

## Inhaled Nitric Oxide

### Selective Pulmonary Vasodilation in Cardiac Surgical Patients

George F. Rich, M.D., Ph.D.,\* Gerald D. Murphy, Jr., M.D.,† C. M. Roos, M.S.,‡ Roger A. Johns, M.D.§

**Background:** Inhaled nitric oxide (NO), an endothelium-derived relaxing factor, is a selective pulmonary vasodilator. The authors investigated whether the pulmonary vasodilation resulting from 20 ppm inhaled NO is related to the degree of pulmonary hypertension or affected by cardiopulmonary bypass (CPB) or the presence of intravenous nitrates.

**Methods:** In patients undergoing cardiac surgery ( $n = 20$ ) or in whom the circulation was supported with a ventricular assist device (VAD;  $n = 5$ ), the lungs were ventilated with 80% O<sub>2</sub> and 20% N<sub>2</sub> followed by the same gas concentrations containing 20 ppm NO for 6 min.

**Results:** Inhaled NO decreased ( $P < 0.05$ ) the pulmonary artery pressure from  $36 \pm 3$  to  $29 \pm 2$  mmHg and  $32 \pm 2$  to  $27 \pm 1$  mmHg, before and after CPB, respectively, and from  $68 \pm 12$  to  $55 \pm 9$  mmHg in patients with a VAD. Similarly, the pulmonary vascular resistance (PVR) decreased ( $P < 0.05$ ) from  $387 \pm 44$  to  $253 \pm 26$  dyne  $\cdot$  cm  $\cdot$  s<sup>-5</sup> and  $260 \pm 27$  to  $182 \pm 18$  dyne  $\cdot$  cm  $\cdot$  s<sup>-5</sup>, before and after CPB, respectively, and from  $1,085 \pm 229$  to  $752 \pm 130$  dyne  $\cdot$  cm  $\cdot$  s<sup>-5</sup> in patients with a VAD. Central venous pressure, cardiac output, systemic hemodynamics, and blood gases did not change after inhalation of NO before or after CPB, whereas arterial oxygen tension, mixed venous hemoglobin saturation, and mean arterial pressure increased ( $P < 0.05$ ) in patients supported with a VAD. All hemodynamic and laboratory data returned to control 6 min after discontinuation of NO. The decrease in PVR was proportional to baseline PVR ( $\Delta PVR = -0.45 PVR_b + 39.9$ ) before CPB. The pre- and post-CPB slopes were identical despite possible damage to the endothelium resulting from CPB and the post-CPB presence of intravenous nitroglycerin (17 of 20 patients).

**Conclusions:** This study demonstrates that 20 ppm inhaled NO is a selective pulmonary vasodilator in cardiac surgical patients before and after CPB and in patients in whom the circulation is supported with a VAD. Furthermore, NO-induced pulmonary vasodilation is proportional to PVR<sub>b</sub> and does not appear to be altered by CPB, the presence of a VAD, or infusion of nitrates. (Key words: Endothelium-derived relaxing factor. Lungs: pulmonary hypertension; vasodilation. Methemoglobin. Nitric oxide.)

THERE is no effective treatment for patients with pulmonary hypertension because of the lack of a selective pulmonary vasodilator. However, there is growing evidence that low concentrations (<80 ppm) of inhaled nitric oxide (NO), which appears to be an endothelium-derived relaxing factor (EDRF),<sup>1-3</sup> vasodilate the pulmonary circulation without affecting systemic hemodynamics.<sup>4-8</sup> Inhaled NO has been demonstrated to attenuate thromboxane-induced pulmonary hypertension in sheep and hypoxic pulmonary vasoconstriction (HPV) in sheep and human volunteers.<sup>4-6</sup> Significant decreases in pulmonary vascular resistance (PVR) also have been reported after inhalation of 40 ppm NO in patients with chronic pulmonary hypertension.<sup>7,8</sup>

Inhaled NO vasodilates constricted but normal pulmonary vessels in a dose-dependent manner.<sup>4</sup> However, it is unknown whether there is a relationship between the baseline PVR (PVR<sub>b</sub>) and the effectiveness of inhaled NO in patients with chronic pulmonary hypertension. Furthermore, it is unknown whether cardiopulmonary bypass (CPB) or the presence of a ventricular assist device (VAD), anesthesia, intravenous nitrates, or inotropic agents alter the effectiveness of inhaled NO. To resolve these issues, we evaluated the hemodynamic changes after inhalation of low concentrations of 20 ppm NO in patients undergoing mitral valve replacement and/or coronary bypass grafting with varying levels of PVR before and after CPB. We also studied the effects of inhaled NO in patients who required a VAD (right or biventricular bypass) to support their circulation.

