Inhaled Nitric Oxide for Children With Congenital Heart Disease and Pulmonary Hypertension

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Background. Endothelium-derived nitric oxide (NO) is a potent vasodilator and a major mediator of pulmonary vascular tone.

Methods. Five infants underwent a trial of inhaled NO with hemodynamic monitoring in the operating room after atrioventricular canal repair. An additional 15 patients with congenital heart disease and refractory pulmonary hypertension were treated with inhaled NO for 1 day to 10 days postoperatively.

Results. In the 5 infants with atrioventricular canal, corrective surgical intervention and conventional therapy (hyperventilation, inspired oxygen fraction of 0.80, and inotropic agents) lowered mean pulmonary artery pressure from 49.5 ± 10.5 to 20.0 ± 2.2 mm Hg ($p < 0.001$). Adding inhaled NO further decreased mean pulmonary artery pressure to 18.0 ± 2.8 mm Hg (p = not significant). Inhaled NO had no effect on ventricular function curves (inflow occlusion) in this group. In the 15 patients with refractory postoperative pulmonary hypertension, 11 had a favorable response to inhaled NO, with a decrease in mean pulmonary artery pressure from 30.9 ± 5.8 to 23.1 ± 5.4 mm Hg ($p < 0.01$) in 8 patients with pulmonary artery catheters.

Conclusions. These studies demonstrate that inhaled NO has minimal beneficial effect on pulmonary artery pressure or cardiac output in infants after repair of atrioventricular canal. Inhaled NO is effective in decreasing PAP postoperatively in select patients with congenital heart disease and pulmonary hypertension refractory to conventional therapeutic modalities.

(Ann Thorac Surg 1995;60:1765–71)

Pulmonary hypertension is a serious complication of congenital heart disease and is frequently a major source of postoperative morbidity and mortality. Pulmonary hypertension in patients with congenital heart disease results from increased pulmonary blood flow or from pulmonary venous obstruction. The response to the increase in flow or venous obstruction is pulmonary artery smooth muscle hypertrophy and hyperplasia leading to pulmonary vasoconstriction. After a corrective intracardiac operation, this pulmonary hypertension often persists and in some cases may lead to a pulmonary hypertensive crisis. Our conventional therapeutic approach to postoperative pulmonary hypertension includes sedation, hyperventilation, supplemental oxygen, inotropic support (dobutamine hydrochloride), and cyclic adenosine monophosphate phosphodiesterase inhibitors such as amrinone lactate. The use of vasodilators such as nitroglycerin and sodium nitroprusside in the treatment of postoperative pulmonary hypertension is limited, as they are not selective to the pulmonary circulation, and their use may lead to systemic hypotension.

In 1987, endothelial-derived relaxing factor, the product of endothelial cells that stimulates relaxation of adjacent vascular smooth muscle and vasodilation, was identified as nitric oxide (NO) [1, 2]. Endogenously, NO is generated from L-arginine by the enzyme NO synthase. Endothelial-derived NO activates soluble guanylate cyclase in adjacent smooth muscle cells, which results in cyclic guanosine monophosphate production and vascular smooth muscle relaxation. Recently, it has been shown that inhalation of gaseous NO produces selective pulmonary vasodilation [3]. At concentrations of less than 80 ppm, inhaled NO lowers pulmonary artery pressure (PAP) and pulmonary vascular resistance (PVR) in hypoxia- and thromboxane-induced animal models of pulmonary hypertension without affecting systemic hemodynamic variables. A number of reports have reproduced these findings in adult patients with pulmonary hypertension secondary to heart disease [4, 5] or adult respiratory distress syndrome [6] and in pediatric patients with persistent fetal circulation [7], diaphragmatic hernia [8], or congenital heart disease [9–11].

The effect of inhaled NO is localized to the pulmonary circulation because its half-life is only seconds, and it has a high affinity to bind to Fe^{2+}- and $S^{=}$-containing proteins. It is presumed that after NO crosses the alveolar basement membrane, it induces pulmonary vasodilation by directly stimulating smooth muscle cyclic guanosine monophosphate production. Once the inhaled NO actually diffuses into the circulation, it is rapidly neutralized by binding to hemoglobin to form methemo-

Accepted for publication Aug 9, 1995.

