

INHALED NITRIC OXIDE AND PERSISTENT PULMONARY HYPERTENSION OF THE NEWBORN

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**ABSTRACT**

**Background** Persistent pulmonary hypertension of the newborn causes systemic arterial hypoxemia because of increased pulmonary vascular resistance and right-to-left shunting of deoxygenated blood. Inhaled nitric oxide decreases pulmonary vascular resistance in newborns. We studied whether inhaled nitric oxide decreases severe hypoxemia in infants with persistent pulmonary hypertension.

**Methods** In a prospective, multicenter study, 58 full-term infants with severe hypoxemia and persistent pulmonary hypertension were randomly assigned to breathe either a control gas (nitrogen) or nitric oxide (80 parts per million), mixed with oxygen from a ventilator. If oxygenation increased after 20 minutes and systemic blood pressure did not decrease, the treatment was considered successful and was continued at lower concentrations. Otherwise, it was discontinued and alternative therapies, including extracorporeal membrane oxygenation, were used.

**Results** Inhaled nitric oxide successfully doubled systemic oxygenation in 16 of 30 infants (53 percent), whereas conventional therapy without inhaled nitric oxide increased oxygenation in only 2 of 28 infants (7 percent). Long-term therapy with inhaled nitric oxide sustained systemic oxygenation in 75 percent of the infants who had initial improvement. Extracorporeal membrane oxygenation was required in 71 percent of the control group and 40 percent of the nitric oxide group (P=0.02). The number of deaths was similar in the two groups. Inhaled nitric oxide did not cause systemic hypotension or increase methemoglobin levels.

**Conclusions** Inhaled nitric oxide improves systemic oxygenation in infants with persistent pulmonary hypertension and may reduce the need for more invasive treatments. (N Engl J Med 1997;336:605-10.)

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**I**NFANTS with persistent pulmonary hypertension have severe cyanosis even when they breathe high concentrations of oxygen. Although the pulmonary hypertension can be associated with other conditions (such as aspiration of meconium and sepsis), it may be idiopathic. Cardiac ultrasonography often reveals shunting of venous blood to the systemic circulation through the ductus arteriosus and the foramen ovale and no structural heart disease. Treatment with high fractions of inspired

oxygen (FiO<sub>2</sub>) and mechanical ventilation improves oxygenation in some infants with pulmonary-artery hypertension, but in many others it does not. Unless other treatments are used, the infants often die. Although intravenous therapy with vasodilator drugs has been used for pulmonary hypertension, it often causes dilation of the systemic circulation and severe hypotension. Extracorporeal membrane oxygenation can save the lives of some infants with severe pulmonary hypertension, but it requires anticoagulation and cannulation of the great vessels, causes important morbidity, and is unavailable at many intensive care nurseries.

Inhaled nitric oxide causes selective pulmonary vasodilation.<sup>1</sup> It diffuses into vascular smooth-muscle cells in the lungs, where it increases concentrations of cyclic guanosine monophosphate, causing vasodilation. Inhaled nitric oxide does not cause systemic hypotension when it diffuses into the intravascular space, because it is inactivated by avid binding to hemoglobin. We previously reported that breathing nitric oxide at a concentration of 5 to 80 parts per million (ppm) completely reversed hypoxic pulmonary vasoconstriction in newborn lambs,<sup>2</sup> and breathing nitric oxide increases oxygenation<sup>3</sup> and survival<sup>4</sup> in lambs with persistent pulmonary hypertension induced by constriction of the ductus arteriosus. Clinical studies suggest that inhaled nitric oxide reduces pulmonary hypertension in children with many forms of congenital heart disease<sup>5</sup> and in adults with primary pulmonary hypertension<sup>6</sup> or the acute respiratory distress syndrome.<sup>7,8</sup> In addition, inhaled nitric oxide increases systemic oxygenation in infants with pulmonary hypertension.<sup>9,10</sup> We therefore conducted a randomized trial in which we examined the

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effects of inhaled nitric oxide on systemic oxygenation in infants with severe hypoxemia and pulmonary hypertension.

## METHODS

This study was approved by the Subcommittee for Human Studies of Massachusetts General Hospital, the human-studies committees at the participating centers, and the Food and Drug Administration. Informed consent was obtained from each infant's family at the time of entry into the study.

