Randomized Controlled Study of Inhaled Nitric Oxide After Operation for Congenital Heart Disease

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Background. **Inhaled nitric oxide selectively decreases pulmonary vascular resistance. This study was performed to determine whether inhaled nitric oxide decreases the incidence of pulmonary hypertensive crises after corrective procedures for congenital heart disease.**

Methods. **Patients with a systolic pulmonary arterial pressure of 50% or more of the systolic systemic arterial pressure during the early postoperative period were randomized to receive 20 parts per million inhaled nitric oxide (n = 20) or conventional therapy alone (n = 20). Acute hemodynamic and blood gas measurements were performed at the onset of therapy. The efficacy of sustained therapy was determined by comparing the number of patients in each group who experienced a pulmonary hypertensive crisis.**

Results. **In comparison to controls, there were no significant differences in the baseline and 1-hour measurements of patients who were treated with nitric oxide. Four patients in the control group and 3 patients in the nitric oxide group experienced a pulmonary hypertensive crisis.**

Conclusions. **Nitric oxide did not substantially improve pulmonary hemodynamics and gas exchange immediately after operation for congenital heart disease. Nitric oxide also failed to significantly decrease the incidence of pulmonary hypertensive crises.**

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Pulmonary hypertension is a significant cause of morbidity and mortality after corrective procedures and heart transplantation in patients with congenital heart disease [1, 2]. Pulmonary endothelial function is decreased with advanced stages of pulmonary vascular disease [3, 4]. The production of nitric oxide by the pulmonary circulation is further impaired during the early postoperative period [5]. When inhaled, nitric oxide selectively decreases the pulmonary vascular resistance of many patients with congenital heart disease and pulmonary hypertension [6, 7]. For this reason, nitric oxide may prevent complications from right ventricular failure or decrease the incidence of pulmonary hypertensive crises after operation when the heart and pulmonary circulation are recovering from the effects of cardiopulmonary bypass. In previous studies [8–18], nitric oxide has been used to acutely decrease pulmonary vascular resistance in patients after surgical palliation or repair. However, previous studies have lacked controls during sustained therapy to determine whether a specific outcome could potentially be improved by treating all patients with moderately severe pulmonary hypertension. Thus, we performed a randomized, controlled study of patients with congenital heart disease after corrective operation or heart transplantation to determine [1] whether inhaled nitric oxide acutely improves blood gases and pulmonary hemodynamics, and [2] whether sustained therapy prevents pulmonary hypertensive crises.

Material and Methods

This study was approved by the Research and Human Subjects Committee of Primary Children's Medical Center (July 29, 1993). Informed consent was obtained from the patients (≥ 18 years of age) or their parents. An Investigational New Drug application for the use of inhaled nitric oxide for postoperative pulmonary hypertension was approved by the US Food and Drug Administration (March 12, 1993). This study was performed from August 1993 to August 1999.

Patients

Patients with congenital heart disease who underwent a biventricular repair or heart transplantation were eligible for enrollment if their systolic pulmonary arterial pressure was 50% or more of the systolic systemic arterial pressure when they were successfully removed from cardiopulmonary bypass. Patients with lower pulmonary arterial pressures are less likely to have problems with

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postoperative pulmonary hypertension [17]. Modified ultrafiltration was performed in all patients immediately after cardiopulmonary bypass. Pulmonary arterial catheters were placed in all patients before they were transferred from the surgical suite to the intensive care unit. Preoperative hemodynamics were not used to enroll patients because heart catheterization was not a prerequisite for operation; however, all patients had at least echocardiographic evidence of pulmonary hypertension before operation. Consent was generally not obtained until an increased pulmonary arterial pressure was confirmed at the completion of operation, although many families were informed of the study before operation.

Patients were randomly assigned to a control group that received conventional therapy or a treatment group that received 20 parts per million (ppm) inhaled nitric oxide. Patients were randomized by a blind draw from sequential groups containing six assignments. Conventional therapy was determined by each patient's attending cardiothoracic surgeon. The research committee of Primary Children's Medical Center required that conventional therapy was not restricted by the study to avoid any conflict with the clinical judgment of the patients' physicians.