Presented at the Forty-sixth Annual Meeting of the American Academy of Pediatrics, Surgical Section, Dallas, TX, Oct 21–23, 1994.

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0003-4975/95/$9.50
SSDI 0003-4975(95)00812-8

Ann Thorac Surg
1995;60:1765–71

globin. The use of NO as an inhalation agent must be carefully monitored because of its rapid conversion in higher concentrations to highly toxic nitrogen dioxide in the presence of oxygen. Nitrogen dioxide forms nitric acid, which rapidly induces pneumonitis and pulmonary edema.

The purpose of this investigation was to study the hemodynamic effects of inhaled NO in pediatric patients with congenital heart disease and pulmonary hypertension. We sought to determine if inhaled NO was an effective postoperative pulmonary vasodilator and whether it would have any effect on cardiac output (CO). The study was carried out first in the operating room immediately after the separation of the patient from cardiopulmonary bypass (CPB) and later was extended to postoperative management in the intensive care unit.

Material and Methods

Nitric Oxide Delivery System

The inhaled NO delivery system was designed in a fashion similar to that described by Wessel and colleagues [12]. Briefly, NO was supplied in cylinders from Scott Specialty Gases (Plumsteadville, PA) at a concentration of 800 ppm. Nitric oxide and nitrogen (N_2) were each fed separately into a low-flow blender at 50 psi (Bird Products, Palm Springs, CA). The resulting mixture of NO and nitrogen then flowed into a second blender where it was mixed with 100% oxygen, and the final delivered inspired oxygen fraction was regulated.

From the second blender, the flow rate of the gas mixture into the ventilator was controlled by a standard flowmeter. Depending on the patient's tidal volume, the gas mixture was fed into either the high-flow or the low-flow inlet of the Servo ventilator (Siemens-Elema, Englewood, CO). Gas flow was regulated to match the patient's minute ventilation in an attempt to keep the bellows of the ventilator empty. For infants on pressure-controlled ventilation, the gas mixture was fed into the inspiratory limb. The actual concentration of NO and nitrogen dioxide at the endotracheal tube was continuously monitored in-line with an NO/NO_X Thermoenvironmental Instruments chemiluminescence analyzer (Franklin, MA). The expiratory gases from the patient circuit were scavenged into the hospital vacuum system.

Patient Protocols

The initial clinical trial of inhaled NO in children with congenital heart disease and pulmonary hypertension was designed to investigate the effects of inhaled NO on the pulmonary vasculature and the cardiac performance. Five infants with complete atrioventricular canal defect and pulmonary hypertension (PVR > 4 U/m^2 or systolic PAP $> 50\%$ aortic pressure) received inhaled NO in the operating room after undergoing repair of the defect and immediately after separation from CPB. The hemodynamic response to inhaled NO was monitored by placing a flow probe (Transonic Inc, Ithaca, NY) around the aorta to measure CO and pressure transducers (Camino Laboratories, San Diego, CA) within the right atrium, left atrium, and pulmonary artery.

After baseline measurements of right atrial pressure, left atrial pressure, PAP, aortic pressure, and CO had been obtained, the patients were ventilated with 20 ppm, 40 ppm, and then 80 ppm NO for 5 minutes each while the hemodynamic response was continuously monitored. Prior to NO exposure and also while the patients were inhaling 80 ppm NO, the superior and inferior venae cavae were briefly occluded to permit measurement of CO at various levels of ventricular preload [13]. A second set of measurements was obtained after discontinuing the inhaled NO to ensure the patients had returned to baseline hemodynamic status.

After the initial experience with inhaled NO in the operating room, the clinical trial was expanded to include patients in the intensive care unit postoperatively. This second group of patients with congenital heart disease and pulmonary hypertension received inhaled NO for severe pulmonary hypertension unresponsive to conventional therapy. Many of these patients had pulmonary artery catheters in place that permitted monitoring of the pulmonary vascular response to inhaled NO. These patients continued to receive inhaled NO until the pulmonary hypertension could be controlled with conventional therapy. In this group of patients, blood methemoglobin levels were monitored by spectrophotometry every 6 hours while they were receiving NO.