\* Assistant Professor of Anesthesiology and Biomedical Engineering.

† Resident in Anesthesiology.

‡ Graduate Student in Biomedical Engineering.

§ Associate Professor of Anesthesiology.

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Address reprint requests to Dr. Rich: Department of Anesthesiology, University of Virginia Health Sciences Center, Box 238, Charlottesville, Virginia 22908.

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### Methods

This study was approved by the Human Investigation Committee at the University of Virginia, and informed consent was obtained from 25 patients. Patients were selected to be studied if they were undergoing mitral valve replacement or coronary artery bypass grafting and had a preoperative mean pulmonary artery pressure (PAP) greater than 20 mmHg. Patients requiring a VAD for circulatory support who had a PAP greater than 20 mmHg also were included.

Patient monitoring included a triple lumen pulmonary artery catheter (7.5-Fr, Baxter, or 7.5-Fr oximetric, Spectromed), pulse oximeter, electrocardiogram, and a 20-G catheter (Jelco) inserted in a radial artery. The aortic pressure, PAP, and central venous pressure (CVP) were transduced through high-pressure tubing attached to three transducers (Viggo-Spectromed T4812ADR) and a Marquette 500 Tram monitoring system. Cardiac output (CO) was determined using triplicate room temperature thermodilution, computed through the Marquette system. Cardiac output in the patients with a VAD was determined from the pump flow after adjusting the VAD to initially capture as much of the CO as possible. The flow was measured using an electromagnetic flow probe (Biomedicus centrifugal pump) or direct controller computer readout (Thoratec pneumatic pump).

Patients undergoing surgery were premedicated with morphine sulfate (0.1 mg/kg) and scopolamine (0.3 mg). All previous medications including calcium channel antagonists, beta antagonists, angiotensin converting enzyme inhibitors, and nitrates were continued perioperatively. Anesthesia was induced with sufentanil (12–17  $\mu$ g/kg) and midazolam (2–6 mg). Metocurine (0.2 mg/kg) and pancuronium (0.05 mg/kg) were used for muscle relaxation. Patients with a VAD were studied within 24 h of implantation in the intensive care unit and were administered additional sedation including morphine sulfate and midazolam as needed. Dobutamine or epinephrine with or without nitroglycerin was administered during separation from CPB. Patients with a VAD also were given sodium nitroprusside as needed to control arterial pressure.

All patients were orotracheally intubated (7.0 or 8.0 mm internal diameter), and ventilation was controlled with a Drager-Narkomed II ventilator (surgical patients) or a Siemens ventilator (intensive care unit patients). Nitric oxide was delivered using a premixed concentration of 100 ppm NO in nitrogen (Roberts Oxygen,

Waynesboro, VA). The NO was administered to the circle breathing system near the endotracheal tube *via* a separate flowmeter. The NO and oxygen flows were adjusted to a ratio of 1:4, which delivered 80% O<sub>2</sub>, 20% N<sub>2</sub>, and 20 ppm NO. The concentration of oxygen and nitrogen delivered to the endotracheal tube was confirmed by Raman spectroscopy (Rascal) or an oxygen meter (Fraser Harlake).

All medications, drug infusions, and routine care were continued during the protocol. Control data were obtained after anesthetic induction and hemodynamic stabilization but before sternal incision. The patients' lungs were ventilated with 80% O<sub>2</sub> and 20% N<sub>2</sub> to maintain a constant fraction of inspired oxygen after inhalation of NO. The hemodynamic data consisted of heart rate, CVP, PAP, pulmonary artery occlusion pressure (PAOP), mean arterial pressure (MAP), and CO. Laboratory data consisted of arterial oxygen tension (PaO<sub>2</sub>), arterial carbon dioxide tension, arterial pH, arterial hemoglobin oxygen saturation, and mixed venous hemoglobin oxygen saturation (SvO<sub>2</sub>). After determination of control data, the patients were administered 20 ppm NO in 80% O<sub>2</sub> and 20% N<sub>2</sub>. After 6 min of NO inhalation, the hemodynamic and laboratory data were recorded again. The NO was discontinued, and the lungs were ventilated with 80% O<sub>2</sub> and 20% N<sub>2</sub> for 6 min before collection of a second set of control data. The protocol was repeated in the operating room after sternal closure at the end of surgery. Patients with a VAD were studied using an identical protocol. Methemoglobin levels were measured at the beginning and end of each study.

Pulmonary vascular resistance was determined by  $[(\text{PAP} - \text{PAOP})/\text{CO}]80$ . Systemic vascular resistance (SVR) was determined by  $[(\text{MAP} - \text{CVP})/\text{CO}]80$ . Data are presented as the mean  $\pm$  SEM. Data from the two control and the NO periods were compared by analysis of variance followed by a Tukey test and considered significant for  $P < 0.05$ .