The study was conducted by laboratory investigators and clinical investigators. The laboratory investigators were aware of each patient's treatment assignment, maintained a fresh supply of the gas, calibrated the system of gas delivery, recorded the methemoglobin values, and notified the principal investigator and the Data Monitoring and Safety Committee when there was any concern about safety. The clinical investigators did not know the treatment assignments, began giving the randomized study treatments using gas from identical-appearing tanks, collected data on the patients (exclusive of the methemoglobin values), and decreased the concentrations of inhaled study gas. The infants' care providers were unaware of the patients' study assignments. They adjusted the  $\text{FiO}_2$ , ventilatory and medical therapy, and made decisions about treatment with extracorporeal membrane oxygenation according to usual practice.

### Criteria for Eligibility

Newborn infants who had severe systemic hypoxemia even though they were receiving mechanical ventilation at an  $\text{FiO}_2$  of 1.0 were studied by cardiac ultrasonography to determine the cause of the shunt. They were enrolled in the study if they had pulmonary hypertension as diagnosed by echocardiography; a postductal partial pressure of arterial oxygen ( $\text{PaO}_2$ ) of 55 mm Hg or less on two consecutive determinations 30 minutes apart while mechanical ventilation was given at an  $\text{FiO}_2$  of 1.0; a full-term gestation (an estimated gestational age of  $\geq 37$  weeks and a birth weight of  $\geq 2500$  g); and catheterization of the descending aorta or a lower-extremity artery for the measurement of blood gas tensions, pH, and blood pressure. Infants were excluded from the study if they had any of the following: previous treatment with extracorporeal membrane oxygenation or high-frequency oscillatory or jet ventilation, a congenital diaphragmatic hernia or suspected lung hypoplasia, structural cardiac lesions (other than a patent ductus arteriosus), uncorrected hypotension (a mean aortic pressure below 40 mm Hg) or polycythemia (an arterial hematocrit of at least 70 percent), an unevacuated pneumothorax, or a phenotype consistent with a lethal chromosomal abnormality. Since infants who have received exogenous surfactant without sustained increases in systemic oxygenation have responses to inhaled nitric oxide similar to those of infants not previously treated with surfactant,<sup>11</sup> they were not excluded from the study.

### Study Design

#### Nitric Oxide Delivery System

Either nitric oxide gas (800 to 1000 ppm in nitrogen; Ohmeda, Cherry Hill, N.J.) or nitrogen (the control gas) was mixed with nitrogen with a gas blender as previously described.<sup>9</sup> The study mixture of gas was then introduced into the inspiratory limb of the breathing circuit of a standard continuous-flow, pressure-limited, time-cycled ventilator with a flowmeter. The  $\text{FiO}_2$  was measured by a polarographic cell placed in the inspiratory circuit distal to the point of entry of the gas. The concentration of the study gas and the  $\text{FiO}_2$  were regulated separately.

To shorten the time during which nitric oxide and oxygen resided in the breathing circuit and to reduce the accumulation of the oxidative products of nitric oxide (such as nitrogen dioxide), the overall rate of gas flow from the ventilator was kept above 10 liters per minute. Inhaled concentrations of nitric oxide and its

oxidative products were measured at the endotracheal tube by chemiluminescence.<sup>12</sup> The exhaled gases and those exiting the chemiluminescence instrument were collected with a Venturi device and discharged into the hospital's vacuum system. In previous studies, this system permitted precise concentrations of nitric oxide gas to be delivered, with low levels of oxidative products.<sup>2,9</sup>