Informed consent was obtained from the parents or legal guardians of all patients. The protocol for the use of inhaled NO and an amended protocol to extend the patient population were approved September 22, 1992, and December 24, 1992, respectively, by the Institutional Review Board of Children's Memorial Institute for Education and Research. In addition, an investigational new drug number was obtained from the Food and Drug Administration for this study.

Statistical Analysis

Values are expressed as the mean ± the standard deviation. Hemodynamic data were compared by a paired t test, and a p value of less than 0.05 was considered to indicate significance. Linear least squares regression analysis was used to evaluate the relationship between CO and left ventricular end-diastolic pressure with and without inhaled NO therapy. We used r^2 statistics to determine the strength of association and fit.

Results

A total of 20 patients with congenital heart disease and pulmonary hypertension aged 1 day to 14 years old (mean age, 0.9 year) received inhaled NO. The duration of treatment ranged from less than 1 hour to 10 days (mean duration, 3.3 ± 3.2 days). The most frequent diagnosis was complete atrioventricular canal defect. In the majority of patients, the pulmonary hypertension was secondary to a large left-to-right intracardiac shunt, but in some patients, it was a result of pulmonary venous obstruction. These patients received inhaled NO in ac-

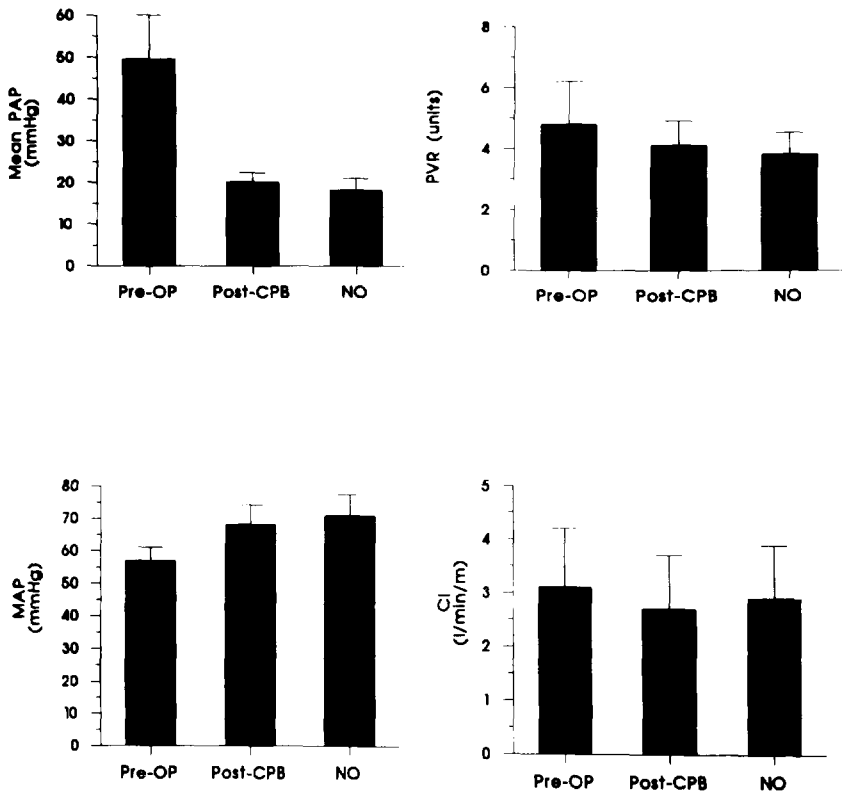

Fig 1. Hemodynamic response to conventional therapy and inhaled nitric oxide (NO) in 5 patients with complete atrioventricular canal defect and pulmonary hypertension. Mean pulmonary artery pressure (PAP), pulmonary vascular resistance (PVR), cardiac index (CI), and mean arterial blood pressure (MAP) were obtained at the time of preoperative cardiac catheterization (Pre-Op), after surgical intracardiac repair and initiation of conventional therapy (Post-CPB), and during ventilation with 80 ppm NO. Compared with Pre-Op, mean PAP was significantly decreased Post-CPB and with inhaled NO ($p < 0.001$). There were no significant differences in any of the hemodynamic variables between Post-CPB and the NO period. Results are expressed as the mean ± the standard deviation.

cordance with one of two institutional review board–approved protocols; one group was treated with inhaled NO in the operating room with hemodynamic monitoring, and the other group received inhaled NO postoperatively in the intensive care unit for clinical indications.