Acute Hemodynamic and Blood Gas Measurements

Heart rate, systemic arterial pressure, pulmonary arterial pressure, atrial pressures, and pulse oximetry were monitored continuously by care providers. Baseline hemodynamic and blood gas measurements were performed when patients were clinically stable after admission to the intensive care unit. Inhaled nitric oxide was then administered to patients in the treatment group in an open labeled, or unblinded manner as previously described [19, 20]. The control group was not given a placebo gas of nitrogen. After a period of approximately 1 hour, the hemodynamic and blood gas measurements were repeated.

Pulmonary Hypertensive Crises During Sustained Therapy

The primary outcome of sustained therapy was determined by comparing the number of patients in each group who experienced a pulmonary hypertensive crisis. For this study, a pulmonary hypertensive crisis was defined as an acute episode of suprasystemic pulmonary arterial pressure associated with a decrease in blood pressure, heart rate, or oxygenation that required a change in medical therapy or ventilatory support. Death was not used to evaluate outcome because a previous study reported a potential lifesaving benefit from nitric oxide therapy [8]. Thus, control patients who experienced a pulmonary hypertensive crisis were allowed to crossover and receive inhaled nitric oxide after failing conventional therapy. Nitric oxide was not discontinued in treated patients who experienced a pulmonary hypertensive crisis unless there was a concern of drug toxicity because life-threatening events may occur when therapy is abruptly withdrawn [21].

Nitric oxide was administered at a concentration of 20 ppm until care providers decided to wean the patient from assisted ventilation. Before extubation, nitric oxide was gradually withdrawn by decreasing the dose during a period of 6 to 12 hours. The amount of supplemental oxygen was transiently increased when nitric oxide was discontinued.

Table 1. Patient Diagnoses

Diagnoses	Control Group (n)	Nitric Oxide Group (n)
Cardiac		
Atrioventricular septal defect	5	7
Atrial or ventricular septal defect	5	6
Total anomalous pulmonary venous return	3	3
Partial anomalous pulmonary venous return	1	0
Pulmonary venous obstruction	3	2
Mitral valve stenosis	0	1
Single ventricle with aortic hypoplasia	1	0
Tetralogy of Fallot	1	0
Stenosis of the aortic and pulmonary valves	1	0
Cor triatriatum	0	1
Other		
Down syndrome	7	8
Lung disease before operation	14	11

Statistical Analysis

Numerical values are expressed as mean ± standard error of the mean. Serial hemodynamic and blood gas measurements were compared by analysis of variance for repeated measures. A factorial analysis of variance or Fisher's exact test was used for comparisons between patient groups. Significant results were determined by p less than 0.05 using a Scheffé's F test (Statview II, Abacus Concepts, Berkeley, CA).

Results

Patients

Nineteen patients were enrolled into each patient group. Two patients were enrolled on two separate occasions; both underwent operation for pulmonary venous obstruction after an initial repair of total anomalous pulmonary venous return. The patients' diagnoses are listed in Table 1. A similar number of patients had Down syndrome in each group. Table 1 also indicates that several patients in each group had radiographic evidence of lung disease before operation. The median age was 6 months (range, 1 day to 3 years) in control patients and 7 months

Table 2. Inotropic and Vasodilatory Agents

Agents	Control Group (n)	Nitric Oxide Group (n)
Dopamine	18	20
Dobutamine	15	17
Nitroprusside	17	19
Milrinone	9	9
Amrinone	5	5
Epinephrine	7	6
Isoproterenol	1	0
Prostaglandin E_1	2	1

(range, 1 day to 20 years) in patients who received inhaled nitric oxide. All patients were treated with a narcotic for pain control and a benzodiazepine for sedation. Neuromuscular blockade was used from the onset of enrollment in 16 control patients and 15 patients who were treated with nitric oxide. Table 2 lists the inotropic and vasodilatory agents that were used at the time of baseline hemodynamic and blood gas measurements.