#### Initiation of Gas Delivery

In patients with severe hypoxemia and pulmonary hypertension, the acute effects of inhaled nitric oxide on systemic oxygenation and blood pressure were compared with those of oxygen and ventilatory therapy without inhaled nitric oxide. During this evaluation period, the ventilatory and medical therapies were not changed. First, arterial-blood gas tensions, pH, blood methemoglobin levels, and systemic blood pressures were determined while the infants were receiving mechanical ventilation at an  $\text{FiO}_2$  of 1.0. Since the study gas would be administered while the infants breathed at an  $\text{FiO}_2$  of 0.9, the effect on systemic oxygenation of decreasing the  $\text{FiO}_2$  from 1.0 to 0.9 was next examined. If, after 10 minutes, the reduction in  $\text{FiO}_2$  decreased the  $\text{PaO}_2$  by 15 percent from the base-line value or if the  $\text{PaO}_2$  fell below 25 mm Hg, the  $\text{FiO}_2$  was increased to 1.0 and the infant was excluded from the study. Otherwise, the infant was randomly assigned to receive either the control gas or 80 ppm of inhaled nitric oxide at an  $\text{FiO}_2$  of 0.9 for 20 minutes, after which the  $\text{PaO}_2$  and arterial pressures were measured. In hypoxemic infants, clinical improvement occurs with increased systemic oxygenation and a decreased oxygenation index (a value calculated as  $100 \times \text{FiO}_2 \times \text{mean airway pressure} \div \text{postductal } \text{PaO}_2$ ). Treatment with either the control gas or inhaled nitric oxide was considered to be successful if it increased the  $\text{PaO}_2$  to more than 55 mm Hg, decreased the oxygenation index to less than 40, and did not decrease the mean systemic blood pressure to less than 40 mm Hg. If treatment with the study gas was successful, the concentration of the gas was decreased progressively, as described below. If the treatment was unsuccessful, the  $\text{FiO}_2$  was increased to 1.0 and other therapies, including extracorporeal membrane oxygenation, could be used as indicated.

Two patients treated unsuccessfully with the control gas had acute, severe decreases in systemic oxygenation while they were awaiting cannulation for extracorporeal membrane oxygenation. In a violation of the study protocol, they were treated with inhaled nitric oxide and had sustained increases in systemic oxygenation, and extracorporeal membrane oxygenation was withheld. Although these patients had successful responses to treatment with inhaled nitric oxide, the data on their short-term responses during the initial treatment with the control gas are reported. They are classified as infants with an unsuccessful response to the control gas and treatment with extracorporeal membrane oxygenation.

#### Continued Administration of the Study Gas

If an infant's initial treatment with gas was successful, the study continued and the infant received the treatment gas continuously in a blinded manner for as long as adequate systemic oxygenation was maintained (that is, as long as the oxygenation index remained below 40). The concentration of gas was reduced after the initial 20-minute study period and twice a day thereafter, according to the following protocol. If the  $\text{PaO}_2$  was greater than 55 mm Hg, the concentration of gas was decreased by 10 ppm (or by an equivalent amount, in the case of the control gas) while the  $\text{FiO}_2$  and the ventilatory and medical therapies remained unchanged. If the  $\text{PaO}_2$  declined by 15 percent or was 55 mm Hg or less 10 minutes after the change, the concentration of gas was raised to the level that had previously been acceptable. Otherwise, the concentration was decreased again until either the delivery system was off or the concentration of nitric oxide had been reduced by a maximum of 40 ppm (or the equivalent, in the case of the control gas).

To assess the effects of the study treatment on systemic oxygenation, the median  $\text{PaO}_2$  and associated  $\text{FiO}_2$  values and the set-

tings of the ventilator were recorded every 12 hours. In addition, blood methemoglobin was measured twice daily.

**Statistical Analysis**

We planned an interim analysis after 50 infants had been studied. The study was to be stopped if inhaled nitric oxide was found to increase the systemic oxygenation significantly as compared with the control gas. (P values of 0.05 or less by a two-sided Fisher's exact test were considered to indicate statistical significance.) That condition was met, and therefore the study was stopped by the Data Monitoring and Safety Committee.

The characteristics of the infants, the initial data on mechanical ventilation and medical therapy, the effect of inhaled nitric oxide on the PaO<sub>2</sub> and oxygenation-index values, the duration of treatment with oxygen and mechanical ventilation, and the duration of hospitalization were compared by analysis of variance; when significant differences were found, a posteriori testing was performed with Scheffé's F test.<sup>13</sup> Inhaled nitric oxide and the control gas were compared by a two-sided Fisher's exact test with regard to their effects on the incidence of successful treatment and of extracorporeal membrane oxygenation. In addition, a stratified exact test of the odds ratio was performed that examined the effect of inhaled nitric oxide (StatXact 1991, Cytel, Cambridge, Mass.). Data are expressed as means ±SD.

**RESULTS**

**Characteristics of the Patients**

Fifty-eight full-term newborn infants with severe systemic hypoxemia and pulmonary-artery hypertension were studied between July 1992 and October 1995 (Table 1). There were no differences between the control group and the nitric oxide group with respect to gestational age, birth weight, Apgar scores, proportion in whom meconium was observed below the vocal cords by direct laryngoscopy at birth, need for evacuation of pneumothoraxes, or positive blood cultures. The infants in both groups had severe hypoxemia despite high levels of ventilatory support at an FiO<sub>2</sub> of 1.0.

