 2.4±0.6%.

DISCUSSION

Our study with 12 neonates showed that inhaled nitric oxide improved gas exchange immediately in most cases of PPHN. All patients except two cases with pulmonary hypoplasia had a marked initial improvement in oxygenation in response to iNO. In our study, 86% of the patients who had baseline OI greater than 40 had acute and sustained improvement in systemic oxygenation, and their mortality rate associated with PPHN was only 29%. Usually, the patients with OI greater than 40 predicted a risk of mortality of approximately 80 percent (15).

NO inhalation therapy has been used recently after a report of that EDRF is NO (16, 17). Recent studies indicate that severe hypoxemia or increased vascular resistance may directly impede the release of nitric oxide, possibly contributing to PPHN (18). So inhalational NO therapy appears to offer a possible alternative to the traditional treatment for PPHN without devastating side effects and hazards commonly seen with intravenous agents and conventional mechanical ventilation. In 1991 short-term NO treatment was tried in newborn babies by Robert et al. (11). Kinsella et al. (12) reported iNO treatment on nine newborns with PPHN who were ECMO candidates. In that report, six patients had sustained improvement in oxygenation and did not require ECMO (12). We saved 70% patients among the patients who would be ECMO candidates with OI greater than 40 by our iNO treatment.

When administered by inhalation, NO diffuses to vascular smooth muscle from the alveolar side. Rapid and avid binding of NO by hemoglobin decreases its availability for causing systemic vasodilation, allowing for selective pulmonary vasodilation (19). In addition, because NO is administered by inhalation, it will most effectively dilate pulmonary blood vessels that are associated with the best-ventilated lung units, enhancing ventilation-perfusion matching (20). In our study, systemic oxygenation was not collectively improved in patients with lung hypoplasia or patients with severe diffuse lung disease, such as meconium aspiration syndrome and pneumonia. Therefore, oxygenation improvement were noted with inhaled nitric oxide to a greater extent in patients with well-aerated lung lesions because of an improved match

in ventilation and perfusion. Karamanoukan et al. reported a patient with congenital hypoplasia of the lungs due to diaphragmatic hernia or oligohydramnios who did not respond to inhaled nitric oxide (21). Our patients with suspected pulmonary hypoplasia and congenital diaphragmatic hernia were not improved oxygenation at inhalational NO therapy and died.

Although the optimal roles for high-frequency oscillatory ventilation and NO in PPHN treatment are unclear, some patients appear to benefit from combined treatment. In randomized trial comparing NO plus intermittent mandatory ventilation and HFOV by Waffarn, there was a higher response rate in NO/HFOV group (22). In our study, all patients received high-frequency oscillatory ventilation, so we were not able to comment the effect and role of HFOV in treatment of PPHN. But we could not exclude the therapeutic effect of HFOV on NO treatment in this study because of a higher response rate and survival rate than those in any other study.

Progressive deterioration after surfactant therapy occurs in subsets of premature neonates with respiratory distress syndrome (RDS), leading to severe pulmonary hypertension with right-to-left shunting across the ductus arteriosus (23). Kinsella et al. reported that NO lowered pulmonary vascular resistance and improved gas exchange in severe experimental hyaline membrane disease (24). This suggested that an early use of low-dose inhaled NO could play a role in the management of premature infants with severe respiratory failure unresponsive to exogenous surfactant therapy. In our present study, there were three patients with RDS, and one neonate improved oxygenation within 1 hour and the other two within 6 hours. One neonate with RDS had chronic lung change, who received 19-day ventilator care and 36- day oxygen therapy. But potential pulmonary and systemic toxic effects of NO in premature infants are unknown. So we should use NO treatment in premature infants carefully and further studies about such side effects in premature subjects are needed.

There has been little data published concerning response time to inhaled NO in PPHN patients. Earlier reports described patients with an immediate and sustained improvement in oxygenation within 15 to 30 min of starting NO inhalation (11, 12). In our study, there were 10 patients with initial response, among 10 responders, seven patient showed a decreased OI within 1 hour. Turbow et al. reported that variable oxygenation response was shown in severe PPHN (25). According to the report of Turbow (25), infant with meconium aspiration syndrome had a variable response time to NO, which is likely related to the complex etiologies of their hypoxemia. Patients with MAS often have obstructive airway disease and severe parenchymal lung disease. This can lead to diffusion block and ventilation/perfusion mismatch, therefore NO may not effectively restore the ventilation-perfusion relationship across atelectatic or edematous respiratory units (26). In our study, one newborn infant with meconium aspiration syndrome was a delayed responder, but later relapsed. One neonate with sepsis caused by pneumonia had an immediate response to iNO but later relapsed. Therefore, decreased cardiac performance and changes in systemic vascular resistance may play a role in refractory hypoxemia associated sepsis (27). In our study, there were 7 neonates with OI greater than 40 and 5 neonates with OI less than 40. Between the two groups, there were no difference in number of responders, rapid responders, nonresponders, and death related to PPHN. So we thought that OI before iNO treatment did not influence the pattern of response to iNO therapy in PPHN.