### Results

The 25 patients enrolled in the study were  $60 \pm 4$  yr of age and weighed  $72 \pm 5$  kg. The effects of inhaled NO were studied in 20 patients before and after CPB. Twelve patients underwent mitral valve replacement for chronic mitral regurgitation (11) or mitral stenosis (1). Two patients underwent mitral and aortic valve replacement for chronic mitral regurgitation and aortic stenosis (1) or aortic insufficiency (1). Two patients

**Table 1. Hemodynamic Data in Patients Undergoing Cardiopulmonary Bypass (CPB)**

Variable	Pre-CPB			Post-CPB		
	Control	Nitric Oxide	Control	Control	Nitric Oxide	Control
HR (beats/min)	76 ± 2	74 ± 3	74 ± 2	90 ± 3	91 ± 2	91 ± 2
CVP (mmHg)	10 ± 1	11 ± 1	10 ± 1	15 ± 1	15 ± 1	15 ± 1
PAP (mmHg)	36 ± 3	29 ± 2*	35 ± 3	32 ± 2	27 ± 1*	32 ± 2
PAOP (mmHg)	17 ± 1	17 ± 1	17 ± 1	15 ± 1	15 ± 1	15 ± 1
MAP (mmHg)	85 ± 3	83 ± 3	82 ± 3	72 ± 2	70 ± 2	72 ± 2
CO (L/min)	3.9 ± 0.2	3.8 ± 0.2	3.7 ± 0.2	5.5 ± 0.3	5.5 ± 0.3	5.5 ± 0.3
SVR (dyne · cm · s <sup>-5</sup> )	1593 ± 77	1568 ± 62	1598 ± 65	900 ± 82	876 ± 74	904 ± 86
PVR (dyne · cm · s <sup>-5</sup> )	387 ± 44	253 ± 26*	374 ± 45	260 ± 27	182 ± 18*	251 ± 23

CO = cardiac output; CVP = central venous pressure; HR = heart rate; MAP = mean arterial pressure; PAOP = pulmonary artery occlusion pressure; PAP = pulmonary artery pressure; PVR = pulmonary vascular resistance; SVR = systemic vascular resistance.

\* Significantly different from control,  $P < 0.05$ .

underwent mitral valve replacement for chronic mitral regurgitation and coronary artery bypass grafting. Four patients underwent coronary artery bypass grafting. Before CPB, the patients did not receive intravenous inotropic or vasodilator infusions. After CPB, 13 of the 20 patients received dobutamine (5–10  $\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ ), and the remaining patients received epinephrine (1–3  $\mu\text{g}/\text{min}$ ). Seventeen of the 20 patients were administered nitroglycerin (0.25–2  $\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ ).

Five patients were studied who required a VAD for circulatory support. Four of these patients could not be separated from CPB after mitral valve replacement and/or coronary artery bypass grafting and received either right ventricular (3) or biventricular bypass

(1). One patient's circulation was supported with biventricular bypass after developing a postpartum cardiomyopathy with an elevated PVR. All patients with a VAD were administered dopamine (3–15  $\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ ) and nitroglycerin (0.5–2  $\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ ). Four of the five patients with a VAD received sodium nitroprusside (1–2  $\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ ).

Inhalation of 20 ppm NO decreased ( $P < 0.05$ ) the PAP before and after CPB and in patients with a VAD (tables 1 and 2). Likewise, PVR decreased ( $P < 0.05$ ) after inhalation of NO (figs. 1–3). In patients with a VAD, inhaled NO increased ( $P < 0.05$ ) the MAP,  $\text{Pa}_{\text{O}_2}$ , and  $\text{Sv}_{\text{O}_2}$  (table 2). These variables returned to control after discontinuation of NO. All other hemodynamic and laboratory data remained unchanged after

**Table 2. Hemodynamic and Laboratory Data in Patients with a Ventricular Assist Device**

Variable	Control	Nitric Oxide	Control
HR (beats/min)	94 ± 7	94 ± 8	94 ± 8
CVP (mmHg)	19 ± 2	18 ± 2	19 ± 2
PAP (mmHg)	68 ± 12	55 ± 9*	67 ± 12
PAOP (mmHg)	18 ± 2	20 ± 3	18 ± 2
MAP (mmHg)	69 ± 4	73 ± 6*	69 ± 5
CO (L/min)	3.8 ± 0.5	3.8 ± 0.4	3.8 ± 0.4
SVR (dyne · cm · s <sup>-5</sup> )	1153 ± 216	1252 ± 224	1154 ± 225
PVR (dyne · cm · s <sup>-5</sup> )	1085 ± 229	752 ± 130*	1018 ± 184
$\text{Pa}_{\text{O}_2}$ (mmHg)	295 ± 33	404 ± 30*	298 ± 13
$\text{Pa}_{\text{CO}_2}$ (mmHg)	36 ± 2	35 ± 2	35 ± 1
pH	7.35 ± 0.01	7.36 ± 0.01	7.35 ± 0.01
$\text{Sa}_{\text{O}_2}$ (%)	99 ± 1	99 ± 1	99 ± 1
$\text{Sv}_{\text{O}_2}$ (%)	56 ± 3	67 ± 2*	59 ± 1