Corrective operation was attempted in all but 1 patient who underwent heart transplantation for a single ventricle and aortic hypoplasia, and 1 patient who was left with a small residual atrial septal defect after closure of a ventricular septal defect. Anatomic obstruction of the pulmonary circulation was identified in 5 patients during the postoperative period. In the control group, 1 patient had residual pulmonary venous obstruction, 1 patient had branch pulmonary artery stenosis, and 1 patient had mild mitral valve stenosis. In the group of patients who received inhaled nitric oxide, 2 patients had residual pulmonary venous obstruction.

Acute Hemodynamic and Blood Gas Measurements

Table 3 lists the mean hemodynamic and blood gas measurements for each group of patients. There were no significant differences in baseline measurements between patient groups. In comparison to baseline measurements, significant changes in heart rate, pulmonary arterial pressure, left atrial pressure, pH, arterial carbon dioxide tension, and the ratio of arterial oxygen tension and fraction of inspired oxygen were observed only in patients who received inhaled nitric oxide. The change in right atrial pressure for treated patients was not statistically significant ($p = 0.065$). Figure 1 shows a small, but significant, decrease in the ratio of systolic pulmonary and systemic arterial pressures. There were no measured differences between patient groups after 1 hour of observation. However, the difference between the changes in ratio of systolic pulmonary and systemic arterial pressures for the two patient groups approached statistical significance ($p = 0.066$).

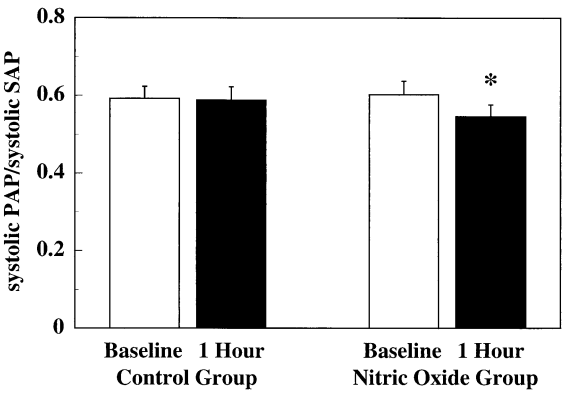

Fig 1. Ratio of systolic pulmonary and systolic systemic arterial pressures. In comparison to baseline, patients developed a small improvement in the ratio of systolic pulmonary and systolic systemic arterial pressures (systolic PAP/systolic SAP) *after the onset of inhaled nitric oxide therapy (*p = 0.011). However, there were no differences between patient groups at baseline or after 1 hour of observation.*

Two control patients and 4 patients who were treated with inhaled nitric oxide acutely experienced a 20% or more decrease in the ratio of systolic pulmonary and systemic arterial pressures. Six control patients and 9 patients who were treated with inhaled nitric oxide acutely experienced a 10% or more decrease in the ratio of systolic pulmonary and systemic arterial pressures. The sample size was large enough to conclude that nitric oxide did not decrease the ratio of systolic pulmonary and systemic arterial pressures by 20% in comparison to controls with a power (1-β) more than 0.75.

Table 3. Acute Hemodynamic and Blood Gas Measurements

	Control Group		Nitric Oxide Group	
Variables	Baseline	1-Hour	Baseline	1-Hour
Heart rate (min^{-1})	159 ± 4	157 ± 4	162 ± 5	155 ± 5[a]
Systolic pulmonary pressure (mm Hg)	47 ± 2	49 ± 2	52 ± 3	47 ± 2[a]
Systolic systemic pressure (mm Hg)	80 ± 2	82 ± 4	89 ± 5	87 ± 4
Right atrial pressure (mm Hg)	9.4 ± 0.9	9.9 ± 0.7	10.5 ± 0.8	9.5 ± 0.6
Left atrial pressure (mm Hg)	10.9 ± 1.0	10.5 ± 0.9	12.0 ± 1.1	11.0 ± 1.1[a]
pH	7.49 ± 0.02	7.47 ± 0.02	7.46 ± 0.02	7.50 ± 0.01[a]
$PaCO_2$ (mm Hg)	40 ± 3	41 ± 3	39 ± 1	36 ± 1[a]
PaO_2/FIO_2(mm Hg)	159 ± 22	181 ± 13	141 ± 15	179 ± 16[a]

$PaCO_2$ = arterial carbon dioxide tension; PaO_2/FIO_2 = ratio between the arterial oxygen tension and the fraction of inspired oxygen.