Although many pharmacologic vasodilators such as prostacyclin and sodium nitroprusside are also capable of lowering pulmonary vascular resistance, these agents often lower systemic arterial pressure and decrease oxygenation in the presence of parenchymal lung disease by aggravating ventilation-perfusion mismatch (28). No infant showed systemic hypotension during iNO in our study.

The principal concerns with toxicity of iNO therapy relate to the direct and indirect effects of NO and its metabolites. NO therapy is known to have side effects such as severe acute pulmonary edema by nitrogen dioxide, potent oxidant, methemoglobinemia and platelet dysfunction. It is essential that gas is monitored during therapy. There are chemiluminescence and electrochemical monitoring devices. The ideal monitoring device of NO & NO_2 should be small and quiet, and provide precise, continuous real-time analysis with minimal sampling volumes (29). We used an electrochemical monitoring device. It is smaller and less expensive, for either nitric oxide or nitrogen dioxide available, and free of the problems associated with large aspirating volumes. We kept the level of nitrogen dioxide at less than 5 ppm. During iNO treatment, methemoglobin concentration in blood was less than 3% in all cases and there was no side effect such as a methemoglobinemia.

According to recent multicenter trials by neonatal inhaled nitric oxide study group (30, 31), inhaled NO improved systemic oxygenation in infants with PPHN and hypoxic respiratory failure, and reduced the needs for ECMO, but had no apparent effect on mortality. ECMO remains the choice of therapy for severe PPHN when other therapy fails. But ECMO procedure is difficult to perform in terms of technique, cost, equipment, and experience in many clinical settings. Therefore, we believe that iNO can be a very effective and relatively safe treat-

ment modality in severe PPHN with easy application. Also, from our clinical study, we have learned that there are different patterns of response and survival rates in sub-group according to the cause of PPHN. Therefore, when we consider these results for the management of PPHN, NO therapy will be more effective in clinical application.