CO = cardiac output; CVP = central venous pressure; HR = heart rate; MAP = mean arterial pressure;  $\text{Pa}_{\text{CO}_2}$  = arterial carbon dioxide tension;  $\text{Pa}_{\text{O}_2}$  = arterial oxygen tension; PAOP = pulmonary artery occlusion pressure; PAP = pulmonary artery pressure; PVR = pulmonary vascular resistance;  $\text{Sa}_{\text{O}_2}$  = arterial oxygen hemoglobin saturation;  $\text{Sv}_{\text{O}_2}$  = mixed venous hemoglobin saturation; SVR = systemic vascular resistance.

CO determined from pump flow.

\* Significantly different from control,  $P < 0.05$ .

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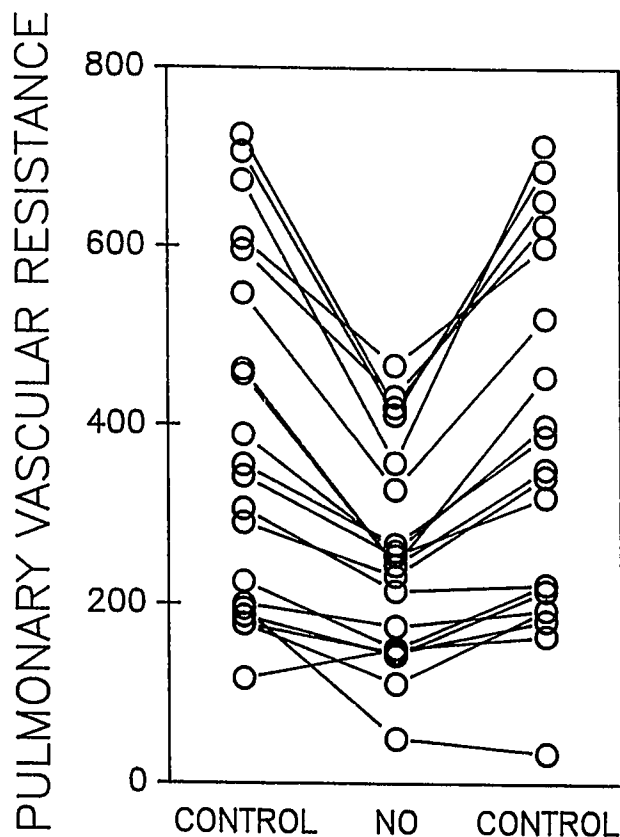


Fig. 1. The pulmonary vascular resistance ( $\text{dyne} \cdot \text{cm} \cdot \text{s}^{-5}$ ) before, during, and after inhalation of nitric oxide for each patient before cardiopulmonary bypass.

inhalation of NO (tables 1–3). Methemoglobin levels were not significantly different before and after inhalation of NO ( $0.5 \pm 0.1$  vs.  $0.5 \pm 0.1\%$ ).

The decrease in PVR after inhalation of NO was proportional to  $\text{PVR}_b$  (figs. 4 and 5). The slope of the change in PVR ( $\Delta\text{PVR}$ ) versus  $\text{PVR}_b$  can be expressed as  $\Delta\text{PVR} = -0.450\text{PVR}_b + 39.88$  and  $\Delta\text{PVR} = -0.445\text{PVR}_b + 37.13$  before and after CPB, respectively. There was no significant difference when comparing these two slopes. Finally, if the before and after CPB data are combined and grouped by  $\text{PVR}_b$  (<200, 200–350, 350–500, and >500  $\text{dyne} \cdot \text{cm} \cdot \text{s}^{-5}$ ), inhaled NO decreased ( $P < 0.05$ ) PVR in each group by  $22 \pm 7\%$ ,  $28 \pm 4\%$ ,  $36 \pm 4\%$ ,  $37 \pm 4\%$ , respectively (fig. 6).