Intraoperative Trial

Five infants, 3 girls and 2 boys aged 5 to 11 months, with complete atrioventricular canal defect and significant pulmonary hypertension received inhaled NO in the operating room. Mean PAP preoperatively was 49.5 ± 10.5 mm Hg, mean PVR was 4.8 units, and mean pulmonary to systemic flow ratio was 3.1:1. The patients underwent intracardiac repair with patch closure of the atrial and ventricular septal defects and atrioventricular valve repair and were then weaned from CPB with conventional therapy for pulmonary hypertension. This included hyperventilation (carbon dioxide tension < 35 mm Hg), inspired oxygen fraction of 0.80, dopamine hydrochloride (2.5 to 5.0 $\mu g \cdot kg^{-1} \cdot min^{-1}$), and dobutamine (5 to 10 $\mu g \cdot kg^{-1} \cdot min^{-1}$). After baseline hemodynamic variables were obtained after CPB, the patients were ventilated with 20 ppm, 40 ppm, and 80 ppm NO while the hemodynamic responses were continuously recorded.

Figure 1 demonstrates the effect of inhaled NO at 80 ppm on mean arterial pressure, cardiac index, mean PAP, and PVR. There were only minor differences in mean arterial pressure, mean PAP, PVR, and cardiac index with inhaled NO compared with baseline measurements made immediately after CPB. There was a decrease in mean PAP from 20.0 ± 2.2 mm Hg to 18.0 ± 2.8 mm Hg and a corresponding decrease in mean PVR from 4.3 ± 0.9 units to 3.8 ± 0.7 units. The response to inhaled NO was limited in these patients because the PAP decreased substantially with elimination of the left-to-right shunt after repair and with the therapy the children received as they were weaned from CPB. Figure 1 demonstrates the decrease in mean PAP and PVR from preoperative cardiac catheterization to the period just after CPB. After CPB, there was a 59% decrease in mean PAP and a 15% decrease in mean PVR.

To investigate the effects of inhaled NO on cardiac function, CO was determined at various levels of ventricular preload before and during treatment with NO in 2 of these 5 patients. Intracavitary filling pressures were manipulated by briefly occluding the superior and inferior venae cavae, thereby permitting rapid measurement of a sequence of COs at different filling pressures. The results from the inflow occlusion procedure in 1 patient are demonstrated in Figure 2. As expected, inhaled NO did not significantly alter CO in these patients. In the patient whose results are illustrated in Figure 2, CO was only slightly increased with inhaled NO. After repair of the atrioventricular canal defect and the initiation of conventional therapy for pulmonary hypertension, ventricular performance was no longer limited by pulmonary hypertension.

Postoperative Trial

An additional 15 children with congenital heart disease and pulmonary hypertension received inhaled NO post-

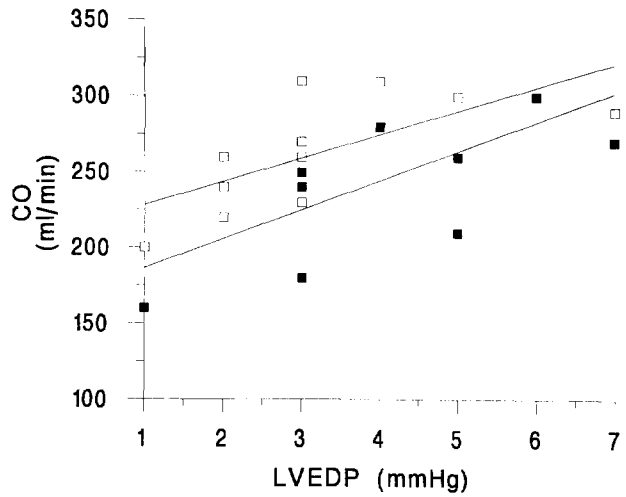

Fig 2. Effect of inhaled nitric oxide (NO) on cardiac output (CO) in a patient with complete atrioventricular canal defect and pulmonary hypertension. Cardiac output was determined at various levels of ventricular preload after surgical intracardiac repair and initiation of conventional therapy (dark squares) *and during ventilation with 80 ppm NO* (open squares). *The overall regression estimates and* r^2 *statistics for the two sets of data points are as follows: before NO: CO = 167.4 + 19.3 (LVEDP) and* $r^2 = 0.47$; *and with NO: CO = 219.9 + 15.5 (LVEDP) and* $r^2 = 0.48$, *where LVEDP = left ventricular end-diastolic pressure.*