**Short-Term Effects of Inhaled Nitric Oxide**

No infant had a significant reduction of systemic oxygenation when the FiO<sub>2</sub> was decreased from 1.0 to 0.9 (data not shown). Breathing nitric oxide increased oxygenation in 16 of 30 infants (53 percent), whereas breathing the control gas did so in only 2 of 28 infants (7 percent, P=0.002). The odds ratio for the relation between the inhalation of nitric oxide and increased oxygenation was 14.9 (95 percent confidence interval, 2.7 to 144.4). Inhaled nitric oxide produced a short-term increase in the mean postductal PaO<sub>2</sub>, from 41±9 mm Hg to 89±70 mm Hg, and a decrease in the oxygenation index from 43±17 to 25±14 (P<0.001 for both), whereas in the control group there was no significant increase in PaO<sub>2</sub> or decrease in the oxygenation index (Fig. 1). In the nitric oxide group, the decrease in the oxygenation index was proportional to the degree of hypoxemia at base line (Fig. 2). The infants with the highest base-line oxygenation indexes had the greatest decreases in the oxygenation index while they were

**TABLE 1. BASE-LINE CHARACTERISTICS AND INITIAL BLOOD GAS VALUES IN INFANTS WITH PERSISTENT PULMONARY HYPERTENSION OF THE NEWBORN.\***

CHARACTERISTIC	CONTROL GROUP (N=28)	NITRIC OXIDE GROUP (N=30)
Gestational age (wk)	40.1 ± 1.2	39.8 ± 1.5
Birth weight (g)	3555 ± 620	3445 ± 579
Sex (M/F)	18/10	16/14
Median Apgar score		
1 min	3	5
5 min	7	7
Meconium below vocal cords (no. of infants)	17	15
Pneumothorax evacuated (no. of infants)	5	6
Bacteremia (no. of infants)	1	1
Vasopressor-drug therapy (no. of infants)	21	21
Bicarbonate therapy (no. of infants)	9	10
PaO <sub>2</sub> (mm Hg)	38 ± 9	41 ± 9
pH	7.47 ± 0.14	7.50 ± 0.12
PaCO <sub>2</sub> (mm Hg)	34 ± 11	32 ± 12
Oxygenation index	46 ± 18	43 ± 17
Mean airway pressure (cm of water)	16 ± 3	16 ± 4
Peak inspiratory pressure (cm of water)	36 ± 8	35 ± 7
Positive end-expiratory pressure (cm of water)	5 ± 1	5 ± 1
Ventilator rate (breaths/min)	73 ± 21	64 ± 19

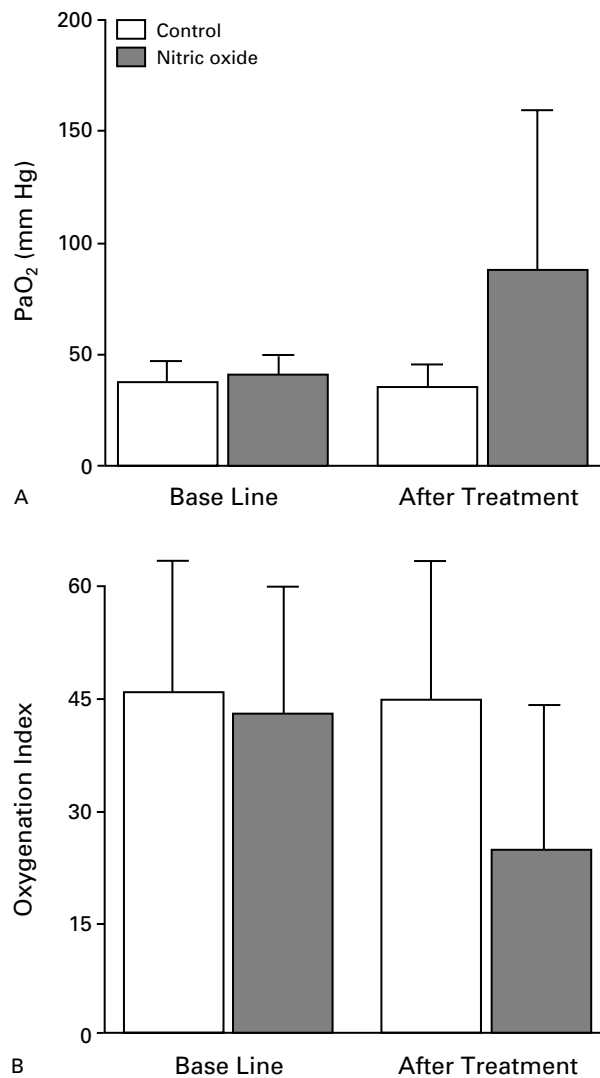
\*Plus-minus values are means ±SD. Blood gases were measured while the infants were receiving mechanical ventilation at a fraction of inspired oxygen of 1.0. Eight infants, four in the control group and four in the nitric oxide group, received surfactant before enrollment in the study. PaO<sub>2</sub> denotes partial pressure of arterial oxygen, and PaCO<sub>2</sub> partial pressure of arterial carbon dioxide.