[a] $p < 0.05$ versus baseline. There were no differences between patient groups at baseline or after 1 hour of therapy.

Table 4. Characteristics of Patients Who Developed Pulmonary Hypertensive Crises

Patient	Age	Diagnosis	Onset of Crisis	Lung Disease	Neuromuscular Blockade
Control group					
1	4 months	Aortic and pulmonary valve stenosis	2 hours	Yes	Yes
2	5 months	Atrioventricular septal defect	5 days	Yes	No
3	7 months	Tetralogy of Fallot, branch pulmonary stenosis	3 days	Yes	Yes
4	6 months	Atrial and ventricular septal defects	2 days	Yes	No
Nitric oxide group					
1	7 months	Pulmonary venous obstruction	12 hours	No	No
2	7 months	Atrioventricular septal defect	16 hours	No	No
3	12 months	Ventricular septal defect	2 hours	Yes	No

Arterial blood gas, right atrial pressure, pulmonary arterial pressure, and systemic arterial pressure measurements and comparisons were performed in all patients. Heart rate comparisons were limited to 17 control patients and 13 patients who received inhaled nitric oxide because heart rate was determined by temporary pacing in 10 patients. Left atrial pressure comparisons were limited to 17 patients in each group because 6 patients did not have a catheter placed in the left atrium. Matching sets of systemic and pulmonary arterial blood gas measurements were inadvertently not performed in all patients at baseline and after 1 hour of observation. However, there was no significant change in the difference between systemic and pulmonary arterial oxygen saturations for 11 patients in the control group or 15 patients in the group of patients who received inhaled nitric oxide.

Patients with and without radiographic evidence of lung disease before operation had similar baseline hemodynamic and blood gas measurements. The presence of lung disease also had no significant effect on these measurements after 1 hour of observation. However, there was a significantly greater increase in the ratio of arterial oxygen tension and fraction of inspired oxygen in patients without lung disease than in patients with lung disease who were treated with inhaled nitric oxide (68 ± 20 mm Hg versus 13 ± 8 mm Hg, $p = 0.012$).

Pulmonary Hypertensive Crises During Sustained Therapy

Pulmonary hypertensive crises occurred in 4 control patients and in 3 patients who were treated with inhaled nitric oxide. The characteristics of these patients are listed in Table 4. A life-threatening episode of pulmonary hypertension occurred in 1 control patient. This episode was refractory to hyperventilation with 100% oxygen, sedation, and neuromuscular blockade. However, when treated with inhaled nitric oxide, a marked increase in the ratio of arterial oxygen tension and fraction of inspired oxygen (136 to 240 mm Hg), and a 47% reduction in the ratio of systolic pulmonary and systemic arterial pressures occurred. In other patients, the crises were less severe. Using a power analysis for contingency tables, more than 2,000 patients may be needed to determine whether nitric oxide decreases the incidence of pulmonary hypertensive crises with a power (1-β) more than 0.90.

The acute hemodynamic and blood gas effects of inhaled nitric oxide in the 4 control patients who experienced a pulmonary hypertensive crisis are listed in Table 5. In each patient, the pulmonary hemodynamics or oxygenation improved. The patient with branch pulmonary artery stenosis even developed an increase in the ratio of arterial oxygen tension and fraction of inspired oxygen (142 to 208 mm Hg) and a 20% reduction in the ratio of systolic pulmonary and systemic arterial pressures when treated with inhaled nitric oxide. No additional patient with anatomic obstruction experienced a pulmonary hypertensive crisis. None of the control patients experienced a pulmonary hypertensive crisis after being treated with inhaled nitric oxide. None of the patients who were initially randomized to the nitric oxide group experienced a subsequent pulmonary hypertensive crisis when neuromuscular blockade and sedation were gradually decreased over a period of 4 to 6 days.