operatively in the intensive care unit. These patients were given this treatment because of severe persistent pulmonary hypertension refractory to conventional therapy or because of transient episodes of pulmonary hypertension associated with hemodynamic deterioration and hypoxia. The diagnoses, surgical procedures, and duration of therapy are summarized in Table 1. Eleven of the 15 patients had a favorable response to inhaled NO as evidenced by either a decrease in PAP or improvement in the clinical course.

Patients 1 through 4 were in unstable condition postoperatively with periods of hypotension associated with hypoxemia despite conventional therapy. They were thought to have reactive pulmonary vasculature with transient episodes of pulmonary hypertension, although PAP was not monitored. They received inhaled NO at low concentrations of 10 to 20 ppm, and the condition of each subsequently stabilized without recurrence of these episodes. Patient 5 also had a favorable clinical response to inhaled NO. This patient was a premature infant with ventricular septal defect, coarctation of the aorta, and patent ductus arteriosus complicated by meconium aspiration requiring urgent institution of extracorporeal membrane oxygenation. The patient was taken to the operating room on extracorporeal membrane oxygenation and after repair of the congenital heart defects, was

Table 1. Patient Diagnoses, Surgical Procedures, Duration of Nitric Oxide Therapy, and Outcome

Patient No.	Age	Diagnoses	Procedure	Duration of Therapy (days)	Outcome
1	1 day	PA/IVS	PV, TA, ↑ ASD, Inn–PA shunt	3.5	Good
2	1 day	Hypoplastic LV	Tx	1.5	Good
3	1 mo	AS, hypoplastic LV, PDA	AV, ligation of PDA, modified Norwood	3	Good
4	4 day	DORV, s/p PAB, s/p E-E	Closure of ASD and VSD, arterial switch, PAB/D	4	Good
5	1 mo	VSD, ASD, CoAo, PDA	Closure of ASD and VSD, E-E	8	Death (intraventricular hemorrhage postop day 26)
6	14 y	Cardiomyopathy	Tx	10	Good
7	3 mo	VSD, RVOTO	Closure of VSD, division of RVOTO	10	Good
8	2 mo	VSD, CoAo	Closure of VSD, E-E	5	Good
9	5 mo	DORV, VSD, MR	↑ VSD, IV tunnel	2	Good
10	7 mo	AVC, tracheal rings	Repair of AVC, tracheoplasty	7.5	Good
11	2 wk	Hypoplastic LV	Tx	4	Good
12	6 mo	AVC, PS, Ebstein's anomaly	Bidirectional Glenn	1	Death (hypoxia)
13	1 wk	Truncus arteriosus, IAA, ASD	Repair of truncus arteriosus	3	Death (*Pseudomonas* pneumonia/sepsis)
14	9 mo	AVC, ToF, PDA	Repair of AVC and ToF	1	Death (anasarca, bronchopulmonary dysplasia)
15	1 day	Cor triatriatum, CoAo	Excision of cor triatriatum, augmentation of PV, ligation of PDA, E-E, closure of ASD	6	Death (pulmonary vein stenosis)

AS = aortic stenosis; ASD = atrial septal defect; AV = aortic valvotomy; AVC = atrioventricular canal; CoAo = coarctation of aorta; DORV = double-outlet right ventricle; E-E = end-to-end anastomosis; IAA = interrupted aortic arch; Inn–PA = innominate artery–pulmonary artery; IV = intraventricular; LV = left ventricle; MR = supravalvular mitral ring; PA/IVS = pulmonary atresia with intact ventricular septum; PAB = pulmonary artery band; PAB/D = removal of pulmonary artery band; PDA = patent ductus arteriosus; PS = pulmonary stenosis; PV = pulmonary valvotomy; RVOTO = right ventricular outflow tract obstruction; S/P = status post; TA = tricuspid annuloplasty; ToF = tetralogy of Fallot; Tx = Heart transplantation; VSD = ventricular septal defect; ↑ = enlargement.

able to be weaned from CPB on inhaled NO and conventional therapy only. The patient did well initially and had been weaned from NO; late in the postoperative course, he died of an intraventricular hemorrhage (postoperative day 26).