breathing nitric oxide. This relation was more pronounced among the infants whose nitric oxide therapy was considered successful. The characteristics of the infants treated with nitric oxide did not differ significantly according to whether the therapy was successful or unsuccessful (Table 2).

**Long-Term Effects**

During the long-term administration of nitric oxide, systemic oxygenation was maintained in 12 of the 16 infants with successful initial responses to therapy (75 percent) (Fig. 3). In the remaining four infants, systemic oxygenation decreased within 12 hours after the start of nitric oxide therapy, and those infants were subsequently treated with extracorporeal membrane oxygenation.

Half the infants needed less than 2 days of nitric oxide therapy (Fig. 4A), and the longest treatment lasted 8.5 days. The median concentration of nitric oxide inhaled decreased progressively (Fig. 4B). Although the

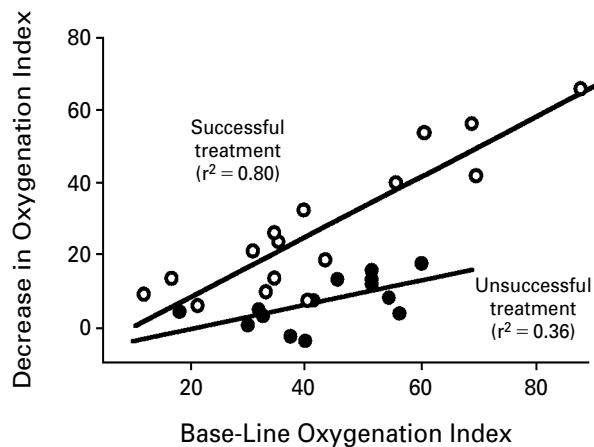


**Figure 1.** Short-Term Effect of Inhaled Nitric Oxide on Systemic Oxygenation in Infants with Severe Hypoxemia and Persistent Pulmonary Hypertension of the Newborn.

The effects of inhaled nitric oxide on postductal PaO<sub>2</sub> (Panel A) and on the oxygenation index (Panel B) are shown. Values are means +SD. As compared with conventional treatment with oxygen and mechanical ventilation without nitric oxide, nitric oxide therapy rapidly increased postductal PaO<sub>2</sub> from base line and decreased the oxygenation index (P<0.001 for all comparisons). The oxygenation index was calculated as described in the Methods section.

study protocol permitted treatment to be ended within 24 hours, rapid reduction in the FiO<sub>2</sub> and levels of ventilatory support by the clinical team did not permit the concentration of nitric oxide inhaled to be reduced to 20 ppm until two days had passed.

The need for extracorporeal membrane oxygenation was less in the nitric oxide group than in the control group. Twenty of the 28 infants in the control group (71 percent) received extracorporeal mem-



**Figure 2.** Relation between the Base-Line Oxygenation Index and the Decrease in the Index after the Start of Treatment with Inhaled Nitric Oxide.

Each symbol represents one infant. Inhaled nitric oxide caused the greatest decreases in the oxygenation index in the infants with the worst indexes before treatment.