Table 5. Acute Hemodynamic and Blood Gas Measurements of the Four Control Patients Who Were Treated With Inhaled Nitric Oxide After Experiencing a Pulmonary Hypertensive Crisis

Variables	Baseline After Pulmonary Hypertensive Crisis	Nitric Oxide (1 hour)
Heart rate (min^{-1})	161 ± 20	157 ± 19[a]
Systolic pulmonary pressure (mm Hg)	67 ± 5	50 ± 6[a]
Systolic systemic pressure (mm Hg)	80 ± 5	83 ± 10
Right atrial pressure (mm Hg)	14.8 ± 0.9	12.0 ± 0.8
Left atrial pressure (mm Hg)	14.7 ± 0.9	14.0 ± 1.0
pH	7.39 ± 0.06	7.44 ± 0.04
$PaCO_2$ (mm Hg)	49 ± 9	43 ± 6
PaO_2/FIO_2 (mm Hg)	137 ± 14	206 ± 16[a]

$PaCO_2$ = arterial carbon dioxide tension; PaO_2/FIO_2 = ratio between the arterial oxygen tension and the fraction of inspired oxygen.

[a] $p < 0.05$ versus baseline.

The patients who experienced a pulmonary hypertensive crisis had similar baseline hemodynamic and blood gas measurements in comparison to the patients who did not experience a pulmonary hypertensive crisis. However, there was a tendency for these patients to have increased baseline differences between systemic and pulmonary arterial oxygen saturations (43% ± 2% versus 32% ± 2%, $p = 0.062$). Five patients with and 2 patients without preoperative lung disease experienced pulmonary hypertensive crises. One of the 4 patients with lung disease who experienced a pulmonary hypertensive crises was being treated with inhaled nitric oxide.

Patients who experienced a pulmonary hypertensive crisis required an increased duration of paralysis (4.6 ± 1.2 days versus 2.1 ± 0.3 days, $p = 0.007$). They did not require a significantly increased duration of assisted ventilation (8.1 ± 1.7 days versus 5.5 ± 0.7 days) or inotropic support (6.0 ± 0.9 days versus 5.0 ± 0.5 days). If the patients who experienced a pulmonary hypertensive crisis were excluded from statistical analysis, control patients and patients who received inhaled nitric oxide required a similar duration of paralysis (2.1 ± 0.5 days versus 2.1 ± 0.4 days), assisted ventilation (5.6 ± 1.3 days versus 5.4 ± 0.7 days), and inotropic support (4.5 ± 0.6 days versus 5.4 ± 0.7 days). Maximum methemoglobin values were slightly increased in patients who were treated with inhaled nitric oxide (1.4% ± 0.1% versus 1.1% ± 0.1%, $p = 0.023$). There were no known complications or adverse effects associated with nitric oxide inhalation or the gradual withdrawal of nitric oxide before extubation. All patients completed the study and were weaned from assisted ventilation.

Comment

In this study, nitric oxide did not acutely improve pulmonary hemodynamics and arterial blood gases in comparison to conventional therapy. Nitric oxide also failed to significantly decrease the incidence of pulmonary hypertensive crises. This study is clearly limited by its size; however, it provides an estimate of the number of patients needed to exclude, with greater power, the possibility that inhaled nitric oxide prevents clinically significant pulmonary hypertensive crises after operation for congenital heart disease.

Patients

Only patients with relatively high pulmonary arterial pressures were enrolled in this study. All patients underwent a biventricular repair or heart transplantation. We may have failed to identify all patients with a systolic pulmonary arterial pressure of 50% or more of the systolic systemic pressure, and some patients with an initially low pulmonary arterial pressure may have developed a subsequent increase in pressure that was not monitored. Thus, we can only speculate that the majority of eligible patients were included in this study.

Our patient groups were reasonably well matched with respect to diagnosis, drug therapy, and baseline hemodynamic and blood gas measurements. The groups were also managed similarly with respect to the duration of neuromuscular blockade, inotropic support, and assisted ventilation.