Eight patients had pulmonary artery catheters after operation to monitor the response to inhaled NO (Fig 3). The effect of inhaled NO on PVR could not be determined, as CO was not measured. The mean postoperative PAP in this group of patients was 30.9 ± 5.8 mm Hg despite conventional therapy. With inhaled NO therapy, there was a 25% decrease in mean PAP to 23.1 ± 5.4 mm Hg ($p < 0.01$). Six of the 8 patients (patients 6 through 11) responded to NO with a decrease in mean PAP and appeared to benefit clinically. Preoperatively, patient 6 had significant pulmonary hypertension with a mean PAP of 38 mm Hg and a PVR of 7.8 units. After heart transplantation, the patient could not be weaned from CPB with conventional therapy for pulmonary hypertension and required inhaled NO to be separated from CPB. She was maintained on inhaled NO, and mean PAP gradually decreased to 18 mm Hg. Patient 7 also had a dramatic response to inhaled NO, with mean PAP decreasing by 45% with only 10 ppm NO. Patient 8 began treatment with inhaled NO immediately after operation and was in stable condition throughout the first postoperative day with a PAP of 36/21 mm Hg. He was weaned from inhaled NO without difficulty and on postoperative day 2, his sedation was lightened and paralysis was discontinued. As the patient awakened, his PAP increased to 55/30 mm Hg and remained there despite conventional therapy. Inhaled NO therapy was reinstituted for 4 more days, with the PAP falling to 29/16 mm Hg.

Four of the 15 patients failed to respond to inhaled NO, and all died. Three of the patients were in grave condition when inhaled NO therapy was instituted, and none demonstrated major clinical response or decrease in PAP. Patient 15 was a neonate with cor triatriatum and coarctation of the aorta. After corrective surgical intervention, which included excision of the cor triatriatum membrane and pericardial patch augmentation of the pulmonary veins, the patient had significant pulmonary hypertension with a mean PAP of 59 mm Hg. Attempts to wean him from CPB were unsuccessful, and the patient's lungs became edematous and grossly hemorrhagic. The patient was placed on extracorporeal membrane oxygenation. Inhaled NO was started on postoperative day 3 and facilitated weaning from extracorporeal membrane oxygenation. However, the patient continued to have systemic pulmonary pressures that failed to improve with continued support, and eventually therapy was withdrawn. Postmortem examination demonstrated extensive pulmonary vein stenosis.

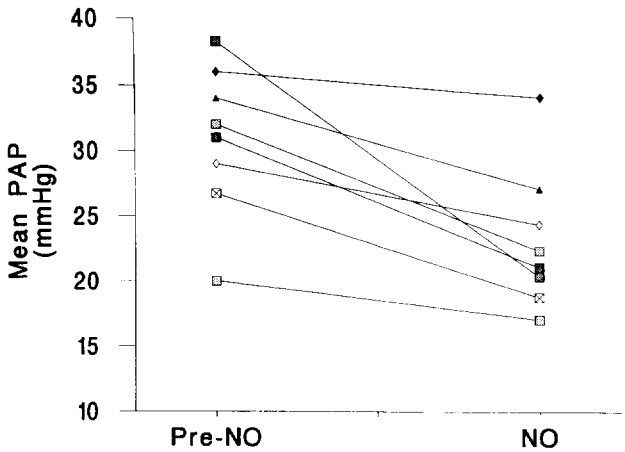

Fig 3. Effect of inhaled nitric oxide (NO) on mean pulmonary artery pressure (PAP) in 8 children with congenital heart disease and postoperative pulmonary hypertension refractory to conventional therapy. Inhaled NO significantly decreased mean PAP from 30.9 ± 5.8 mm Hg to 23.1 ± 5.4 mm Hg (p < 0.01).