**TABLE 2.** CHARACTERISTICS OF THE INFANTS IN THE NITRIC OXIDE GROUP ACCORDING TO THE OUTCOME OF THERAPY.\*

CHARACTERISTIC	THERAPY SUCCESSFUL (N = 16)	THERAPY UNSUCCESSFUL (N = 14)
Birth weight (g)	3526 ± 551	3352 ± 617
Sex (M/F)	7/9	8/6
Median Apgar score		
1 min	3	5
5 min	5	7
PaO <sub>2</sub> (mm Hg)	44 ± 11	39 ± 7
Age at treatment (days)	1.3 ± 1.5	2.0 ± 2.0
pH	7.48 ± 0.11	7.52 ± 0.13
PaCO <sub>2</sub> (mm Hg)	32 ± 12	33 ± 12
Oxygenation index	39 ± 18	42 ± 10
Mean airway pressure (cm of water)	16 ± 5	16 ± 3
Peak inspiratory pressure (cm of water)	36 ± 9	34 ± 6
Positive end-expiratory pressure (cm of water)	5 ± 2	5 ± 1
Ventilator rate (breaths/min)	66 ± 20	62 ± 18

\*Plus-minus values are means ±SD. PaO<sub>2</sub> denotes partial pressure of arterial oxygen, and PaCO<sub>2</sub> partial pressure of arterial carbon dioxide.

brane oxygenation, as compared with only 12 of the 30 infants in the nitric oxide group (40 percent, P=0.02). The odds ratio for the relation between the inhalation of nitric oxide and decreased use of extracorporeal membrane oxygenation was 3.8 (95 percent confidence interval, 1.1 to 13.1). The duration of oxygen or ventilatory therapy and the length of hospitalization of the patients treated with extracorporeal membrane oxygenation did not dif-

fer from those of the patients treated with inhaled nitric oxide (data not shown). Two patients in each group died in the hospital; none of these deaths could be directly attributed to the use of inhaled nitric oxide.

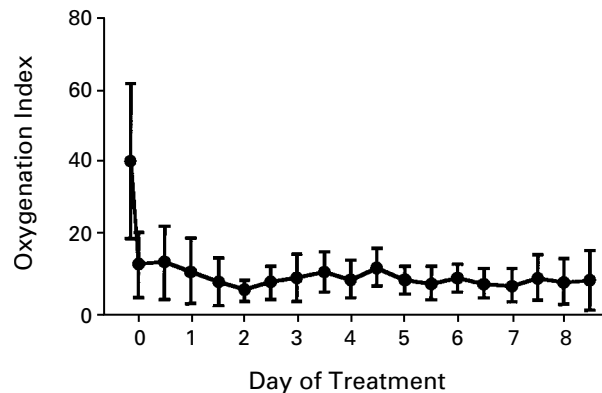
#### Side Effects

Nitric oxide therapy did not cause systemic hypotension in any infant. The therapy was, however, associated with a small increase in methemoglobin levels (Fig. 4B). The maximal value in most infants was reached during the first day of therapy, and in 90 percent of infants the values were less than 10 percent. In one infant, the blood methemoglobin level increased from 1 percent to 18.2 percent on the first day of treatment. Because the infant's oxygenation had improved, nitric oxide therapy was continued. The methemoglobin level subsequently decreased, and the infant's clinical course was uneventful.

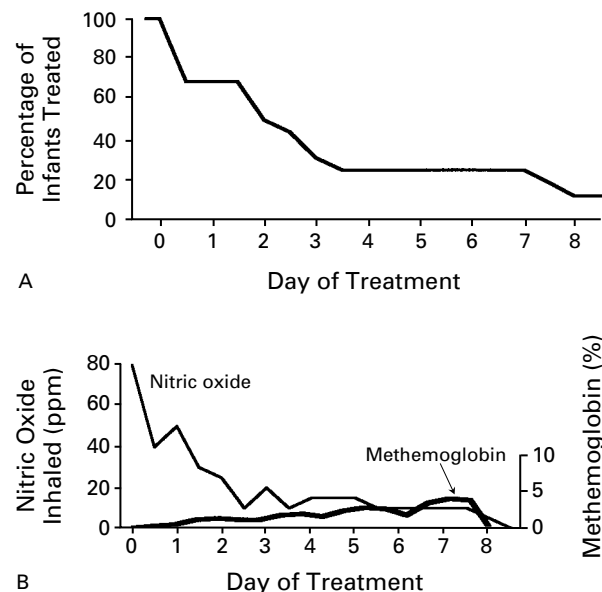
#### DISCUSSION

The morbidity and mortality associated with persistent pulmonary hypertension of the newborn are related to the severity and duration of systemic hypoxemia. If the hypoxemia is not treated, many infants die. Current treatments are often ineffective, and more invasive therapies, such as extracorporeal membrane oxygenation, cause morbidity and sometimes death. For these reasons, a rapid-acting, easily administered agent that selectively dilates the pulmonary vasculature and increases systemic oxygenation is greatly needed. In this study, we found that inhaled nitric oxide rapidly increased oxygenation in infants with severe hypoxemia and pulmonary-artery hypertension, without causing systemic hypotension. In addition, long-term therapy with inhaled nitric oxide caused lasting improvement in oxygenation and reduced the requirement for extracorporeal membrane oxygenation.