### Discussion

Existing therapies for pulmonary hypertension are not selective to the pulmonary circulation, and hence can

decrease systemic arterial pressure. Decreased systemic pressure in turn may decrease coronary perfusion pressure and worsen right ventricular ischemia.<sup>9,10</sup> This study demonstrates that 20 ppm inhaled NO is a potentially useful therapy as a selective pulmonary vasodilator in cardiac surgical patients before and after CPB and in patients supported with a VAD.

Inhaled NO has been documented to decrease PVR in constricted but normal vessels in sheep and humans.<sup>4–6</sup> Inhaled NO (40 ppm) also has been demonstrated to be a selective pulmonary vasodilator in patients with chronic pulmonary hypertension.<sup>7,8</sup> The surgical patients in this study had PVR that ranged from normal (<200  $\text{dyne} \cdot \text{cm} \cdot \text{s}^{-5}$ ) to levels as high as 725  $\text{dyne} \cdot \text{cm} \cdot \text{s}^{-5}$ , resulting from chronic mitral regurgitation or stenosis and/or myocardial disease. Patients who required a VAD had severe pulmonary hypertension with  $\text{PVR} > 1,000$   $\text{dyne} \cdot \text{cm} \cdot \text{s}^{-5}$ . We used a lower concentration of inhaled NO than previously investi-

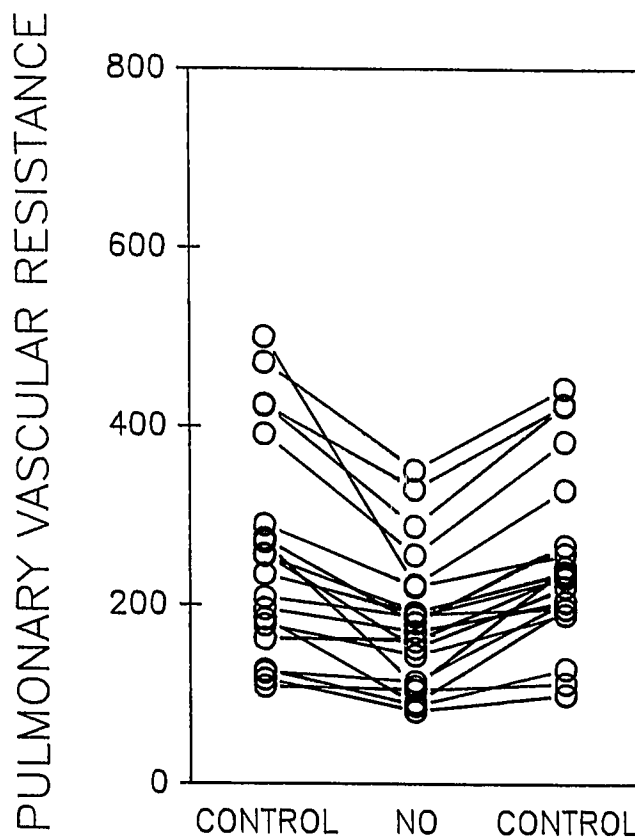


Fig. 2. The pulmonary vascular resistance ( $\text{dyne} \cdot \text{cm} \cdot \text{s}^{-5}$ ) before, during, and after inhalation of nitric oxide for each patient after cardiopulmonary bypass.

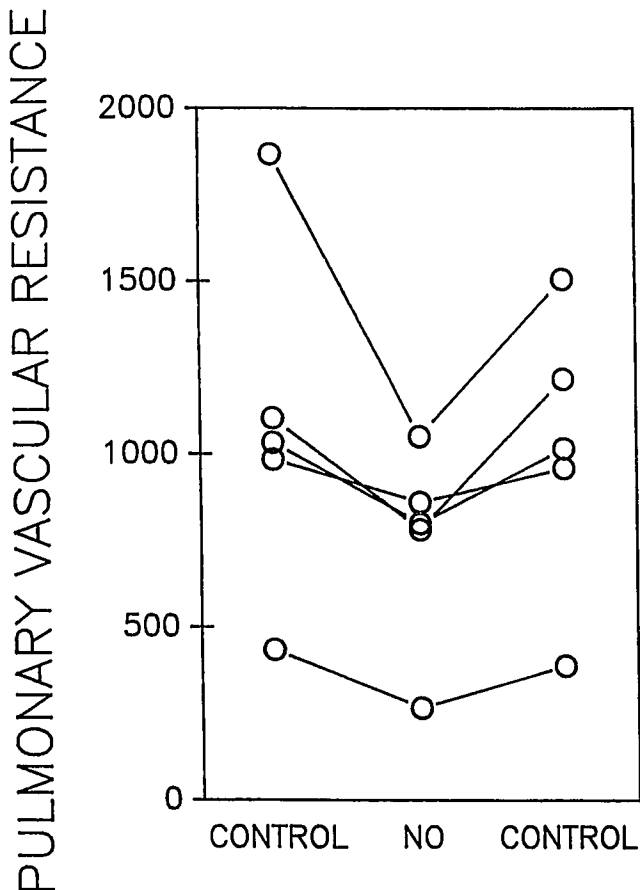


Fig. 3. The pulmonary vascular resistance ( $\text{dyne} \cdot \text{cm} \cdot \text{s}^{-5}$ ) before, during, and after inhalation of nitric oxide for each patient supported with a VAD.

gated in patients (20 ppm) and demonstrated a significant decrease in PVR.