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REFERENCES

1. Gersony WM, Duc GV, Sinclair JC. *"PFC" syndrome (persistent of the fetal circulation). Circulation 1969; 40(Supp13): 87.*
2. Gersony WM. *Neonatal pulmonary hypertension: pathophysiology, classification and etiology. Clin Perinatol 1984; 11: 517-24.*
3. Drummond WH, Peckam GJ, Fox WW. *The clinical profile of the newborn with persistent pulmonary hypertension. Clin Pediatr 1977; 16: 335-41.*
4. Roberts JD, Shaul PW. *Advances in the treatment of persistent pulmonary hypertension of the newborn. Pediatr Clin North Am 1993; 40: 983-1004.*
5. Bartlett RH, Roloff DW, Cornell RG, Andrews AF, Dillon PW, Zwischenberger JB. *Extracorporeal circulation in neonatal respiratory failure; a prospective randomized study. Pediatrics 1985; 76: 479-87.*
6. Hageman JR, Adams MA, Gardner TH. *Pulmonary complications of hyperventilation therapy for persistent pulmonary hypertension. Crit Care Med 1985; 13: 1013-4.*
7. Hofkosh PE, Thompson AE, Nozza RJ. *Ten years of extracorporeal membrane oxygenation. Pediatrics 1991; 87: 549-55.*
8. Abman SH, Chatfield BA, Rodman DM, Hall SL, McMurty IF. *Role of endothelium-derived relaxing factor during transition of pulmonary circulation at birth. Am J Physiol 1990; 259: H1921-7.*
9. Davidson D, Eldermedash A. *Endothelium-derived relaxing factor: evidence that it regulates pulmonary vascular resitance in the isolated newborn guinea pig lung. Pediatr Res 1991; 29: 538-42.*
10. Tiktinsky MN, Morin FC. *Increasing oxygen tension dilates fetal pulmonary circulation by endothelium-derived relaxing factor. Am J Physiol 1993; 265: H376-80.*
11. Roberts JD, Polander DM, Lang P, Zapol WM. *Inhalational nitric oxide in persistent pulmonary hypertension of the newborn. Lancet 1992; 340: 818-9.*
12. Kinsella JP, Neish SR, Abman SH. *Low-dose inhalational nitric oxide in persistent pulmonary hypertension of the newborn. Lancet 1992; 340: 819-20.*
13. Chang YS, Park WS, Choi JH, Yun CK. *Hemodynamic effect of nitric oxide inhalation in the acute hypoxic pulmonary hypertension induced newborn piglet. J Korean Pediatr Soc 1997; 40: 1394-409.*
14. Chang YS, Kang IS, Park WS, Lee SK, Kim HH, Lee HJ. *Two cases of nitric oxide inhalation for treatment of severe pulmonary hypertension after surgical repair of congenital diaphragmatic hernia. J Korean Pediatr Soc 1996; 39: 1611-9.*
15. Walsh-Sucks MC. *Persistent pulmonary hypertension of the newborn; the black box revisited. Clin Percental 1993; 20: 127-43.*
16. Palmer RAJ, Ferrite EG, Monacle S. *Nitric oxide release accounts for the biologic activity of endothelial-derived relaxing factor. Nature 1987; 327: 524-6.*
17. Ignazio LA, Barns RE, Bugs GM. *Endothelial-derived relaxing factor form pulmonary artery and vein possesses pharmacologic and chemical properties identical to those of nitric oxide radical. Cir Res 1987; 61: 866-79.*
18. Rodman DA. *Effects of hypnosis on endothelial-dependent relaxation of rat pulmonary artery. Am J Physiol 1990; 258: 1207-14.*
19. Roberts AD, Planer DA, Toadery ID, Lang P, Zapol WM. *Inhaled nitric oxide (NO): a selective pulmonary vasodilator for the treatment of persistent pulmonary hypertension of the newborn (PPHN). Circulation 1991; 84: A1279.*
20. Ronald WD, Joanna ML, Keith SW, Robert MW. *Acute response to inhaled nitric oxide in newborns with respiratory failure and pulmonary hypertension. Pediatrics 1996; 98: 698-705.*
21. Karamanoukian HL, Glick PL, Zayek M, Steinhorn RH, Zwass MS, Fienman JR, Morin FC. *Inhaled nitric oxide in congenital hypoplasia of lungs due to diaphragmatic hernia or oligohydramnios. Pediatrics 1994; 94: 715-8.*
22. Waffarn F, Turbow R, Yang L, Sills J, Hallman M. *Treatment of persistent pulmonary hypertension of the newborn: a randomized trial comparing intermittent mandatory ventilation and high frequency oscillatory ventilation for delivery nitric oxide. Pediatr Res 1995; 37: 243A.*
23. Evans NJ, Archer LNJ. *Doppler assessment of pulmonary artery pressure and extrapulmonary shunting in the acute phase of hyaline membrane disease. Arch Dis Child 1991; 66: 6-11.*
24. Abman SH, Kinsella JP, Schaffer MS, Wilkening RB. *Inhaled nitric oxide therapy in a premature newborn with severe respiratory distress and pulmonary hypertension. Pediatrics 1993; 92: 606-9.*
25. Turbow R, Waffarn F, Yang L, Sills J, Hallman M. *Variable oxygenation response to inhaled nitric oxide in severe persistent pulmonary hypertension of the newborn. Acta Paediatr 1995; 84: 1305-8.*
26. Kinsella JP, Neish SR, Ivy DD, Shaffer E, Abman SH. *Clin-*

ical responses to prolonged treatment of PPHN with low doses of inhaled NO. J Pediatr 1993; 123: 103-8.

27. Szabo C, Thiemermann C, Wu C, Perretti M, Vane J. *Attenuation of the induction of nitric oxide synthase by endogenous glucocorticoids account for endotoxin tolerance in vivo. Proc Natl Acad Sci USA 1994; 91: 271-5.*
28. Radermacher P, Santak P, Becker H, Falke KJ. *Prostaglandin E1 and nitroglycerin induced pulmonary capillary pressure but worsen V/Q distribution in patient with adult respiratory distress syndrome. Anesthesiology 1989; 70: 601-9.*
29. Wessel DL, Adatla I, Thompson JE, Hickey PR. *Delivery and monitoring of inhaled nitric oxide in patients with pulmonary hypertension. Crit Care Med 1994; 22: 930-8.*
30. 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.*
31. The Inhaled Nitric Oxide Study Group. *Inhaled nitric oxide and persistent pulmonary hypertension of the newborn. N Engl J Med 1997; 336: 605-10.*