Patients with anatomic obstruction in the pulmonary circulation were not excluded to report our complete results. Adatia and associates [15] have reported that these patients may not respond to inhaled nitric oxide. However, anatomic obstruction may be associated with an element of pulmonary vasoconstriction that is responsive to therapy, particularly if the obstruction is not severe bilaterally. Only 1 patient with residual anatomic obstruction experienced a pulmonary hypertensive crisis.

The criteria for patient selection may have influenced the outcome of our study. Additional studies will need to determine whether the acute and sustained effects of inhaled nitric oxide are more pronounced in patient groups defined by higher pulmonary arterial pressure, lung disease, or systolic right ventricular dysfunction.

Acute Hemodynamic and Blood Gas Measurements

Our study supports previous claims that nitric oxide acutely causes significant hemodynamic and blood gas improvements in comparison to baseline measurements. Unfortunately, none of our acute measurements in treated patients improved significantly in comparison to controls. It is possible that a larger study may identify a statistically significant difference in hemodynamic and blood gas measurements. However, our study indicates with a power (1-β) more than 0.75 that it is unlikely for an acute improvement in pulmonary hemodynamics to exceed 20% in comparison to controls. Thus, nitric oxide may not improve pulmonary hemodynamics enough to justify therapy for all patients with a postoperative pulmonary arterial pressure of 50% or more of the systemic arterial pressure.

Inhaled nitric oxide has decreased the pulmonary vascular resistance of patients with congenital heart disease during heart catheterization [6, 7]. Nitric oxide has also decreased mean pulmonary arterial pressure in comparison to conventional therapy when additional vasodilatory agents were not being used during a 20-minute period after repair of congenital heart disease [17]. Russell and associates [17] used different statistical methods; however, it is also possible that a significant decrease in pulmonary arterial pressure was not observed in our study because an intravenous nitric oxide donor was being used for systemic afterload reduction in the majority of patients.

Pulmonary Hypertensive Crises During Sustained Therapy

Pulmonary hypertensive crises occurred in both patient groups. Our results suggest that a very large study will be required to definitely exclude a benefit from sustained therapy. A larger study will also be needed to determine whether lung disease is a predisposing factor for pulmonary hypertensive crises. Our study is being closed because several institutions will need to collaborate to enroll an adequate number of patients to address these questions.

In contrast to our findings, a preliminary report of a case-control study [18] indicates that inhaled nitric oxide does decrease the incidence of pulmonary hypertensive crises after operation for congenital heart disease. This study will need to be evaluated in greater detail to determine whether the postoperative care and clinical characteristics of patients were similar in each group. It is possible that no crisis would have occurred in our treated patients if neuromuscular blockade or an increased level of pain management and sedation were used in all patients throughout the initial postoperative day. Our ability to identify a potential benefit from sustained therapy may have been improved by enforcing uniform standards for all aspects of conventional therapy. However, we agreed with our research committee that it would not be appropriate to impose restrictions on the judgment of care providers during a potential period of several days. Our findings may reflect the actual efficacy of sustained nitric oxide therapy in a true clinical setting where rigid strategies of assisted ventilation and drug therapy would not be enforced.

We did not attempt to grade the severity of pulmonary hypertensive crises. In 1 control patient, however, an episode was refractory to conventional therapy and death appeared inevitable until the onset of nitric oxide inhalation. Goldman and associates [14] have reported that nitric oxide may reduce the need for extracorporeal support in children with critical postoperative pulmonary hypertension. We agree that a trial of nitric oxide may be justified in patients who experience a pulmonary hypertensive crisis.

Nitric oxide did not have a significant impact on the duration of neuromuscular blockade, assisted ventilation, or inotropic support in patients whose postoperative course was not complicated by a pulmonary hypertensive crisis.

In conclusion, nitric oxide did not substantially improve pulmonary hemodynamics and gas exchange after operation for congenital heart disease. It also failed to significantly decrease the incidence of pulmonary hypertensive crises. Nitric oxide may have a role in the treatment of severe pulmonary hypertension; however, at this time there is no evidence that a specific outcome will be improved by empirically treating all patients who have increased pulmonary arterial pressure after operation.

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