The effectiveness of inhaled NO as a pulmonary vasodilator was directly proportional to  $\text{PVR}_b$ . As might be expected, the greatest decrease in PVR ( $37 \pm 4\%$ ) after inhalation of NO occurred in the patients with

the highest  $\text{PVR}_b$  ( $>500 \text{ dyne} \cdot \text{cm} \cdot \text{s}^{-5}$ ). The patients in this study with a normal  $\text{PVR}$  ( $<200 \text{ dyne} \cdot \text{cm} \cdot \text{s}^{-5}$ ) demonstrated significantly less of a decrease in PVR ( $22 \pm 7\%$ ). This is predictable based on previous sheep and human experiments in which inhaled NO did not decrease PVR if the pulmonary vasculature was not precontracted.<sup>4</sup>

Pulmonary vascular resistance remained increased ( $>200 \text{ dyne} \cdot \text{cm} \cdot \text{s}^{-5}$ ) in the majority of patients despite inhalation of NO. We did not administer higher concentrations of NO in an attempt to further decrease PVR. Although a dose-response relationship has been established for inhaled NO in animal models,<sup>4</sup> the dose-response relationship in humans with chronic pulmonary hypertension remains unknown.

In cardiac surgical patients, 20 ppm inhaled NO decreased PVR but did not affect CVP, CO, and systemic hemodynamics. Likewise, Girard *et al.* demonstrated in patients after mitral valve replacement that 40 ppm inhaled NO did not affect CO, MAP, and SVR.<sup>8</sup> Our study also agrees with the results of Pepke-Zaba *et al.*, who demonstrated that 40 ppm inhaled NO did not increase CO despite the decrease in PVR and constant CVP in human volunteers with pulmonary hypertension.<sup>7</sup> It is possible that, in our study, the CO was limited by left ventricular function or that there was a subtle decrease in right ventricular preload that was not reflected in the CVP. Further studies will be required to determine if and when inhaled NO improves right ventricular function as a result of decreasing PVR.

In the patients requiring a VAD for circulatory support, inhaled NO not only decreased PVR but also improved oxygenation and increased systemic perfusion as demonstrated by the increase in  $\text{Pa}_{\text{O}_2}$ , MAP, and  $\text{Sv}_{\text{O}_2}$ . The increase in systemic perfusion, despite a constant pump flow, is most likely the result of improved right ventricular function and an increase in CO from the natural heart. If total flow (pump flow + natural

Table 3. Laboratory Data in Patients Undergoing Cardiopulmonary Bypass (CPB)

Variable	Pre-CPB			Post-CPB		
	Control	Nitric Oxide	Control	Control	Nitric Oxide	Control
$\text{Pa}_{\text{O}_2}$ (mmHg)	$366 \pm 24$	$359 \pm 24$	$366 \pm 22$	$309 \pm 29$	$301 \pm 23$	$288 \pm 21$
$\text{Pa}_{\text{CO}_2}$ (mmHg)	$35 \pm 1$	$34 \pm 1$	$34 \pm 1$	$35 \pm 1$	$35 \pm 1$	$36 \pm 1$
pH	$7.42 \pm 0.01$	$7.43 \pm 0.01$	$7.43 \pm 0.01$	$7.34 \pm 0.01$	$7.34 \pm 0.01$	$7.34 \pm 0.01$
$\text{Sa}_{\text{O}_2}$ (%)	$99 \pm 1$	$99 \pm 1$	$99 \pm 1$	$99 \pm 1$	$99 \pm 1$	$99 \pm 1$
$\text{Sv}_{\text{O}_2}$ (%)	$72 \pm 2$	$71 \pm 2$	$71 \pm 2$	$72 \pm 2$	$72 \pm 2$	$72 \pm 3$

$\text{Pa}_{\text{CO}_2}$  = arterial carbon dioxide tension;  $\text{Pa}_{\text{O}_2}$  = arterial oxygen tension;  $\text{Sa}_{\text{O}_2}$  = arterial oxygen hemoglobin saturation;  $\text{Sv}_{\text{O}_2}$  = mixed venous hemoglobin saturation.