Although many infants had increases in systemic oxygenation with inhaled nitric oxide, some did not. In pilot studies, 46 to 100 percent of infants had short-term increases in systemic oxygenation in response to inhaled nitric oxide.<sup>9,10,14</sup> Although the infants we studied who responded to inhaled nitric oxide did not appear to differ clinically from the infants who did not, there are several factors that could limit the increase in oxygenation due to inhaled nitric oxide. It is possible that the thickened pulmonary arteries of some infants continue to restrict the flow of blood when they are relaxed by nitric oxide. Also, inflammation of the airways due to pneumonia or the aspiration of meconium may decrease the response to nitric oxide by two mechanisms. Airway edema may reduce the diffusion of nitric oxide into constricted vessels. In addition, atelectasis may cause intrapulmonary shunting and hypoxemia that is not remedied by vasodilators. Biochemical and molecu-



**Figure 3.** Long-Term Effect of Treatment with Inhaled Nitric Oxide on the Mean ( $\pm$ SD) Oxygenation Index of Infants with Severe Persistent Pulmonary Hypertension of the Newborn.



**Figure 4.** Duration of Nitric Oxide Treatment, Concentrations of Inhaled Gas, and Methemoglobin Values in Infants with Persistent Pulmonary Hypertension of the Newborn.

Panel A shows the proportion of infants breathing nitric oxide on each day of the treatment period. Panel B shows the median concentrations of nitric oxide in inspired air and the blood methemoglobin values over the course of treatment. The maximal duration of therapy was 8.5 days, but half the infants inhaled nitric oxide for 2 days or less. The median level of inhaled nitric oxide rapidly decreased to 20 ppm or less by two days. Although the methemoglobin values increased with prolonged nitric oxide treatment, they did not increase greatly in most infants.

lar factors may also prevent inhaled nitric oxide from causing pulmonary vasodilation. Chronic pulmonary hypertension in rats<sup>15</sup> and fetal sheep<sup>16,17</sup> decreases the activity of soluble guanylate cyclase, an important receptor of nitric oxide. Study of mechanisms of resistance to inhaled nitric oxide may give insight into new therapies that augment the pulmonary vasodilatory effect of the gas.

We found that inhaled nitric oxide decreases the need for extracorporeal membrane oxygenation in infants with severe persistent pulmonary hypertension of the newborn. Although that procedure saves the lives of some newborn infants with severe systemic hypoxemia, it is invasive, expensive, and unavailable in many intensive care units and is associated with substantial morbidity.

Although breathing lower concentrations of nitric oxide increases systemic oxygenation in some newborn infants with hypoxemia,<sup>10,18</sup> the optimal concentration of inhaled nitric oxide is not known. Because we studied whether inhaled nitric oxide increases systemic oxygenation, we chose the concentration of gas that is believed to cause the greatest pulmonary vasodilation. Our studies of young sheep<sup>1</sup> and newborn lambs<sup>2,3</sup> demonstrated maximal reductions in pulmonary vasoconstriction with a concentration of inhaled nitric oxide of 80 ppm. Although lower concentrations can increase systemic oxygenation, the concentration that permits reductions in mechanical ventilation, oxygen support, and right ventricular afterload and that can improve cardiac output and reduce injury to the lung is unknown.

In conclusion, inhaled nitric oxide increased systemic oxygenation rapidly in many infants with severe persistent pulmonary hypertension of the newborn, without causing hypotension. In many infants, continued treatment with nitric oxide constantly improved oxygenation and reduced the need for extracorporeal membrane oxygenation.

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Massachusetts General Hospital has a patent on the use of inhaled nitric oxide in the treatment of pulmonary disease. During the study period, Drs. Zapol and Morin were consultants to the Ohmeda Corporation, the company holding the license for the patent.

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