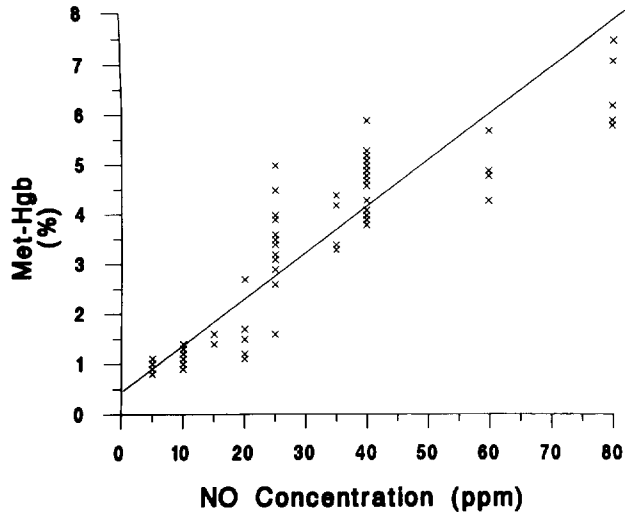

Fig 4. Correlation between concentration of inhaled nitric oxide (NO) delivered and formation of methemoglobin (Met-Hgb). Regression estimates and r^2 statistics demonstrate a direct correlation between NO concentration and blood methemoglobin level: Met-Hgb (%) = 0.77 ± 0.08 (NO) and $r^2 = 0.90$.

Toxicity

There were no postoperative complications that could be directly attributed to inhaled NO. Five patients had postoperative pulmonary complications, right upper lobe atelectasis with collapse in 3 and pneumonia in 2. There was a direct correlation between the concentration of NO delivered and the patient's methemoglobin level (Fig 4). When elevated blood methemoglobin levels did occur, they were easily rectified by decreasing the dose of NO by 50% and following the methemoglobin levels more closely. We found that concentrations of 80 ppm or higher of NO could not be consistently delivered without exceeding 5 ppm of nitrogen dioxide. There was also a correlation between the concentration of NO used and the amount of nitrogen dioxide that formed in the delivery system (data not shown).

Comment

Nitric oxide is a critical intercellular and intracellular messenger with numerous important biologic actions. Endothelial-derived NO is the primary mediator of vascular tone and patency. Endothelial NO activates soluble guanylate cyclase in adjacent vascular smooth muscle cells, which leads to cyclic guanosine monophosphate production and subsequent vascular smooth muscle relaxation. In experimental animal models and humans, it has been shown that the administration of an NO inhibitor results in an increase in arterial blood pressure and systemic vascular resistance, findings indicating that there is continuous endothelial NO production regulating basal vascular tone [14–16]. It has been demonstrated also that the administration of an NO inhibitor blocks the hypotensive response to endotoxemia, which suggests that the inappropriate vasodilation seen in certain disease states may be secondary to excessive NO production [17]. Vascular tone in the pulmonary circulation is also NO dependent. In experimental animal models, hypoxia-induced pulmonary hypertension is augmented by the administration of an NO inhibitor [18, 19].

The clinical utility of exogenously administered NO as an antihypertensive is limited by its short half-life and strong affinity to bind to hemoglobin. Frostell and associates [3] were the first to report that the inhalation of gaseous NO selectively dilates the pulmonary vasculature. Inhaled NO at concentrations of 5 ppm to 80 ppm decreased the PAP and PVR in an animal model of pulmonary hypertension induced by hypoxia or the infusion of a thromboxane analogue. Pepke-Zaba and coworkers [20] were the first to document the effects of inhaled NO in humans by demonstrating that inhaled NO selectively decreased PVR in a group of patients with primary pulmonary hypertension. Since these original studies, there have been a number of reports [4–11] demonstrating the utility of inhaled NO in the treatment of pulmonary hypertension in a variety of patient populations.

Roberts and colleagues [21] studied the effects of inhaled NO on pulmonary hypertension in 10 pediatric patients with congenital heart disease. A brief trial of inhaled NO during cardiac catheterization in children with congenital heart disease produced a significant decrease in PAP and PVR and an increase in the intracardiac shunt. Wessel and coauthors [22] investigated the effects of acetylcholine (endothelium-dependent vasodilator) and inhaled NO (endothelium-independent vasodilator) in pediatric patients with congenital heart disease and pulmonary hypertension. They demonstrated that the vasodilatory response to an intrapulmonary infusion of acetylcholine was markedly attenuated after CPB. In contrast, inhalation of NO after CPB lowered PVR by 33% and resulted in a threefold increase in plasma cyclic guanosine monophosphate levels. These data indicate that inhaled NO is an effective pulmonary vasodilator postoperatively in patients with congenital heart disease. Further, the pathophysiology of postoperative pulmonary hypertension may in part be due to CPB–induced endothelial dysfunction.