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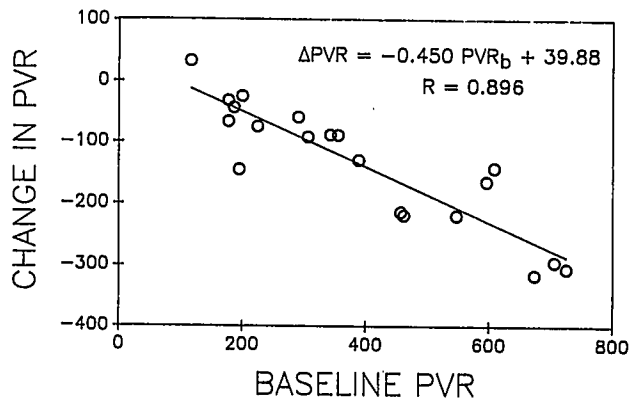


Fig. 4. Changes in pulmonary vascular resistance ( $\text{dyne} \cdot \text{cm} \cdot \text{s}^{-5}$ ) after inhalation of nitric oxide versus the baseline pulmonary vascular resistance before cardiopulmonary bypass.

heart output) increased, PVR decreased even further with inhalation of NO. This suggests that inhaled NO may improve systemic hemodynamics when right ventricular failure and an elevated PVR are limiting hemodynamic factors.

It is now recognized that the vascular effects of nitrates are modulated by the presence of a functional vascular endothelium. For example, nitroglycerin and sodium nitroprusside-induced vasodilation is augmented after removal of endothelium in *in vitro* preparations.<sup>11-14</sup> This is likely a result of endogenous EDRF/NO production, because the inhibitor of NO synthase (mono-methyl-L-arginine) prevents the endothelium modulation of nitrate effectiveness.<sup>13</sup> Whether this modulation also applies to inhaled NO is unknown. It is also unknown whether intravenous infusions of nitrates, which exert their effects by releasing

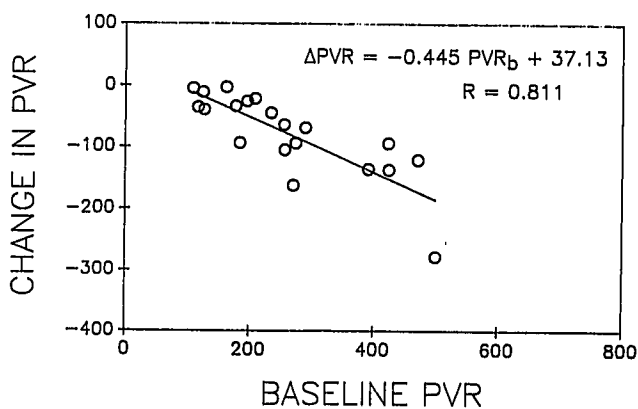


Fig. 5. Changes in pulmonary vascular resistance ( $\text{dyne} \cdot \text{cm} \cdot \text{s}^{-5}$ ) after inhalation of nitric oxide versus the baseline pulmonary vascular resistance after cardiopulmonary bypass.

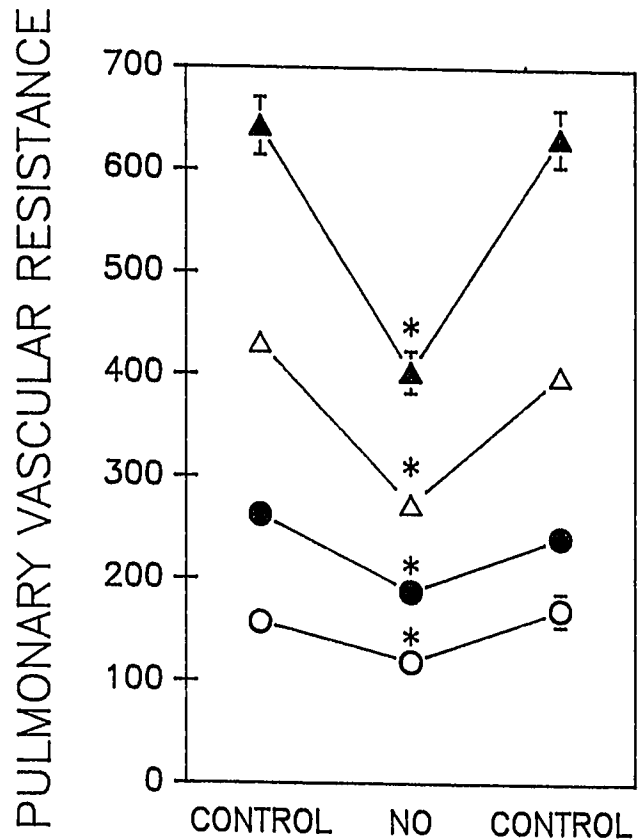


Fig. 6. The pulmonary vascular resistance ( $\text{dyne} \cdot \text{cm} \cdot \text{s}^{-5}$ ) before, during, and after inhalation of nitric oxide when pre- and post-cardiopulmonary bypass data are combined and grouped by baseline pulmonary vascular resistance: <200, 200-350, 350-500, >500. All are significantly different after inhalation of nitric oxide ( $P < 0.05$ ).

NO,<sup>15-17</sup> alter the vasodilating effects of inhaled NO. Our study suggests that, if modulation of inhaled NO by endothelium or infusion of nitrates occurs, it represents little clinical significance. First, the effects of inhaled NO were not altered by CPB, which functionally and anatomically damages the pulmonary endothelium.<sup>18,19</sup> Second, 17 of 20 patients received intravenous infusion of nitroglycerin after CPB, yet the effects of inhaled NO were not altered. Finally, inhaled NO was also effective in the patients supported with a VAD who were receiving sodium nitroprusside.

Inhaled NO produced pulmonary vasodilation in the presence of other therapies normally used to decrease PVR. The patients were anesthetized, the majority were receiving intravenous nitrates,  $\text{PaO}_2$  was greater than normal, and arterial carbon dioxide tension was normal. However, the possibility remains that, if higher doses of nitrates were used, the vasodilating effects of inhaled

NO might have been decreased. Nevertheless, this study demonstrates that inhaled NO provides significant additional pulmonary vasodilation to patients who continue to have an elevated PVR despite traditional therapy.

The absence of systemic vasodilation after inhalation of NO was confirmed in this study. This agrees with previous animal and human studies that show that short periods of inhaled NO in concentrations up to 80 ppm do not vasodilate the systemic circulation.<sup>4-8</sup> The lack of systemic effects probably results from the rapid inactivation of NO by hemoglobin.<sup>15,20,21</sup> The reaction of hemoglobin and NO forms nitrosyl hemoglobin and, subsequently, methemoglobin. Nevertheless, inhalation of low concentrations of 20 ppm NO did not significantly increase methemoglobin levels in our acute study. Likewise, previous animal and human studies have not identified elevated methemoglobin levels as a significant problem despite inhalation of NO for periods as long as 24 h.<sup>4,5,22,23</sup>

In our study, the vasodilating effects of inhaled NO can be characterized by a relatively fast onset with equally rapid reversibility. This contrasts with Frostell *et al.*'s study in human volunteers in which HPV was rapidly attenuated but immediate reversibility was not apparent.<sup>6</sup> However, our study agrees with all other previous sheep and other human studies that demonstrate the rapid onset and reversibility of inhaled NO in concentrations up to 80 ppm.<sup>4-8</sup>

Inhaled NO has been observed to increase oxygenation in animal models and humans with adult respiratory distress syndrome.<sup>24,25</sup> Pulmonary vasodilation is likely to occur only in ventilated regions; therefore, inhaled NO may increase PaO<sub>2</sub> in patients with ventilation/perfusion mismatching. This may have contributed to the increase in PaO<sub>2</sub> observed in our patients supported with a VAD. We did not observe improved oxygenation in our surgical patients; however, none were initially hypoxemic or likely to have significant ventilation/perfusion mismatching.

Although inhaled NO rapidly and reversibly decreased PVR in our acute studies, the long-term beneficial vasodilating effects are unclear. Studies in infants with persistent pulmonary hypertension suggest that inhaled NO may produce pulmonary vasodilation without tachyphylaxis for up to 24 h.<sup>23</sup> This resulted in improved oxygenation in these newborns previously treated with extracorporeal membrane oxygenation.<sup>22,23</sup> Long-term beneficial effects of inhaled NO have not been documented in adults. Furthermore, be-

fore initiating long-term therapy in patients, the potential toxic effects of long-term inhalation of NO (and NO<sub>2</sub>) must be evaluated. Inhalation of 43 ppm NO for 6 days does not produce evidence of toxicity by light or electron microscopy in rodents<sup>26</sup>; however, high levels of intracellular NO have been shown to be toxic in *in vitro* preparations.<sup>27</sup>

In conclusion, this study demonstrates that 20 ppm inhaled NO is a selective pulmonary vasodilator in cardiac surgical patients before and after CPB and in patients whose circulation is supported with a VAD. Pulmonary vasodilation is proportional to PVR<sub>b</sub> and does not appear to be altered by CPB, the presence of a VAD, or infusion of intravenous nitrates. Further evaluation will be necessary to determine whether inhaled NO is safe and effective for long-term therapy.

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