This study was designed to investigate the effects of inhaled NO on the pulmonary circulation in children with congenital heart disease and pulmonary hypertension. Under the intraoperative protocol, the patients received a brief trial of inhaled NO in the operating room with full hemodynamic monitoring. The purpose of this portion of the investigation was to gain experience with the delivery of inhaled NO while also studying its hemodynamic consequences. The patient population chosen had severe pulmonary hypertension preoperatively and was expected to have significant residual pulmonary hypertension after corrective intracardiac surgical intervention. However, after repair of the atrioventricular canal defect and conventional treatment with hyperventilation, supplemental oxygen, and inotropic agents, we found that this patient population had only mild residual pulmonary hypertension. In this setting, inhaled NO had minimal effect on pulmonary hemodynamics or CO.

Under the postoperative protocol, patients received inhaled NO for therapeutic indications. This portion of the study included patients with persistent pulmonary hypertension after intracardiac operation that was refractory to conventional therapy and patients with transient episodes of pulmonary hypertension associated with hemodynamic compromise postoperatively. In general, this group of patients had significant pulmonary hypertension and was hemodynamically unstable when NO therapy was instituted. This is reflected in the overall hospital mortality of 33%. In this setting, we found that 73% of the patients had a favorable response to inhaled NO therapy. More importantly, in a few cases it appeared that inhaled NO therapy was critical to the patient's survival. The degree of response to inhaled NO was quite variable. Inhaled NO appeared to be very effective in preventing transient episodes of postoperative pulmonary hypertensive crisis. The condition of all 5 patients with episodes of pulmonary hypertensive crisis stabilized after inhaled NO therapy was instituted. In all of these patients and many of the patients with persistent refractory pulmonary hypertension, only low concentrations of inhaled NO (10 to 20 ppm) were necessary to observe the vasodilatory effect. Miller and associates [10] reported similar findings, demonstrating that concentrations as low as 2 ppm were effective in lowering PVR. Our experience has been that if no response to inhaled NO has occurred with either 20 ppm or 40 ppm, the patient will not respond to inhaled NO at higher concentrations.

The few postoperative pulmonary complications that occurred were most likely not attributable to inhaled NO therapy. Two of the 3 patients with atelectasis and right upper lobe collapse had only a brief trial of NO in the operating room, and the pneumonia in 2 other patients developed long after their exposure to inhaled NO. In 4 patients, pulmonary function seemed to improve with inhaled NO therapy. In these patients, there was a substantial increase in oxygenation concomitant with the institution of NO therapy. This change in oxygenation may have been secondary to improved hemodynamics or

a decrease in the intrapulmonary shunt. Rossaint and associates [6] have demonstrated a significant increase in oxygenation in adult patients with severe adult respiratory distress syndrome treated with inhaled NO. In that study, the increase in oxygenation was accompanied by a 3% decrease in the intrapulmonary shunt, a finding suggesting that inhaled NO may improve oxygenation by dilating blood vessels only in ventilated lung regions. In our experience, the improvement in oxygenation with inhaled NO was variable and may have resulted from one of a number of respiratory interventions that typically occurred as a patient was started on inhaled NO.

In summary, these data demonstrate that in most patients with atrioventricular canal defect, complete surgical repair in combination with conventional therapy is very effective in controlling pulmonary hypertension. However, in those patients with congenital heart disease and postoperative pulmonary hypertension refractory to conventional therapies, inhaled NO therapy is effective in lowering PAP and is potentially lifesaving. We are encouraged by the results in this group of patients, many of whom received inhaled NO under difficult clinical circumstances. In most cases, inhaled NO appeared to have a positive impact on the clinical course. We believe the role of inhaled NO in patients with congenital heart disease and pulmonary hypertension is as an adjunct to conventional therapy.

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